AS PER PCI REGULATIONS
SECOND YEAR B. PHARM.

SEMESTER-IV

PHARMACOLOGY-I

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Mrs. SOWMYA B. A.

NIRALI PRAKASHAN
ADVANCEMENT OF KNOWLEDGE

A Text Book Of

PHARMACOLOGY - I

As Per PCI Regulations

SECOND YEAR B. PHARM.

Semester - IV

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Preface

Clinical role of pharmacists have been identified during last 9 years after establishment of regulations for Pharm. D in 2008 followed by establishment of Pharmacy practice regulations in 2015 by Pharmacy Council of India. The practice of Pharmacy needs some time to get strong footing in our country. During such time, subject like Pharmacology-I need strong base by budding pharmacists.

The subject of Pharmacology has a different context for pharmacists in comparison to doctors. While doctors give more importance to clinical effects, pharmacists are more concerned with mechanism of action, and effects of drugs on animals can have equal relevance in case of pharmacists. Trade names have equal relevance to both doctors and pharmacists. This approach has been reflected in the content. Strong background of physiology is needed for understanding of Pharmacology-I. Trade names of drugs have been included in the appendix. The list is not exhaustive but includes common tradenames.

The content is as per new regulations of PCI and contains several additions as compared to syllabi of conventional universities. It is expected that the book will be welcomed by teachers and students of pharmacy. Still if there is any constructive criticism, it will be appreciated and considered while revising next edition of the book. We appeal to all the readers to forward their suggestions on the contents of the book.

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Syllabus

Unit I **[08 Hours]**

1. General Pharmacology

(a) Introduction to Pharmacology: Definition, historical landmarks and scope of pharmacology, nature and source of drugs, essential drugs concept and routes of drug administration, Agonists, antagonists (competitive and non competitive), spare receptors, addiction, tolerance, dependence, tachyphylaxis, idiosyncrasy, allergy.

(b) Pharmacokinetics: Membrane transport, absorption, distribution, metabolism and excretion of drugs. Enzyme induction, enzyme inhibition, kinetics of elimination

Unit II **[12 Hours]**

General Pharmacology

(a) Pharmacodynamics: Principles and mechanisms of drug action. Receptor theories and classification of receptors, regulation of receptors. drug receptors interactions signal transduction mechanisms, G-protein–coupled receptors, ion channel receptor, trans-membrane enzyme linked receptors, trans-membrane JAK-STAT binding receptor and receptors that regulate transcription factors, dose response relationship, therapeutic index, combined effects of drugs and factors modifying drug action.

(b) Adverse drug reactions.

(c) Drug interactions (pharmacokinetic and pharmacodynamic)

(d) Drug discovery and clinical evaluation of new drugs: Drug discovery phase, preclinical evaluation phase, clinical trial phase, phases of clinical trials and pharmacovigilance.

Unit III **[10 Hours]**

2. Pharmacology of drugs acting on peripheral nervous system

(a) Organization and function of ANS.
(b) Neurohumoral transmission, co-transmission and classification of neurotransmitters.
(c) Parasympathomimetics, Parasympatholytics, Sympathomimetics, sympatholytics.
(d) Neuromuscular blocking agents and skeletal muscle relaxants (peripheral).
(e) Local anesthetic agents.
(f) Drugs used in myasthenia gravis and glaucoma

Unit IV **[08 Hours]**

3. Pharmacology of drugs acting on central nervous system

(a) Neurohumoral transmission in the C.N.S.special emphasis on importance of various neurotransmitters like with GABA, Glutamate, Glycine, serotonin, dopamine.
(b) General anesthetics and pre-anesthetics**.**
(c) Sedatives, hypnotics and centrally acting muscle relaxants.
(d) Anti-epileptics
(e) Alcohols and disulfiram

Unit V **[07 Hours]**

4. Pharmacology of drugs acting on central nervous system

(a) Psychopharmacological agents: Antipsychotics, antidepressants, anti-anxiety agents, anti-manics and hallucinogens.
(b) Drugs used in Parkinsons disease and Alzheimer's disease.
(c) CNS stimulants and nootropics.
(d) Opioid analgesics and antagonists
(e) Drug addiction, drug abuse, tolerance and dependence.

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Contents

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Unit... 1

GENERAL PHARMACOLOGY - I

♦ LEARNING OBJECTIVES ♦

After completing this chapter, student should be able to understand:

- *History, Landmarks and Scope of Pharmacology*
- *Nature and Sources of Drugs*
- *Concept of Essential Drugs*
- *Basic Concepts of Agonists, Antagonists, Spare Receptors*
- *Special terms like Addiction, Tolerance, Dependence, Allergy etc.*
- *Concepts of Pharmacokinetics involving ADME*
- *Enzyme Induction, Inhibition and Kinetics*

1.1 INTRODUCTION TO PHARMACOLOGY

1.1.1 Definitions

- **Active ingredient (Active Substance, Compound, Active Pharmaceutical Ingredient)**

  Ingredient that alone or in combination with one or more other ingredients is considered to fulfil the intended activity of a medicine.

- **Acute care**

  A type of health care in which a patient is treated for an acute (immediate and severe) episode of illness, for the subsequent treatment of injuries related to an accident or other trauma, or during recovery from surgery.

- **Adherence**

  The extent to which a person's behaviour - taking medication, following a diet, and/or executing life-style changes, corresponds with agreed recommendations from a health care provider.

- **Adverse reaction**

  A response to a reaction which is noxoious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.

- **Batch (Lot)**

  A specific quantity of material produced in a process or series of processes so that it is expected to be homogenous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

- **Bioavailability**

  It is defined as, "the rate and extent to which the active substance or active moiety is absorbed from a pharmaceutical form and becomes available at the site of action".

- **Bioequivalence**

  Two medicines are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and if their bioavailabilities after administration in the same molar dose are similar to such degree that their effects, with respect to both efficacy and safety, will be essentially the same.

- **Biological marker (Biomarker)**

  A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

- **Biological medicine**

  It is a product, the active substance of which is a biological substance.

- **Bio-similar**

  It is defined as, "a biological medicine that is developed to be similar to an existing biological medicine (the "reference medicine")". Biosimilar medicines can only be marketed following the patent expiry of reference medicine.

- **Brand Name (Innovator's Name/Proprietary Product Name/Medicine Speciality Product Name/Medicinal Product Speciality Name)**

  It is the name given for marketing purposes to any ready-prepared medicine placed on the market under a special name and in a special pack. A brand name may be a protected trade mark.

- **Bulk product**

  It is defined, "as any product that has completed all processing stages up to, but not including, final packaging".

- **Burden of disease**

  It is a measurement of the gap between a population's current health and the optimal state where all people attain full life expectancy without suffering major ill-health.

- **Chronic care**

  The ongoing provision of medical, functional, psychological, social, environmental and spiritual care services that enable people with serious and persistent health and/or mental conditions to optimize their functional independence and well-being, from the time of condition onset until problem resolution or death.

- **Chronic condition (Chronic Disease)**

  A disease which has one or more of the following characteristics: is permanent; leaves residual disability; is caused by no reversible pathological alteration; requires special training of the patient for rehabilitation; or may be expected to require a long period of supervision, observation or care.

- **Clinical pharmacology**

  It is defined as, "the study of effects of the pharmaceuticals in humans".

- **Clinical trial (Clinical study)**

  Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or the pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy.

- **Combination product**

  It is defined as, "a medicine that contains more than one active ingredient".

- **Community care**

  Services and support to help people with care needs to live as independently as possible in their communities. (Considered as synonym for the out-patient health care sector in contract to the hospital sector).

- **Community pharmacy**

  It is defined as, "health care facility dispensing medicines (prescription-only medicines/ POM and Over-the-Counter/OTC medicines), reimbursable and non-reimbursable medicines to out-patients".

- **Co-morbid condition (co-morbidity)**

  It is defined as, "conditions that exist at the same time as the primary condition in the same patient. Two or more conditions may interact in such a way as to prolong a stay in hospital or hinder successful rehabilitation".

- **Complication**

  A medical condition that arises during a course of treatment and is expected to increase the length of stay by at least one day for most patients.

- **Cost-benefit analysis**

  It compares the cost of a medicinal intervention to its benefit. Both costs and benefits must be measured in the same monetary units (e.g. Rupees, Euro or Dollars).

- **Cost-effectiveness**

  It is defined, "as value for money". A specific health care treatment is said to be 'cost-effective' if it gives greater health gain than could be achieved by using the resources in other ways.

- **Counterfeit medicine**

  It describes a product with a false representation of its identity and/or source. This applies to the product, its container or other packaging or labelling information. Counterfeiting can apply to both branded and generic medicines.

- **Defined daily dose (DDD)**

  The DDD is a unit of measurement defined as, "the assumed average maintenance dose per day for a pharmaceutical used for its main indication in the adult".

- **Disability-Adjusted Life Years (DALYs)**

  It is defined as, "a measure of the burden of the disease on a defined population and the effectiveness of the intervention". DALYs are advocates as an alternative to Quality Adjusted Life Years (QALY) and claimed to be a valid indicator of population health.

- **Disease**

  A failure of the adaptive mechanisms of an organism to counteract adequately, normally or appropriately to stimuli and stresses to which the organism is subjected, resulting in a disturbance in the function or structure of some part of the organism.

- **Dispensing**

  To supply a clinically appropriate medicine to a patient or care giver, usually against a written prescription, for self-administration by another professional, and to advise on safe and effective use.

- **Drug utilisation research**

  It is defined as, "the research on marketing, distribution, prescription, and use of medicines in a society, with special emphasis on the resulting medical, social and economic consequences".

- **Effectiveness**

  It is the extent to which an intervention does more good than harm when provided under the usual circumstances of health care practice.

- **Efficacy**

  It is the extent to which an intervention does more good than harm under ideal circumstances.

- **Emergency**

  Sudden unexpected onset of illness or injury which requires the immediate care and attention of a qualified physician, and which, if not treated immediately, would jeopardise or impair the health of the individual.

- **Essential medicines**

  These are the medicines that satisfy the priority healthcare needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost effectiveness.

- **Excepient**

  A substance, other than the active ingredient, which has been appropriately evaluated for safety and is included in a medicine delivery system to:

  - Aid in the processing of the medicine delivery system during its manufacture;
  - Protect, support or enhance stability, bioavailability, or patient acceptability;
  - Assist in product identification; or
  - Enhance any other attribute of the overall safety and effectiveness of the medicine during storage or use.

- **Fixed dose combination (FDC) product**
  It is defined as, "a combination of two or more active substances in a fixed ratio of doses". It may be administered as single entity products given concurrently or as a finished pharmaceutical product.
- **Generic (Generic medicine)**
  A pharmaceutical product (medicine) which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicine, and whose bioequivalence with the reference medicine has been demonstrated by appropriate bioavailability studies.
- **Generic substitution**
  Practice of substituting a medicine, whether marketed under a trade name or a generic name (branded or unbranded generic), with a less expensive medicine (e.g. branded or unbranded generic), often containing the same active ingredient(s).
- **Good clinical practice (GCP)**
  A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and the reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.
- **Good distribution practices (GDP)**
  This is that part of quality assurance which ensures that the quality of a pharmaceutical product is maintained through adequate control throughout the numerous activities which occur during the distribution process.
- **Good manufacturing practices (GMP)**
  This is that part of quality assurance which ensures that pharmaceutical products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorisation.
- **Haemovigilance**
  It is defined as, "a set of organised surveillance procedures relating to serious adverse or unexpected events or reactions in donors or recipients of blood products, and the epidemiological follow-up of donors".
- **Health**
  It is defined as, "a state of complete physical, social and mental well-being, and not merely the absence of disease or infirmity".
- **Herbal medicine**
  It is defined as, "any medicine, exclusively containing as active ingredients, one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations".
- **Herbal substances**
  They are defined as, "whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried form, but sometimes fresh". Certain exudates that are not being subjected to a specific treatment are also considered to be herbal substances.

- **Herbal preparations**
  They are defined as, "preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation". These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, express juices and processed exudates.
- **Home care**
  It comprises medical and paramedical services delivered to patients at home.
- **Homeopathic medicines**
  Any medicine prepared from substances called homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia or, in the absence thereof, by the Pharmacopoeias currently used officially in the Member States.
- **Hospice (Hospice care)**
  It is defined as, "a facility or a programme providing care for the terminally ill".
- **Hospital pharmacists**
  Health care professionals who provide services to patients and health care professionals in hospitals are called as hospital pharmacists.
- **Hospital pharmacy**
  It is the health care service, which comprises the art, practise, and profession of choosing, preparing, storing, compounding and dispensing pharmaceuticals and medical devices, advising health care professionals and patients on their safe, effective and efficient use.
- **Illness**
  A person's own perceptions, experience and evaluation of a disease or condition, or how he or she feels is called as illness; e.g. an individual may feel pain, discomfort, weakness, depression or anxiety, but a disease may or may not be present.
- **Infusion**
  Administration, from a syringe or other rigid or collapsible container e.g. plastic bag, of a volume of sterile solution of an injectable medicine directly into a tissue, organ, vein or artery, at a constant rate, under gravity or by means of an electronic or mechanical pump or other means of rate control, over a defined period usually of at least 10 minutes is called as infusion.
- **In-patient care**
  An in-patient is a patient who is formally admitted (or hospitalised) to an institution for treatment and/or care and stays for a minimum of one night in the hospital or other institution providing in-patient care. In-patient care is delivered in hospitals, or in nursing and residential care facilities or in other establishments.
- **International Non-proprietary Name (INN, Generic name)**
  The shortened scientific name based on the active ingredient is called as INN. WHO is responsible for assigning INNs to pharmaceutical substances. INN is a unique name that is globally recognised and is public property.

- **Internet pharmacy (Online pharmacy)**

  It is an umbrella term for retailers of prescription-only medicines (POM) and Over-the-Counter (OTC) medicines who sell their products via World Wide Web.

- **Life expectancy**

  A statistical abstraction based on existing age-specific death rates is termed as life expectancy.

- **Medical device**

  A medical device is any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by its manufacturer to be used for human beings for the purpose of:

  - Diagnosis, prevention, monitoring, treatment or alleviation of disease, diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;
  - Investigation, replacement or modification of the anatomy or of a physiological process;
  - Control of conception, and which does not achieve its principle intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

- **Medication error**

  Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer, is termed as medication error.

- **Medicine (Pharmaceutical, Pharmaceutical product, Medication, Medicinal product)**

  (a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

  (b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis is termed as medicine.

- **Mortality rate**

  An estimate of the proportion of a population that dies during a specified period is called as mortality rate.

- **Out-patient**

  An out-patient is a person who goes to a health care facility for a consultation/ treatment, and who leaves the facility within several hours of the start of the consultation without being admitted to the facility as a patient.

- **Out-patient care (Ambulatory care, Community care)**

  It comprises of medical and para-medical services delivered to out-patients.

- **Palliative care**

  The active total care offered to a person and that person's family when it is recognised that the illness is no longer curable, in order to concentrate on the person's quality of life and the alleviation of distressing symptoms is called as palliative care.

- **Patent**

  It is a set of exclusive rights granted by a state (National Government) to an inventor or their assignee for a limited period of time in exchange for public disclosure for its invention.

- **Pharmaceutical alternatives**

  Medicines are pharmaceutical alternatives if they contain the same active moiety but differ in chemical form (salt, ester etc.) of that moiety in the dosage form or strength.

- **Pharmaceutical care**

  It is the responsible provision of medicine therapy for the purpose of achieving definite outcomes that improve a patient's quality of life. These outcomes are:
  - Cure of a disease
  - Elimination or reduction of a patients' symptomatology
  - Arresting or slowing of a disease process; or
  - Preventing a disease or symptomatology.

- **Pharmaceutical equivalence**

  Medicines are pharmaceutically equivalent if they contain the same amount of the same active substance(s) in the same dosage forms that meet the same or comparable standards.

- **Pharmacovigilance**

  It is the process and science of monitoring the safety of medicines and taking action to reduce risks and increased benefits from medicines. It comprises of:
  - Collecting and managing data on safety of medicines,
  - Looking at the data to detect signals (any new or changing safety issue), evaluating the data and making decisions with regard to safety issues,
  - Acting to protect public health (including regulatory action); communicating with stakeholders,
  - Audit, both the outcomes of action taken and of the key processes involved.

- **Polypharmacy**

  The administration of many medicines at the same time or the administration of excessive number of medicines is called as polypharmacy.

- **Quality-Adjusted Life Years (QALYs)**

  It is a measure of health outcome which looks at both length of life and quality of life. QALYs are calculated by estimating the years of life remaining for a patient following a particular care pathway and weighing each year with a quality of life score (on a zero to one scale). One QALY = one year of life in perfect health, or two years at 50% health, and so on.

- **Rational use of medicines**
  It requires that, patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community.
- **Reference product (Reference medicine)**
  A medicine which has been granted a marketing authorisation by a country or by the regulatory authority on the basis of submitted quality, pre-clinical and clinical data, to which the application for marketing authorisation for a generic or a bio-similar product refers.
- **Risk**
  The probability that an event will occur, e.g., that an individual will become ill or die within a stated period of time or by a certain age.
- **Risk-benefit balance**
  An evaluation of the positive therapeutic effects of the medicine in relation to its risks (any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health and any risk of undesirable effects on the environment) is called risk-benefit balance.
- **Self-medication**
  It is the treatment of common health problems with medicines especially designed and labelled for use without medical supervision and approved as safe and effective for such use.
- **Therapeutic benefit (Therapeutic value)**
  The effect conveyed on a patient following administration of a pharmaceutical which restores, corrects or modifies a physiological function(s) for that patient is called as therapeutic benefit.
- **Therapeutic equivalence**
  Two pharmaceutical products are considered to be therapeutically equivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and after administration in the same molar dose, their effects, with respect to both efficacy and safety, are essentially the same when administered to patients by the same route under the conditions specified in the labelling.
- **Therapeutic group**
  A group of medicines according to their indications of use are called as a therapeutic group.
- **Tertiary care**
  Services provided by highly specialised providers (e.g. neurosurgeons, thoracic surgeons, intensive care units), usually in in-patient facility is called as tertiary care.
- **Vulnerable groups**
  Groups within a society facing higher risks of poverty and social exclusion compared to the general population are called as vulnerable groups; e.g. people with disabilities, isolated elderly people, children, migrants, ex-prisoners and drug addicts.

1.1.2 Historical Landmarks and Scope of Pharmacology

The science of pharmacology has evolved over the period of time. Knowledge about various events during evolution of drugs constitutes historical landmarks of pharmacology. Along with knowing the history, the scope of pharmacology is also advancing with time. Both the topics are of interest to students of Pharmacology.

1.1.2.1 Historical Landmarks

The knowledge of primitive pharmacology developed from human experiences with use of plants. Some plants were safe while others were toxic. Based on this knowledge, a catalogue of good and bad evolved and was passed down through oral traditions. Over the period of time, the knowledge was transformed to include natural sources which appeared to cure some diseases.

The oldest recorded event cites about events in 16th Century bc when beer, turpentine, myrrh, juniper berries and poppy and other therapies were described to treat disease. Similar historical records exist for most ancient civilizations including the Sumerian, Indian and Chinese. In India, Ayurveda has older traditions even before 16th century BCE. Sumerians around 3400 BCE cultivated the opium poppy in lower Mesopotamia and recorded its action in clay tablets. It was referred to as the "joy plant" and its reputation lead to its spread across neighbouring civilizations like Egypt. Around 460 BCE Hippocrates, a famous Greek physician and teacher of medicine, described opium as having narcotic properties and described use of opium in treating internal diseases. In 330 BCE, Alexander the great, introduced opium to Persia and India and by the year 400 it reached China. In the 10th century, the noted Islamic physician Avicenna of Persia described opium as the "most powerful stupefacients". About the year 1200, the Indian medical treatises T*he Shodal Gadanigraph* and *Sharangdhar-Samahita* describe the use of opium for diahorrhoea and sexual debility. In the 1300's opium disappeared from European historical record till 1527; during which Paracelsus prescribed opium as a pain killer.

The modern era began in 1680 when the English apothecary, Thomas Sydenham introduced Sydenham's Laudanum which mentioned about many opium proprietary brands useful for various ailments. In 1803, the German Friedrich Serturner dissolved opium in acid and then neutralised it with ammonia resulting in formation of morphine which exhibited long-lasting and predictable effects. By 1827, morphine became a commercial product. In 1874, an English researcher, Wright synthesised heroin which went into commercial production in Germany by 1898.

The molecular basis of opioid action was revealed by Snyder and Pert who located the molecular site of action for opium in 1972. These opioid receptors were found in neural tissues and mediate the pain reducing effect. Later Hughes and Kosterlitz discovered that humans produce endogenous morphine-like compounds, called as enkephalins, which act on opioid receptors.

Besides opium there are few more milestones in historical development of pharmacology. In early 19th century, physiologists performed many pharmacological studies.

Magendie studied the action of Nux Vomica (a strychnine-containing plant drug) on dogs and showed that the spinal cord was the site of convulsant action. His work was presented to the Parris academy in 1809. Later in 1842, Bernard discovered that the arrow poison curare acts at the neuro-muscular junction to interrupt the stimulation of muscle by nerve impulses. Till 1846, the science of effect of drugs developed under physiology only. It was only in 1847, Buchheim was appointed as professor of pharmacology at University of Dorpat in Estonia (then a part of Russia). Initially there were no funds and professor Buchheim built a laboratory on his own expense in the basement of his home. His studies were mostly descriptive. His student Schmiedeberg (1838-1921) is recognised as founder of modern pharmacology. He obtained his medical doctorate in 1866 with a thesis on the measurement of chloroform in blood. He worked at Dorpat till 1869. In 1872, he became professor of pharmacology at the University of Starssburg, receiving generous Government support for developing an institute of pharmacology. He studied the pharmacology of chloroform and chloral hydrate. In 1869, he showed that muscarine evoked the same effect on heart as electrical stimulation of the vagus nerve. In 1885, he introduced urethane as a hypnotic. He was largely responsible for the pre-eminence of German pharmaceutical industry up to Second World War.

In USA, the first chair in pharmacology was established in the University of Michigan in 1890 under Abel who was trained under Schmiedeberg. In 1893, Abel went to Johns Hopkins University in Baltimore. His contributions include isolation of epinephrine from adrenal gland extracts (1897-98), isolation of histamine from pituitary extract (1919), and preparation of pure crystalline insulin (1926). His student Hunt discovered acetyl choline in adrenal extracts in 1906.

Pharmacology largely depends on experiments conducted in laboratory animals; however there are isolated cases where human beings have been used to study the effect of drugs. Serturner, the German pharmacist who isolated the first alkaloid from opium in 1805, administered a dose of 100 mg to himself and his three friends. All of them experienced the symptoms of severe opium poisoning for several days. Another interesting story where human beings were used for testing drugs occurred in 1940s. Biological assays (bioassays) of digitalis performed in frogs, pigeons and cats were highly unsatisfactory. In 1942, a group of cardiologists published "a method for bioassay of digitalis in humans". The assay was based on changes in ECG of patients. Of 97 patients in whom ECG was tried, only 18 proved to be satisfactory assay subjects.

Animals are primarily used to detect toxicity of substances,. Most frequently pharmacological studies are conducted in mammals. Mice are preferred because of their small size, ease of breeding and short generation time. Rats, guinea pigs, rabbits and dogs are also used; each has special characteristics that make it optimal for certain type of tests. The efforts of animal activists have restricted use of animals for experimental study on drugs. In India, permission from the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) is necessary for conducting any animal experiments. It is suggested that animals should be used only for research and development and not for education/demonstration. Every pharmacy college is supposed to take permission from CPCSEA, with one of their representative in the committee.

Early in the development of pharmacological techniques, it was found that an isolated organ or tissue remained functional for several hours in a bath containing a physiologic solution of salts through which oxygen was bubbled. Magnus (1802-1870) first applied this method to a strip of small intestine. Later Heymans (1904) worked with mammalian heart and Bernard experimented with isolated nerve-muscle preparation. In 1924, Allen and Doisy used ovarictomized rats to test the action of estrogenic hormone.

With advancement of knowledge of human biochemistry and molecular biology, pharmacological actions are often studied on actions of enzymes and receptors. The drug Captopril was developed by Ondetti and co-workers at Squib in 1970s to inhibit the enzyme - Angiotensin Converting Enzyme (ACE). Subsequently, it was proved that inhibitors of ACE work as anti-hypertensive drugs. Knowledge of cell receptors is yet another milestone. Adrenalin is the neurotransmitter for sympathetic nervous system. Adrenalin acts on α- and β- receptors. Propranolol was the first β-adrenergic receptor blocking agent. From 1964, β-blockers have been used for treating hypertension and cardiac arrhythmia.

Synthetic organic chemistry was born in 1828, when Wohler synthesised urea from inorganic substances. Several substances, existing in the body or their derivatives were synthesised in laboratories as an extension of developments in organic chemistry. With the knowledge of receptors, a complimentary substance can be synthesised in laboratories. With the help of Structure – Activity Relationship (SAR) derivatives of main active moiety can be synthesised. In recent years, developments in medicinal chemistry have greatly contributed to development of various synthetic drugs.

1.1.2.2 Scope of Pharmacology

The science of Pharmacology has interfaces with Anatomy and Physiology, Organic and Inorganic Chemistry, Microbiology and Pathophysiology. Pharmacology is related to action and uses of drugs. In development of new drugs, pharmacology has greatest contribution. It has two main components: pharmacodynamics and pharmacokinetics. Pharmacodynamics deals with what drug does to the human/animal body. It involves study of action of drugs on receptors, its mechanism of action, indications for clinical use, contra-indications and adverse reactions caused by drugs. Pharmacokinetics deals with what body does towards drugs. It has four main components: Absorption, Distribution, Metabolism and Excretion (ADME). Out of these four components, absorption, distribution and excretion are dependent on transport through membranes without any chemical change in the entity. In metabolism, there is chemical change in the moiety because of action of enzymes in the body. Cytochromal enzymes in the liver are the main metabolising enzymes in the liver. A drug may have n number of metabolites. Every metabolite can have different action in the body. Thus, what we observe as action(s) of drugs is the net effect of main drug moiety and its metabolites. Several factors can alter ADME of drugs. It is the main reason why we get different kinds of actions for the same drug in different individuals.

Clinical pharmacology and therapeutics primarily deals with actions of drug in human beings. It incorporates indications, therapeutic uses, contra-indications, posology, bio-availability, prescription writing and drug nomenclature. The science of clinical toxicology is

an extension of clinical pharmacology. Forensic toxicology addresses to medico-legal aspects of use of drugs. Pharmacovigilance is gaining vital importance in last few decades. It involves study of adverse reactions of drugs and their safety. Based on observations on pharmacovigilance, some drugs have been withdrawn from the market due to severe adverse reactions.

1.1.3 Nature and Sources of Drugs

Several drug candidates have been derived from various naturally occurring medicinal sources. They can be broadly divided in to four major categories:

- Plant sources
- Animal sources
- Microbial sources
- Marine sources.

In addition to the above mentioned natural sources, two other sources need specific mention. A drug may be derived either as a semi-synthetic product from any of the naturally occurring resources or it may be of totally synthetic origin. Having knowledge about the receptor and Quantitative Structure-Activity Relationship (QSAR), one may predict possible structure of a drug. Subsequently, a drug with optimum biological action can be synthesised, tested and evaluated for possible clinical activity.

The use of plants as medicines has a long history. Opium has been the first known drug from plant sources. Plants continue to be a significant part of traditional medicine and herbal medicine. Several important drugs like Taxol, Camptothecin, Morphine and Quinine have been isolated from plant sources.

Animals have been sources for some drugs. Insulin and heparin are two common names of drugs of animal origin. Till last few decades insulin was obtained from pancreas of animals. Now insulin is available by genetic engineering from microbial sources. Heparin is obtained from lungs of animals. Epibatidine, obtained from the skin of an Ecuadorian poison frog, is ten times more potent than morphine. Teprotide, extracted from a Brazilian snake viper, has led to the development of Cilazapril and Comptopril, which are effective against hypertension.

Microorganisms as a source of potential drug candidates were not explored till the discovery of penicillin in 1929. Subsequently several antibiotics have been obtained either from microbial sources or from their semi-synthetic derivatives.

Marine organisms have also been sources for new drugs. The first active compounds to be isolated from marine species were Spongouridine and Spongothymidine from the Carribean sponge *Cryptotheca crypta* in 1950s. These compounds are nucleotides and show a great potential as anticancer and antiviral agents. Discodermolide, isolated from the marine sponge, *Discodermia gissoluta* has a strong antitumour activity and has mode of action similar to that of Paclitaxol. Few antibiotics also originate from ocean.

Several derivatives of antibiotics, β-blockers, anti-protozoal drugs, anti-malarial drugs are of totally synthetic origin. The examples of the categories of drugs are illustrative only. In recent years most of the new drugs are of synthetic origin based on the knowledge about the receptor.

1.1.4 Essential Drugs Concept

Although a large number of medicines are available in the market, all of them may not be necessary for majority of population. Based on this observation, World Health Organisation (WHO) proposed a concept of 'essential medicines' in 1977. According to this concept, essential medicines are those that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on safety and efficacy, and comparative cost-effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate times, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford. The implementation of the concept of essential medicines is intended to be flexible and adaptable to many different situations; exactly which medicines are regarded as essential remains responsibility of that country.

In the first, 1977 version of list of essential medicines, 208 medicines were identified to address the global burden of disease at that time. The list is revised by a committee of independent experts after every two years to reflect new health challenges, pharmaceutical developments and changing resistance patterns by microorganisms. In 2007, 30^{th} anniversary of WHO was celebrated. By then 156 of 193 WHO member states have official essential medicine lists, of which 127 countries have been updating it in past 5-10 years. The list of essential medicines published in 2007 contains 340 medicines including drugs for malaria, HIV/AIDS, tuberculosis, reproductive health, chronic diseases like cancer and diabetes. The list of essential medicines published in October 2007 contained for the first time "Essential Medicines for children". The list of essential medicines for children is also updated every two years. In the year 2015, 19^{th} model list of essential medicines and 5^{th} revised list of essential medicines for children has been published by WHO. The 20^{th} revision of essential medicines and the 6^{th} revision of essential medicines for children is in the process.

Government of India has published a list of essential medicines. Few states have implemented it. In the year 2013, eighth edition of essential medicines list for the National Capital Territory of Delhi has been published. Few other states like Rajasthan, Kerala, Karnataka and Madhya Pradesh have essential lists prepared by an expert committee and the concept is implemented in these states.

1.1.5 Routes of Drug Administration

Route of administration refers to the starting point for the drug's introduction in to the body up to the place where it acts upon the target organ or system. The route of administration for the drug depends on a number of factors like nature of the drug, its pharmacokinetics, and the nature and urgency of the medical condition. The main routes of administration are: local and systemic. The local route is further sub-classified into topical like administration to eye, ear, nose etc. The systemic route is further divided as enteral and parenteral. Enteral route consists of oral, rectal and sub-lingual. Parenteral route consists of inhalation, and various injections like sub-cutaneous, intra-muscular and vascular types. Definitions of all routes of administration are presented below:

- **Enteral**
  It means through gastro-intestinal tract. It includes oral, sublingual and rectal routes.
- **Parenteral**
  It means through routes other than enteral. It includes all types of injections, inhalations.
- **Local**
  It includes administration of a drug at the site where the desired action is intended. It includes topical administration in oral cavity, gastro-intestinal tract, rectum/anal canal, eye, ear, nose, bronchi, skin, intra-arterial, injection in deep tissues e.g. joints.
- **Systemic**
  It includes drugs administered to enter the blood to produce systemic effects.
- **Oral**
  It means drugs taken by mouth e.g. tablets, capsules, syrups, mixtures etc.
- **Intravenous**
  It includes drugs injected directly in to blood stream through a vein. It may be administered as: bolus, slow intravenous injection or an intravenous infusion.
- **Intrathecal**
  It includes drugs injected in to the sun-arachnoid space e.g. spinal anaesthetics like lignocaine.
- **Intra-articular**
  It includes drugs injected directly in to the joint space e.g. hydrocortisone injection for rheumatoid arthritis.
- **Subcutaneous**
  It includes drugs injected in to the sub-cutaneous tissues of the thigh, abdomen and arm e.g. adrenalin, insulin etc.
- **Intradermal**
  It includes drugs injected in to the dermis layer of the skin e.g. tuberculin and allergy tests.
- **Intramuscular**
  It includes drugs injected in to large muscles such as deltoid, gluteus maximus and vastus lateralis. A volume of 5-10 ml can be given at a time e.g. paracetamol, diclofenac.
- **Intraosseous**
  It includes injecting a drug directly in to the marrow of a bone.
- **Transdermal (patch)**
  It includes administration of a drug in the form of a patch or ointment that delivers the drug into the circulation for systemic effect.
- **Rectal**
  It includes administration of drugs in the form of suppository or enema in to the rectum.
- **Sublingual**
  In this case, the preparation is kept under the tongue. The drug is absorbed through the buccal membrane and enters the systemic circulation bypassing the liver e.g. nitroglycerine for acute angina attack.
- **Inhalation**
  It includes volatile gases and liquids which are given by inhalation for systemic effects e.g. general anaesthetics.
- **Endotracheal**
  It includes a catheter inserted in to the trachea for primary purpose of establishing and maintaining an airway to ensure adequate exchange of oxygen and carbon dioxide.

The broad classification is presented in Fig. 1.1.

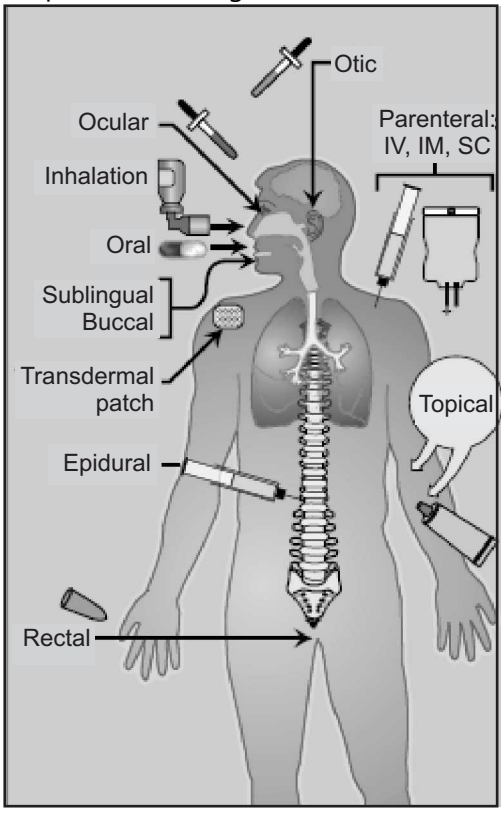


Fig. 1.1: Routes of administration

Fig. 1.2 indicates pictorial presentation of various injectable routes.

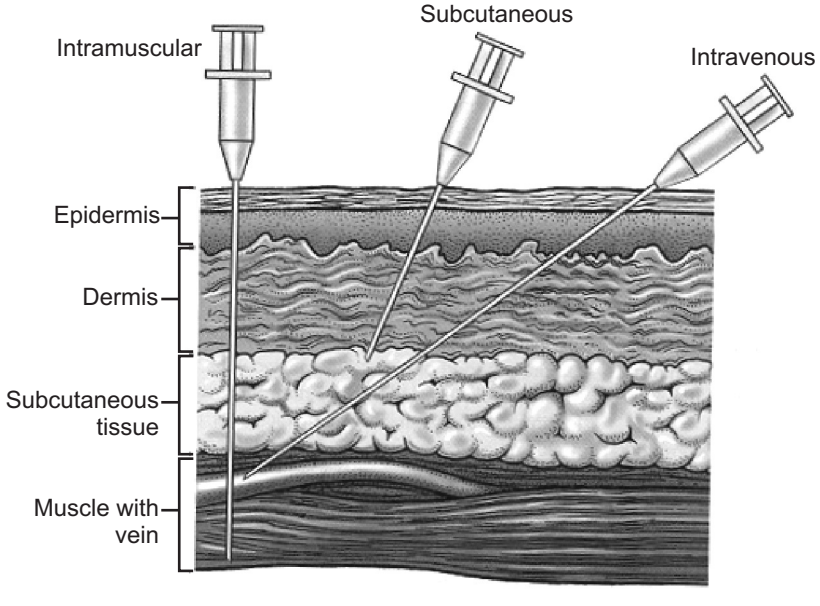


Fig. 1.2: Injectable routes of drug administration

Brief characteristics of different routes of administration are presented in table 1.1.

Table 1.1: Absorption pattern, advantages and disadvantages of most common routes of administration

Sr. No.	Name of route	Absorption pattern	Advantages	Disadvantages
1.	Oral	Variable; affected by many factors.	Safest and most common, convenient, and economical	• Limited absorption of some drugs. • Food may affect absorption. • Patient compliance is necessary. • Drugs may be metabolised before systemic absorption.
2.	Intravenous	Absorption not required.	• Can have immediate effects. • Ideal if dosed in large volumes. • Suitable for irritating substances and complex mixtures. • Valuable in emergency situations. • Dosage titration permissible. • Ideal for high molecular weight proteins and peptides.	• Unsuitable for oily substances. • Bolus injection may result in adverse effects. • Most substances must be slowly injected. • Strict aseptic techniques needed.
3.	Subcutaneous	Depends on drug diluents; Aqueous solution: prompt; Depot preparations: Slow and sustained	• Suitable for slow-release drugs. • Ideal for some poorly soluble suspensions.	• Pain or necrosis if drug is irritating. • Unsuitable for drugs adminis-tered in large volumes.

contd. …

4.	Intramuscular	Depends on drug diluents; Aqueous solution: prompt; Depot preparations: Slow and sustained	• Suitable if drug volume is moderate. • Suitable for oily vehicles and some irritating substances. • Preferable to intravenous if patient can self-administer.	• Affects certain lab tests (creatine kinase). • Can be painful. • Can cause intramuscular haemorrhage. • Avoided during anticoagulant therapy.
5.	Transdermal	Slow and sustained.	• Bypasses the first-pass effect. • Convenient and painless. • Ideal for lipophilic and poorly bioavailable drugs. • Ideal for drugs which are quickly eliminated.	• Some patients are allergic, causing irritation. • Drug must be highly lipophilic • May cause. delayed delivery to the site. • Limited to drugs which can be taken in small daily doses.
6.	Rectal	Erratic and variable.	• Partially bypasses first-pass effect. • Bypasses destruction by stomach acid. • Ideal if drug causes vomiting. • Ideal in patients who are vomiting or comatose.	• Drugs may irritate the rectal mucosa. • Not a well-accepted route.
7.	Inhalation	Systemic absorption may occur; it is undesirable.	• Absorption is rapid; can have immediate effects. • Ideal for gases. • Effective for patients with respiratory problems. • Dose can be titrated. • Localised effect to target lungs: lower doses can be used. • Fewer systemic side effects.	• Most addictive route (drug can enter the brain quickly). • Patient may have difficulty in regulating dose. • Some patients may have difficulty in using inhalers.

contd. …

8.	Sublingual	Depends on the drug: few drugs have rapid direct systemic absorption. Most drugs are absorbed incompletely and erratically.	• Bypasses first-pass effect. • Bypasses destruction by stomach acid. • Drug stability is maintained because pH of saliva is relatively neutral. • May cause immediate pharmacological effects.	• Limited to certain types of drugs. • Limited to drugs which can be taken in small doses. • May lose part of the drug dose if swallowed.

Duration in which the effect can initiate also depends on route of administration. Table 1.2 provides information in this context.

Table 1.2: Effect of route of administration on initiation of effect of drugs

Sr. No.	Route of administration	Time until effect
1.	Intravenous	30-60 seconds
2.	Intraosseous	30-60 seconds
3.	Endotracheal	2-3 minutes
4.	Inhalation	2-3 minutes
5.	Sublingual	3-5 minutes
6.	Intramuscular	10-20 minutes
7.	Subcutaneous	15-30 minutes
8.	Rectal	5-30 minutes
9.	Oral	39-90 minutes
10.	Transdermal (topical)	Variable (minutes to hours)

Drug and patient related factors determine the selection of routes for drug administration. The factors are:

- Characteristics of drugs.
- Emergency/routine use.
- Site of action of the drug - local or systemic.
- Condition of the patient (unconscious, vomiting, diarrhoea).
- Age of the patient.
- Effect of gastric pH, digestive enzymes and first-pass metabolism.
- Patient's/doctor's choice.

1.1.6 Agonists

An agonist is a chemical which binds to a receptor and activates the receptor to produce a biological response. Receptors can be activated by either endogenous agonists (like hormones or neurotransmitters) or exogenous agonists (like drugs). Agonists can be divided into following sub-categories:

- **Full agonists**

  They bind to and activate a receptor with the maximum response that an agonist can elicit at the receptor e.g. isoproterenol mimics the action of adrenaline at β-adrenoceptors.

- **Co-agonists**

  A co-agonist works with other co-agonists to produce the desired effect together; e.g. NMDA receptor activation requires binding of glutamate, glycine and D-serine co-agonists.

- **Selective agonists**

  A selective agonist is selective for a specific type of receptor only; e.g. buspirone is a selective agonist for serotonin 5-HT1A.

- **Partial agonists**

  Partial agonists like buprinorpine also bind and activate a given receptor but have only partial efficacy at the receptor relative to a full agonist, even at maximal receptor occupancy.

- **Inverse agonists**

  An inverse agonist is an agent which binds to the same receptor binding-site as an agonist and inhibits the constitutive activity of the receptor. Inverse agonists exert the opposite pharmacological effect to that of an agonist. This is unlike an antagonist; e.g. Cannabinoid inverse agonists rimonabant.

- **Super agonists**

  It is a term used to identify a compound which is capable of producing a greater response than the endogenous agonists for the target receptor.

- **Irreversible agonists**

  An irreversible agonist is a type of agonist which binds permanently to a receptor through formation of covalent bonds.

1.1.7 Antagonists (Competitive and Non-competitive)

An antagonist is a type of receptor ligand or drug which blocks or dampens a biological response by binding to and blocking a receptor rather than activating it like an agonist. They are sometimes called as blockers e.g. α-blockers, β-blockers, calcium channel blockers etc. Antagonists have affinity but no efficacy for their cognate receptors. The concept of affinity and efficacy is presented below.

Affinity

The affinity of an antagonist for its binding site is its ability to bind to a receptor. It determines the duration of inhibition of agonist activity. It can be measured experimentally.

Efficacy and Potency

By definition, antagonists display no efficacy to activate the receptors to which they bind. Antagonists do not maintain the ability to activate a receptor. However, once bound they will inhibit the function of agonists, inverse agonists and partial agonists.

Thus, antagonists can have variable affinity but no efficacy.

Antagonists are of different types: Competitive, Non-competitive and Uncompetitive.

1.1.7.1 Competitive Antagonists

Competitive antagonists bind to receptors at the same binding site (active site) as the endogenous ligand or agonist, but without activating the receptor. Agonists and antagonists compete for the same binding site on the receptor. Once bound, an antagonist will block binding of agonist. Sufficient concentration of an antagonist will displace the agonist from the binding sites, resulting in a lower frequency of receptor activation. The level of activity of the receptor will depend on relative affinity of each molecule for the site and their relative concentrations. Competitive antagonists are used to prevent the activity of drugs and to reverse the effects of drugs that have already been consumed. Naloxone is an antagonist of morphine/heroine and is used to reverse effects of opioid overdose.

Competitive antagonists are sub-classified as reversible (surmountable) or irreversible (insurmountable) competitive antagonists, depending on how they interact with their receptor protein targets. In case of irreversible antagonism, the bond with receptor is probably of covalent nature.

1.1.7.2 Non-competitive Antagonists

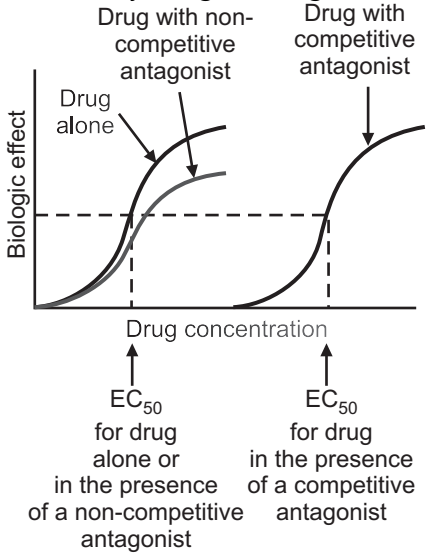
A non-competitive antagonist is a type of unsurmountable antagonist that may act in one of two ways: by binding to the active site of receptor or by binding to an allosteric site of the receptor. If it binds to the allosteric site, it is called as allosteric antagonist. In both the cases, end-results are functionally similar. Unlike competitive antagonists, which affect the amount of agonists necessary to achieve a maximal response but do not affect the magnitude of that maximal response, non-competitive antagonists reduce the magnitude of the maximum response that can be attained by any amount of agonists. This property makes the title as “non-competitive” because their effects cannot be negated, no matter how much agonist is present. Cyclothiazide is known to be a reversible non-competitive antagonist of mGluR1 receptor.

1.1.7.3 Uncompetitive Antagonists

Uncompetitive antagonists differ from non-competitive antagonists in that, they require receptor activation by an agonist before they can bind to a separate allosteric binding site. This type of antagonism produces a kinetic profile in which the same amount of antagonist blocks higher concentrations of agonists better than lower concentrations of agonists. Memantine, used for treating Alzheimer’s disease, is an uncompetitive antagonist of the NMDA receptor.

Dose-response Curve

Dose-response relationships, or exposure-response relationship can be conveniently used to know the type of antagonism. Dose-response relationship describes the change in effect of an organism caused by differing levels of exposure (or doses) to a stress or (usually a drug) after a certain exposure time. Biologic effect is usually placed on Y-axis in terms of percentage. Drug concentration is depicted on X-axis in terms of units of dose. Dose-response curve is usually S-shaped as depicted in Fig. 1.3. The dose corres-ponding to 50% of the response is termed as EC_{50}, (effective concentration for 50% effect). In case of a competitive antagonist, the dose-response curve shows a parallel right shift with increase in value of EC_{50}. Unlike this, in case of non-competitive or uncompetitive antagonists, shift to the right is not parallel and there is only a slight change in the value of EC_{50}.



EC_{50} = Drug dose that shows 50% of maximal response.

Fig. 1.3: Effect of drug antagonists

1.1.8 Spare Receptors

Spare receptors are defined as those receptors without combining with which maximal response can be obtained. In order to understand this concept, understanding of receptor occupancy theory is essential.

Receptor Occupancy Theory

Consider dose response curves A, B and C for an agonist along with various antagonists. (Fig. 1.4) In this graph, X-axis indicates log agonist (M) indicating that log molar concentration of agonist is plotted. Y-axis indicates percentage of maximal effect. In Fig. 1.4, maximal responses, as shown in dose-response curves B and C have been obtained with incremental change in concentrations of agonists in presence of antagonists, as needed for 50% of effects. Further, the maximal response (100%) has not changed as indicated in dose response curve B and C, even in presence of antagonist which has occupied certain fraction of receptors. In other words, maximal response in case of dose-response curve A was obtained without binding to all receptors. These receptors, without binding with which maximal response was obtained, are termed as spare receptors.

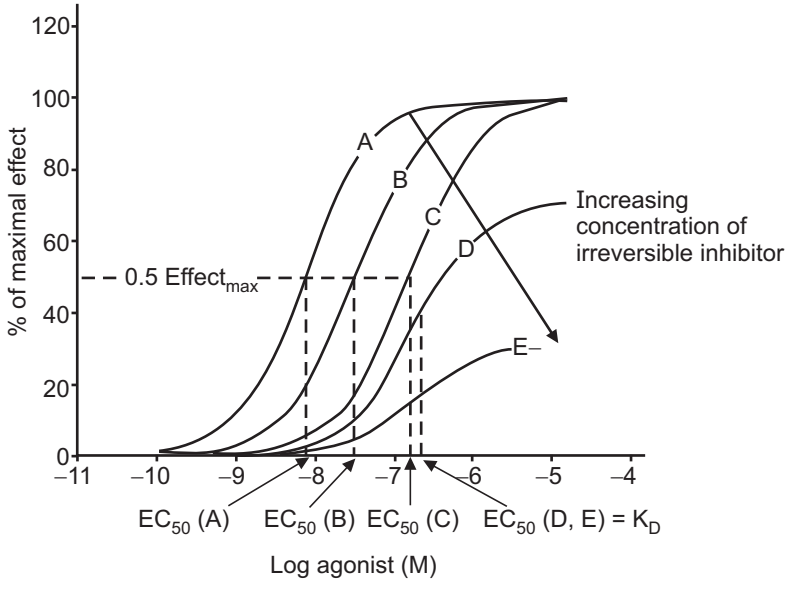


Fig. 1.4: Pharmacodynamics

1.1.9 Addiction

Addiction is a brain disorder characterised by compulsive engagement in rewarding stimuli despite adverse consequences. It is related to addictive behaviour which is both rewarding and reinforcing. Rewarding stimuli are interpreted by brain as intrinsically positive and desirable or as something to be approached. Reinforcing stimuli increase the probability of repeating behaviours paired with them. Addiction is caused by addictive drug, consumption of which compels addictive behaviour.

1.1.10 Tolerance

Drug tolerance is defined as, "the diminishing effect of drug resulting from repeated administration at a given dose". Drug tolerance is a pharmacological concept describing subjects' reduced reaction to a drug following its repeated use. Increasing its dosage may re-amplify the drug's effects, however this may accelerate tolerance, further reducing the drug's effects. Drug tolerance is indicative of drug use but is not necessarily associated with drug dependence or addiction. The process of tolerance development is reversible and can involve both physiological factors and psychological factors.

It is divided in to three types: pharmacodynamic, pharmacokinetic (metabolic) and behavioural. Pharmacodynamic tolerance begins when the cellular response to a substance is reduced with repeated use. A common cause is high concentration of a substance constantly binding with a receptor, desensitizing it through constant interaction. Usually, it occurs after sustained exposure to a drug. Pharmacokinetic tolerance occurs because of a decreased quantity of the substance reaching the site it affects, this may be caused by increase in induction of enzymes required for degradation of drug e.g. CYP450 enzymes. Alcohol is a common example. In addition to enzyme induction, several other mechanisms contribute to tolerance. Behavioural tolerance occurs with the use of some psycho-active drugs, where tolerance to a behavioural effect of a drug occurs with repeated use of the drug. Amphetamine causes behavioural tolerance.

1.1.11 Dependence

It is defined as, "an adaptive state associated with a withdrawal syndrome upon cessation of repeated exposure to a stimulus (e.g. drug intake)". Withdrawal syndrome is identified as a set of symptoms that occur upon cessation of repeated drug use.

Dependence is of two types: physical and psychological. Physical dependence involves persistent physical-somatic withdrawal symptoms (e.g. fatigue and delirium tremens). Psychological dependence involves emotional-motivational withdrawal symptoms (e.g. dysphoria and anhedonia).

1.1.12 Tachyphylaxis

Tachyphylaxis is a sub-category of drug tolerance referring to cases of sudden, short-term onset of tolerance following the administration of drug. It is a rapid and short term onset of drug tolerance. It can occur after an initial dose or after a series of small doses. Increasing the dose of the drug may be able to restore the original response. Tachyphylaxis is characterised by the rate sensitivity: the response of the system depends on the rate with which a stimulus is presented. To be specific, a high-intensity prolonged stimulus or often-repeated stimulus may bring about a diminished response also known as desensitization. Opioids, nicotine, nitroglycerine and metoclopramide are examples of some drugs which are known to cause tachyphylaxis.

1.1.13 Idiosyncrasy

Idiosyncratic drug reactions occur rarely and unpredictably amongst the population. They frequently occur with exposure to new drugs. They are listed as rare adverse drug reactions. They do not appear to be concentration dependent. A minimal amount of drug will cause an immune response but only after second administration; since development of antibodies need time and first dose is mandatory. The proposed mechanism of most idiosyncratic drug reactions is immune-mediated toxicity. The classical example is allergy caused by penicillin. A drug may cause an immune response if it binds to a larger molecule. In few cases a metabolite rather than the parent drug may bind to proteins. Thus a drug/its metabolite, injury or infection may sensitize a person and can cause idiosyncratic reactions. These reactions are studied under toxicology.

1.1.14 Allergy

Allergic reaction to a drug will not occur on the first exposure to a substance. The first exposure allows the body to create antibodies and memory lymphocyte cells for the antigen. Subsequently antibodies or lymphocytes interact with the antigen causing what we understand as allergic reactions.

Following signs and symptoms are observed with allergy:

- Hives
- Itching
- Rash
- Fever
- Facial swelling

- Shortness of breath due to the short term constriction of lung airways or long-term damage to lung tissues.
- Anaphylaxis, a life threatening drug reaction causing low blood pressure.
- Cardiac symptoms such as chest pain, shortness of breath, fatigue, chest palpitation, light headedness, syncope and eosinophilic myocarditis.

Following drugs are known to cause allergy:

- **Antibiotics:** Penicillin, Sulphonamides, Tetracyclines
- **Analgesic:** Codine, NSAIDs
- **Anti-epileptic:** Phenytoin, Carbamazepine

The list is given for illustration only. It is not an exhaustive list.

Risk Factors

Risk factors for drug allergies can be attributed to the drug itself or the characteristics of the patient. Drug-specific risk factors include dose, route of administration, duration of treatment, repetitive exposure to the drug. The patient related factors include concurrent illness, age, sex, specific genetic polymorphism and inherent predisposition to react to multiple unrelated drugs. A drug allergy is more likely with large doses and extended exposure.

Mechanisms

Drug allergies are related to drug hypersensitivity. Drug hypersensitivity reactions are the mediators of a drug allergy. There are two mechanisms for drug allergy: IgE mediated or non-IgE mediated. In IgE-mediated reactions drug allergens bind to IgE antibodies, which are attached to mast cells and basophils, resulting in IgE cross-linking, cell activation and release of performed and newly formed mediators. In case of non-IgE mediated reactions, probably other immunoglobulins are involved.

1.2 PHARMACOKINETICS

1.2.1 Membrane Transport

Membrane transport refers to the collection of mechanisms which regulate passage of solutes like ions and small molecules through biological membrane, which are lipid bilayers containing proteins embedded in them. Regulation of passage through the membrane is due to selective membrane permeability - a characteristic of biological membranes which allows them to separate substances of distinct chemical nature. Alternatively, it can be stated that biological membranes are permeable to certain substances but not to others.

The movements of most solutes through the membrane are mediated by membrane transport proteins which are specialised to varying degrees in the transport of specific molecules. There are different types of cells; hence specific transport proteins exist for each cell type during a specific physiological state. The differential expression of proteins is regulated through the differential transcription of the genes coding for these proteins. In addition, production of these proteins can be activated by cellular signalling pathways, at the biochemical level, or even by cytoplasmic vesicles.

Transport Types:

There are two types of transports in biological tissues viz Passive transport and Active transport.

1. Passive transport

It is a movement of ions and other atomic/molecular substances across cell membrane without the input of metabolic energy. The concentration gradient of the transported substances acts as a source of energy. The rate of passive transport depends on the permeability of cell membrane, which in turn, depends on the organisation and characteristics of the membrane lipids. There are four mechanisms for passive transport: diffusion, facilitated diffusion, filtration and osmosis.

(i) Diffusion: Diffusion is net movement of material from an area of high concentration to an area with lower concentration. The difference of concentration between two sides of membrane is called as concentration gradient. Diffusion continues only till the gradient is eliminated. (Fig. 1.5)

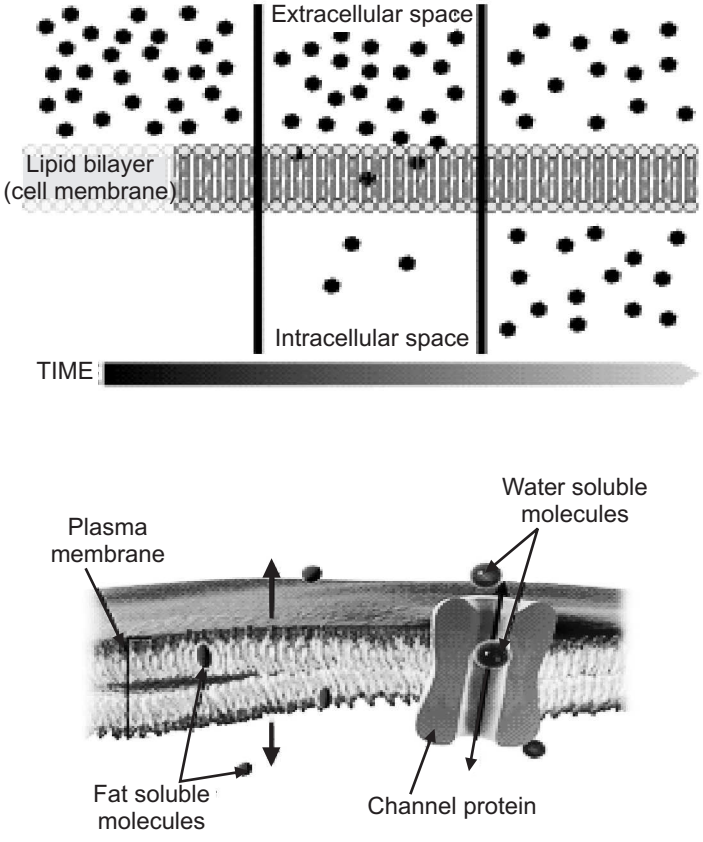


Fig. 1.5: Passive diffusion

(ii) Facilitated diffusion: Facilitated diffusion is also called as carrier-mediated osmosis. It is the movement of molecules across the cell membrane via special transport proteins embedded within the cell membrane (Fig. 1.6). It is a passive process. Carrier proteins allow

diffusion of molecules across the cell membrane by undergoing conformational alterations to allow molecules to pass across the membrane. It may be achieved as a consequence of charged gradients in addition to concentration gradients.

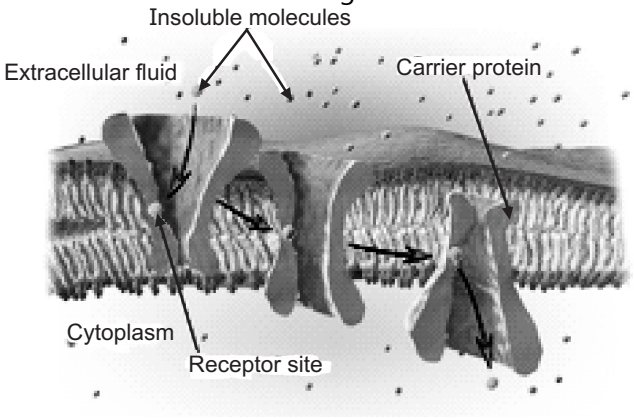


Fig. 1.6: Facilitated diffusion

(iii) Filtration: Filtration is movement of water and solute molecules across the cell membrane due to hydrostatic pressure generated by the cardiovascular system. Depending on the size of the membrane pores, only solutes of a certain size may pass through it (Fig. 1.7). An example of water along with ions like sodium, potassium passing through the membrane pores of Bowman's capsule, while retaining albumin in the blood can be cited.

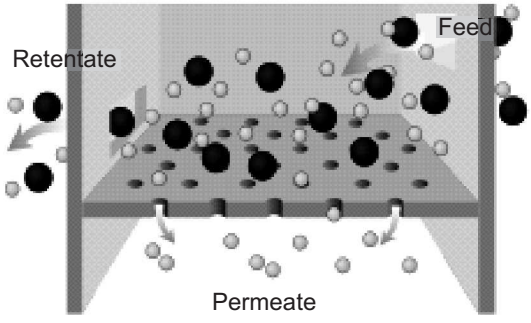


Fig. 1.7: Filtration

(iv) Osmosis: Osmosis is the movement of water molecules across a selectively permeable membrane. It can be easily explained by behaviour of red blood cells in a solution of sodium chloride. Depending on the concentration of sodium chloride, the solution can be labelled as one of the three types: isotonic, hypertonic or hypotonic. Three words indicate that the pressure exerted by sodium chloride is the same, higher or lower than that of pressure exerted by the solutes in red blood cells (RBCs). RBCs do not change their shape in isotonic solution. They shrink in hypertonic solution and swell in hypotonic solution. It is due to movement of water across cell membrane.

2. Active transport

Active transport is the movement of molecules across a cell membrane from a region of lower concentration to a region of higher concentration- in the direction against the concentration gradient. This is due to expenditure of metabolic energy. Unlike passive transport, which uses the kinetic energy and natural property of molecules moving down a

gradient, active transport uses metabolic energy to move them against a concentration gradient, polar repulsion or other resistance. Active transport is associated with accumulating high concentrations of molecules which the cell needs: e.g. sodium/ potassium/calcium ions, glucose, amino acids etc. if the process uses energy in the form of ATP, it is termed as primary active transport. Secondary active transport involves use of an electrochemical gradient.

The best example of primary active transport is of sodium-potassium pump. The pump maintains the membrane potential by moving three sodium ions out of the cell for every two potassium ions moved into the cell by hydrolysis of one ATP molecule. The pump is enzyme dependent on activity of sodium and potassium ions with ability to hydrolyse ATP. It is located on the membrane of the cell. An example of secondary active transport is that of enzyme ATP synthase. The energy derived from pumping of proton across a cell membrane is frequently used as the energy source in secondary active transport. In humans, sodium is commonly co-transported ion across the plasma membrane, whose electrochemical gradient is then used to power the active transport of a second ion or a molecule against its gradient.

1.2.2 Absorption

Absorption is the transfer of the drug from its site of administration to the bloodstream. The rate and extent of absorption depends on the route of administration, the formulation and chemical properties of the drug, and physiological factors which can impact the site of absorption. It is illustrated in Fig. 1.8. When a drug is administered intravenously, the entire dose is available in systemic circulation. Administration of a drug by any other route may result in less availability of drug due to incomplete absorption. When a tablet or capsule is swallowed, it must dissolve before its absorption. The process is called as dissolution. Once dissolution has occurred, the drug molecules pass through the membrane of the cells lining gastrointestinal tract to reach the blood stream. The drug will be absorbed by one of the mechanisms mentioned earlier. The rate and extent of absorption of a drug is termed as its bioavailability.

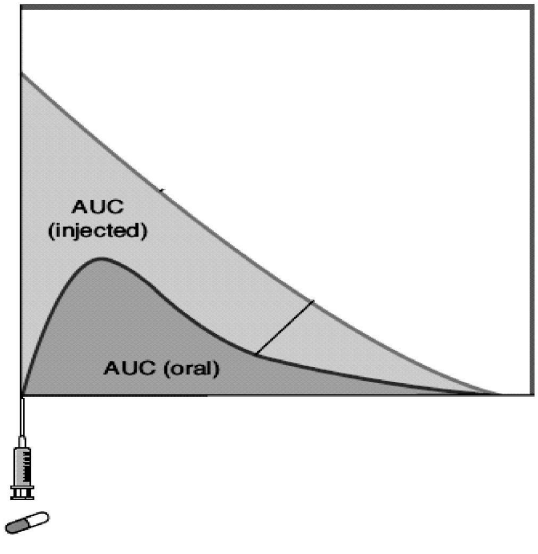


Fig. 1.8: Plasma concentration of an oral/intravenous drug

Bioavailability

When a graph of plasma concentration of a drug is plotted against time, one gets a curve as depicted in Fig. 1.8. The area under curve (AUC) of plasma concentration versus time represents the total amount of drug reaching systemic circulation. AUC will have a different shape depending on the route of administration. The AUC obtained after intravenous administration is considered to be 100%. This is termed as absolute bioavailability of a drug. Any other route (intramuscular, subcutaneous, oral, dermal etc.) will have lesser bioavailability. The ratio of AUC for any formulation/ route of administration in comparison to intravenous formulation is termed as relative bioavailability of a drug.

The acid environment or presence of food in the stomach, the solubility and other chemical properties of the drug, and the effect of initial exposure to metabolic processes in the liver may reduce the amount of drug which reaches the systemic circulation after oral administration, thereby reducing the bioavailability of the drug. If the drug is subject to metabolism by the liver, the amount of drug reaching the systemic circulation is decreased; e.g. propranolol, enalapril. As a result, substantial drug is lost due to metabolism during a single passage through the liver. This is called as first pass effect. When the drugs are highly susceptible to the first pass effect, the oral dose needed to cause a response will be significantly higher than the intravenous dose used to cause the same response.

Bioavailability becomes an important parameter in drug-product selection. While two generic products may contain the same active ingredients, they may not have the same dissolution or absorption characteristics. Hence, they cannot be considered bioequivalent. In case of extended-release products, the change in dissolution characteristics is intentional. In some cases, products are poorly manufactured and should be avoided. Generic equivalent products approved by Food and Drug Administration (FDA) must meet a standard of less than 20% variation from the comparison product. Bioequivalency data is published by the USFDA's Centre for Drug Evaluation and Research, referred to as "Orange Book", and is available on the web.

Factors affecting absorption

A number of patient-specific factors can affect absorption. Proper absorption needs adequate blood flow to the site of administration. Most absorption after oral administration occurs in small intestine because of larger surface area and greater blood flow. If small intestine is partially removed, as in case of bariatric surgery, impairment of absorption of drugs can occur.

Contact time with epithelial lining of gastrointestinal tract is an important factor in drug absorption. In patients with severe diarrhoea, drug absorption may be adversely affected because of rapid transit time in gastrointestinal tract. Contrary to this, if gastric emptying time is delayed, as in case of large fatty meal, it may delay and potentially reduce absorption. Some medications exhibit drug-food or drug-drug interactions with other compounds present in gastrointestinal tract. The interaction between tetracycline and dairy

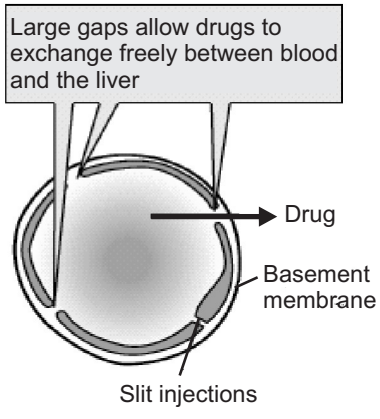
products or antacids is an example. Absence of hydrochloric acid in stomach is called as achlohydria. It is common in elderly population. Patients with achlorhydria may experience inadequate tablet dissolution and therefore poor drug absorption.

1.2.3 Distribution

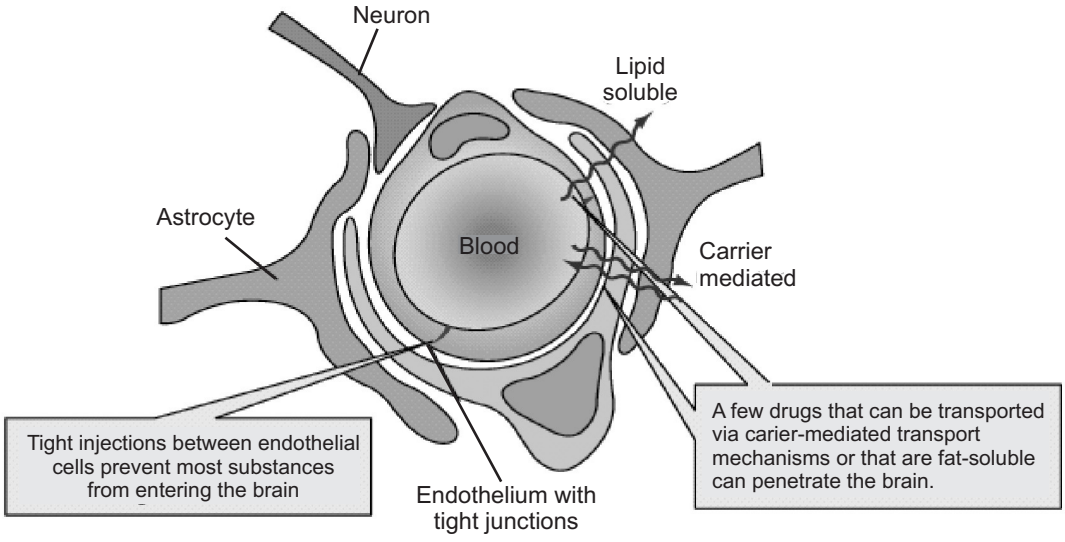
Once a drug is absorbed in systemic circulation, it can be carried throughout the body. This process is called as distribution. It is a reversible process. Some molecules may be interacting with receptors on cell membranes or inside of cells, while other molecules may move back into the blood stream. The delivery of a drug from the blood stream to the site of drug action depends on blood flow, capillary permeability, degree of binding to blood and tissue proteins, and relative lipid-solubility of the drug molecule.

Blood flow to the different organs of the body is unequal. The most vital organs like brain, liver and kidneys receive greatest supply of blood. Skeletal muscles and bone receive relatively less blood supply and adipose tissue/fat receives minimum blood supply. Penetration into central nervous system is yet another factor. The anatomical structure of capillary networking in the brain creates a barrier to passage of many drugs in the CNS. This is called as blood-brain barrier. Lipid-soluble substances enter the brain very easily. This explains why fat-soluble anaesthetic gases easily penetrate the brain to cause anaesthesia while water soluble penicillin antibiotics penetrate the CNS to a lesser degree.

If impermeable capillaries of the brain are compared with highly permeable capillary walls in liver and spleen (Fig. 1.9), the anatomical difference and the distribution characteristics can be clearly seen. Capillaries of the liver have gaps between their cells which allow large proteins to pass through the capillary basement membrane. In order to function, the liver must have access to amino acids, sugars and other large molecules from the blood stream. These molecules undergo chemical processing in the liver, and then must be moved out of hepatic cells and back to the blood stream. Unlike liver, capillaries of the brain have endothelium with tight junctions. This prevents entry of water soluble substances in the brain. Only few drugs which can be transported by carrier mediated mechanisms or are fat soluble can penetrate the brain. Thus, permeability of capillaries decide distribution of drug to the organ.



(a) Structure of endothelial cells in the liver



(b) Structure of capillaries in the brain

Fig. 1.9: Structure of capillaries

Factors affecting distribution of drugs:

Most drugs reversibly bind to plasma proteins in varying degree. Albumin is the most abundant plasma protein with an ability to bind drugs. Only free fraction of the drug is biologically active. There is an equilibrium between free and bound drug to proteins like albumin. Albumin acts as a reservoir for administered drug. Some drugs may have binding of 95-98% to albumin. With highly protein bound drugs, low albumin levels (as in case of protein calorie malnutrition or chronic illness) may lead to toxicity because of lesser binding sites. Hence, identifying patient's serum albumin level can help in deciding dose of a highly protein bound drug.

Competition for binding sites is yet another factor. If two drugs can compete for the same site on albumin and one drug is capable of displacing another drug from the site of binding, then an interesting drug interaction is observed. Known example of this is phenylbutazone displacing warfarin from protein binding sites. In this case, a patient receiving warfarin earlier will get the effects of anticoagulation by administration of phenylbutazone. The cause is displacement of warfarin due to phenylbutazone.

Other patient variables that can affect distribution include body composition, cardiac decompensation (heart failure), and age of the patient. These factors affect volume of distribution (V_d) of a drug. V_d is the hypothetical volume needed to account for all of the drug in the body based on serum concentration in a blood sample. Higher V_d indicates lower serum concentration and greater distribution of drug in the body. Lower V_d indicates higher serum concentration and limited distribution of drug in the body.

Dosing of medications in infants and children requires special consideration. It is to be noted that "children are not simply small adults". Bodies of children/infants contain a high

percentage of water and low percentage of muscle and fat. Especially in neonates, albumin may be lower. All these variations can alter V_d significantly; hence dosage for neonates/infants/children should be carefully adjusted.

1.2.4 Metabolism

While the drugs are getting distributed in different parts of body, there are chemical changes in their structures due to interaction with various enzymes or due to other chemical reactions. The process of chemical change is called as biotransformation or metabolism. Liver is major site for drug metabolism, but specific drugs may undergo metabolism in other tissues. The purpose of metabolism is to convert the drug into more water soluble compounds. There are two types of metabolic processes which drugs undergo.

In the first type of reaction, drugs are converted into more polar compounds through oxidation-reduction reactions or hydrolysis. These reactions use microsomal enzymes located in the liver, called as cytochrome P450 enzyme system. In enzyme-catalysed reactions, the rate of reaction is accelerated by presence of enzymes. Since the quantum of enzymes is limited, metabolism is considered as a saturable process. Once enzymes are saturated, blood levels of drug increase exponentially which may lead to toxicity. Examples include metabolism of alcohol or phenytoin.

The second type of metabolism involves conjugation reactions. In this type of reactions, drugs undergoing metabolism are joined with another substance like glucuronic acid, sulphuric acid, acetic acid or an amino acid. Glucuronidation reaction is the most common. As a result of conjugation reaction, the drug or its metabolite is converted to more water soluble compound which is easier for kidneys to excrete.

For some drugs initially administered compound, called as pro-drug is not biologically active. Metabolism converts the pro-drug into the active compound. Fosphenytoin is a pro-drug of phenytoin and is used for controlling seizures. Fosphenytoin is more completely and quickly absorbed when given by intra-muscular injection than phenytoin.

Factors affecting metabolism

Metabolism of drugs can vary widely between population groups. Deficiency of some enzymes may be of genetic origin and may result in poor tolerance of certain drugs. An example of ethanol metabolism can be cited. Asians and Native Americans have difficulty in metabolising alcohol which requires acetylation for its metabolism. These individuals exhibit low tolerance towards alcohol; and can suffer adverse reactions at much higher rate than average population. Age is another important variable for metabolism. In elderly population, rate of metabolism comes down. Organ function gradually declines with increasing age. Contrary to this, children require special consideration of drug dosing because of immaturity of their organ systems.

Drug interactions may occur between two drugs which are metabolised by the same enzyme systems in the liver. If two drugs are metabolised by the same enzyme system and one has higher affinity for enzyme, then levels of second drug can build up. In some cases, the drug being metabolised may induce production of more of the enzymes. Enzyme

induction sets the stage for another type of drug interaction because the increased production of metabolising enzymes may result in higher rates of removal and the need for an increased dose of the second drug. Sometimes a drug may induce its own enzymes. Then it is called as self-inducer. Self-induction is one of the reasons for addiction of drugs explaining why additional doses are required over the period of time.

1.2.5 Excretion

When a drug is distributed throughout the body and is getting metabolised, there has to be some way by which it is excreted; otherwise its concentration along with its metabolites will continue to rise with each successive dose. The complete removal of drug from the body is termed as its elimination. Elimination of the drug includes its metabolism and excretion through kidneys and to a lesser degree into bile. Excretion in urine is one of the most important mechanisms of drug removal.

Kidneys act as a filter for drug and create urine as a vehicle for removal of waste. Blood enters the kidney through renal arteries and is filtered by the glomerulus. The glomerular filtrate becomes concentrated and substances are removed as it passes through the renal tubule, finally getting converted to urine. Drug molecules in blood which are not bound to albumin also get filtered in the glomerular filtrate. When drugs have not been converted to water soluble compounds in the liver, they are likely to be reabsorbed into blood at the end of filtration process and will cycle through the body again. If they are water soluble, they will be excreted in urine.

When a medication is given repeatedly, the total amount of drug in the body will increase up to a point and then stabilise. At this point, the amount being taken by the patient is equal to the amount being removed by the liver and kidneys. This state of equilibrium is called as steady state, and drug levels remain fairly constant unless there is a dose change, or interruption in treatment, or failure of the organs of elimination. The therapeutic effects of many drugs are closely correlated to a specific range of steady state serum drug levels, which modify from drug to drug.

Factors affecting elimination or excretion

Complete elimination of a drug from the body is dependent on normal liver and kidney function. The kidney is major organ of excretion; the liver contributes to elimination through metabolism and excretion into feces via bile. When a patient has reduced renal function or other problem which increases half-life of a drug, dosage adjustment is necessary to avoid accumulation of drug in the body.

Kidney or liver failure, or conditions where blood flow to these organs is reduced selection of drug and it's does is complicated. Drugs which are dependent on excretion through the kidneys are not the best choice for the patients with renal failure. Similarly patients with liver disease will better tolerate drugs which can be cleared exclusively through the kidneys. Age is also a factor related to drug excretion. Very young and very old will have lower rates of excretion. Doses often require reduction in these patients. Drug interactions, such as when multiple drugs compete for metabolic processes, can also reduce drug removal.

1.2.6 Enzyme Induction

Enzyme induction is a process in which a molecule like drug induces i.e. initiates or enhances the expression of an enzyme. Liver is the principal site of drug metabolising activity. The enzymes concerned with drug metabolism are located in the hepatic endoplasmic reticulum. The enzymes catalysing these reactions are versatile and non-specific while the rate of activity may be under strong genetic influences. Numerous external and physiological factors may affect drug metabolising enzyme systems. The factors are categorised into four major types:

- **Patient related factors**
  Patient related factors include age, sex, pregnancy and circadian rhythm of the body.
- **Diseases and drugs-related factors**
  Disease and drugs-related factors include infections, malignancy, enzyme inducers and enzyme inhibitors.
- **Organ function and disease**
  Organ function and disease related factors include functioning of liver, kidney, gastrointestinal system, cardiovascular system and endocrine system
- **Environment/life style**
  Environmental and life style factors include occupation, exercise, diet, alcohol and tobacco.

All these factors are interrelated to genetic constitution. Fig. 1.10 depicts all these factors.

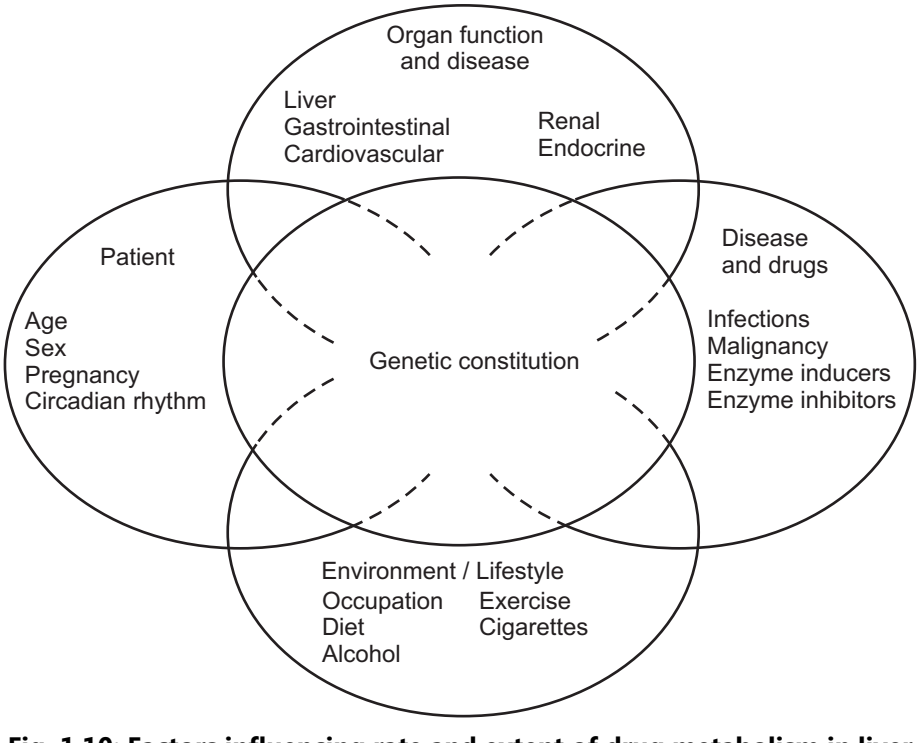


Fig. 1.10: Factors influencing rate and extent of drug metabolism in liver

The classes of enzyme inducing drugs include following categories:

- Phenobarbitone and a wide variety of structurally unrelated compounds.
- Polycyclic aromatic hydrocarbons like 3-methylcholanthrene.
- Steroids including pregnenalone derivatives.
- Ethanol

List of some enzyme inducers is presented in table 1.3.

Table 1.3: List of some enzyme inducers

Sr. No.	Name(s) of drugs/substances
1.	Barbiturates; specially primidone (phenobarbitone)
2.	Carbamazepine
3.	Cigarette smoke
4.	Dichloralphenazone
5.	Ethanol (chronic)
6.	Glutethimide
7.	Griseofulvin
8.	Marijuana smoke
9.	Meprobamate
10.	Phenetoin
11.	Rifampicin
12.	Sulfinpyrazone

There are various clinical consequences of liver drug-metabolising enzyme induction by Phenobarbital-like drugs; e.g. a drug can increase its own rate of metabolism. Due to induction of cytochrome P 450 enzyme, Phenobarbital needs higher dose for the same effect on repeated administration. This type of tolerance is called as pharmacokinetic tolerance. Clinical importance of enzyme induction can be summarised as follows:

- Reduction in some normal body constituents; e.g. adrenal steroids, sex hormones, vitamin D, bilirubin.
- Development of tolerance; e.g. alcohol, barbiturates (auto induction).
- Increased drug toxicity; e.g. paracetamol, polycyclic hydrocarbons (benzopyrine, DDT).

In addition to self induction, the metabolism of other drugs and endogenous compounds can also be increased. This is called as cross-induction. Some examples of cross-induction are mentioned in table 1.4.

Table 1.4: Some examples of cross-induction

Sr. No.	Enzyme inducer drug/substance	Drugs whose metabolism is increased
1.	Cigarette (benzopyrene)	Benzodiazepines, paracetamol, propoxyphene, theophylline
2.	Ethanol	Barbiturates, phenytoin, warfarin, tolbutamide
3.	Barbiturates (phenobarbitone)	Phenytoin, warfarin, corticosteroids, phenothiazines, doxycycline, digitoxin, quinidine, calcium channel blockers, β-blockers.
4.	Carbamazepine	Corticosteroids, doxycycline, haloperidol.
5.	Phenytoin	Digitoxin, quinidine, hydrocortisone, β-blockers, methadone, doxycycline, theophylline.
6.	Rifampicin	Oral contraceptives, corticosteroids, digitoxin, quinidine, theophylline, phenytoin, warfarin, β-blockers, calcium channel blockers, tolbutamide.
7.	Grieseofulvin	Warfarin.

1.2.7 Enzyme Inhibition

Drugs can inhibit metabolising enzyme activity. Enzyme-inhibition can either be non-specific of hepatic microsomal mixed function oxidase (MFO) enzymes or of enzymes with specific functions; e.g. xanthine oxidase, aldehyde dehydrogenase, cholinesterase, monoamino oxidase (MAO). The inhibition of hepatic MFO can either be due to hepatic dysfunction or administration of drug. Table 1.5 lists enzyme inhibitors and the drugs for which the metabolism is inhibited.

Table 1.5: Enzymes, enzyme inhibitors and interacting drugs

Sr. No.	Enzymes	Enzyme inhibitors	Drugs whose metabolism is inhibited
1.	Hepatic microsomal	Cimetidine	Chlordiazepoxide, diazepam, phenytoin, anti-depressants, theophylline, lidocaine, propranolol, quinidine, testosterone, warfarin
2.		Erythromycin	Theophylline, warfarin, cyclosporine, carbamazetine
3.		Sodium valproate	Phenytoin, phenobarbital, primidone
4.		Quinolones	Theophylline
5.		Chloramphenicol	Phenytoin, tolbutamine, warfarin
6.		Verapamil	Theophylline

contd. …

7.		Diltiazem	Carbamazepine
8.		Propoxyphene	Cyclosporine, carbamazepine
9.	Xanthine oxidase	Allopurinol	6-Mercaptopurine, azathioprine
10.	Monoamino oxidase	MAO inhibitors	Pethidine, Tricyclic anti-depressants
11.	Aldehyde dehydrogenase	Disulfiram, metronidazole	Alcohol, phenytoin, warfarin, some benzodiazepines
12.	Cholinesterase	Echophiophate	Suxamethonium, procaine, propanidid
13.	Angiotensin converting enzyme	Captopril, enalapril	Angiotensin I, bradykinin

Whenever an enzyme is inhibited, the plasma half-life, drug efficacy as well as toxicity of the drug whose metabolism is affected (drugs indicated in column (3) of table 1.3) are significantly enhanced. In case the drug undergoes hepatic first pass effect, the bioavailability and toxicity of the drug will be markedly enhanced in presence of enzyme inhibition. Enzyme inhibition may produce undesirable drug-drug interaction because of enhanced concentration of the drug of which metabolism is inhibited.

1.2.8 Kinetics of Drug Elimination

Usually two kinds of elimination kinetics are involved in drug elimination: zero-order and first order. In zero-order elimination kinetics, elimination of a constant quantity of the drug per unit time is eliminated from the organism. Thus, it is not dependent on concentration of drug in the blood; hence called as zero-order kinetics. In case of first order elimination kinetics, elimination of a constant fraction of the drug quantity present in the organism is eliminated per unit time. Thus, the elimination is dependent on concentration of the drug; hence it is called as first order kinetics.

Zero-order elimination kinetics

If a graph of drug concentration versus time is plotted, the profile during elimination phase is linear in nature.

First-order elimination kinetics

If the amount of drug A is decreasing at a rate which is proportional to concentration of A, the amount of drug A remaining in the body, then the rate of elimination of drug A can be described as:

$$\frac{dA}{dt} = -k.A$$

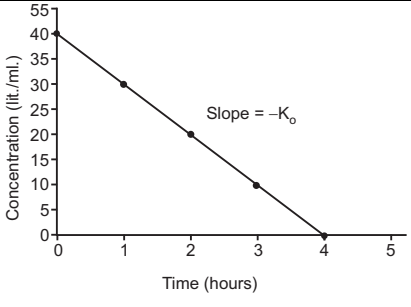
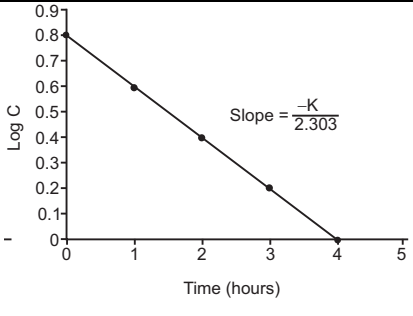
where, k = The first order rate constant.

In case of first order reaction, the reaction proceeds at a rate that is dependent on the concentration of A present in the body. It is assumed that the process of ADME follow first-order reactions and most drugs are eliminated in this manner.

Most drugs used in clinical practice at therapeutic doses show first order process; i.e. the rate of elimination is dependent on concentration of drug remaining in the body. However, there are notable exceptions; e.g. phenytoin and high-dose salicylates. For drugs which show a first order elimination process, it can be shown that, as the amount of drug administered increases, the body will eliminate the drug at higher rate and the drug may not accumulate in the body. However, if you continue to increase the amount of administered drug then all drugs will change from showing a first order process to a zero-order process, e.g. in an overdose situation.

The difference between zero-order kinetics and first-order kinetics is depicted in table 1.6.

Table 1.6: Comparison between zero-order and first-order kinetics

Sr. No.	Parameter	Zero-order kinetics	First-order kinetics
1.	Definition	The process that takes place at a constant rate independent of drug concentration.	The process is directly proportional to the drug concentration.
2.	Nature of process	Constant rate.	Linear kinetic.
3.	Rate of process	Rate cannot be increased even if drug concentration is increased.	Rate increases linearly with increase in concentration.
4.	Salient feature	Process is independent of concentration of drug.	Process is dependent on concentration of drug.
5.	General expression	$\frac{dc}{dt} = -K_0 C^o = -K_0$	$\frac{dc}{dt} = -KC^1 = -KC$
6.	Rate constant	K_0	K
7.	Units of rate constant	mg/min	min^{-1} or $hour^{-1}$ i.e. per min or per hour
8.	General equation	$C = C_0 - K_0t$; where C_0 is initial concentration and C = concentration of drug at time t.	$C = C_0 e^{-Kt}$ or $\log C = \log C_0 - \frac{Kt}{2.303}$
9.	Plot	 **Fig. 1.11 (a) Zero-order kinetics**	 **Fig. 1.11 (b) First-order kinetics**

contd. …

10.	Half-life	$t_{1/2} = \frac{0.5\ C_0}{K_0}$	$t_{1/2} = \frac{0.693}{K}$
11.	Feature of half-life	Half-life depends on initial drug concentration.	Half-life is concentration independent and a constant value.
12.	End-stage nature	At some time, the process comes to an end.	Theoretically, it never comes to an end.
13.	Examples	Intra venous infusion, controlled/sustained drug delivery systems.	Absorption, distribution, metabolism and excretion (ADME), not linked with carriers or unsaturable state if linked with carriers.

QUESTIONS

Long Answer Questions:

1. Trace history of the subject of pharmacology from 17th century.
2. What is the scope of subject of pharmacology.
3. Enlist and describe various routes of drug administration.
4. Describe advantages and disadvantages of any two routes of administration.
5. Describe the concept of agonists and antagonists.
6. Discuss different types of antagonism.
7. What is pharmacokinetics? Discuss its components.
8. Describe factors controlling metabolism of drugs.
9. With suitable examples comment on consequences of enzyme induction.
10. With suitable examples comment on consequences of enzyme inhibition.
11. Compare and contrast zero order kinetics and first order kinetics.

Small Answer Questions:

1. Define following terms:
   - Adverse reactions
   - Bioavailability
   - Bioequivalence
   - Biomarker
   - Biosimilar
   - Clinical trial
   - Counterfit medicines
   - Medical device
   - Essential medicines
   - Exciepients
   - Generic medicine
   - Good clinical practice
   - Haemovigilance

- Infusion
- Palliative care
- Pharmacovigilance
- Rational use of medicines
- Therapeutic equivalence
- Vulnerable groups
- Tolerance
- Tachyphylaxis
- Idiosyncrasy
- Allergy

2. Write short notes on:
   - Passive transport
   - Active transport
   - Bioavailability
   - Absorption of drugs
   - Distribution of drugs
   - Distribution of drugs
   - Excretion of drugs
   - Enzyme induction
   - Enzyme inhibition

■■■

Unit ... 2

GENERAL PHARMACOLOGY - II

♦ LEARNING OBJECTIVES ♦

After completing this chapter, student should be able to understand:

- *Principles of Pharmacodynamics including Mechanism of Drug Action*
- *Receptor Theories, Classification and Regulation of Receptors, Drug Receptor Interactions*
- *Various Signal Transduction Mechanisms*
- *Dose Response Curve, Therapeutic Index, Combination of Drugs*
- *Adverse Drug Reactions*
- *Drug Interactions*
- *Drug Discovery and Clinical Evaluation of New Drugs*

- General pharmacology consists of four main components: Pharmacodynamics, Adverse drug reactions, Drug interactions and Drug discovery. They are discussed below.

2.1 PHARMACODYNAMICS

- It is defined as, "the study of the actions and effects of drugs at all levels of organisation of living material and of the handling of the drugs by the organism". It includes following components:
  - The biological effects produced by drugs.
  - The site(s) at which and mechanism(s) by which the biologic effects are produced.
  - The factors which influence safety and effectiveness of drugs.
  - Principles and mechanism of drug action.
- In simpler words, pharmacodynamics involves what drug does to the body and how does it do it.

2.1.1 Principles and Mechanisms of Drug Action

Principles

Drugs do not create any new functions to any physiological system but can only increase, decrease or replace existing functions by following one of the following principles:

- **Stimulation**
  There is increase in level of physiological activity of specialised cells or physiological system; e.g. Pilocarpine may stimulate salivary secretion and induce contraction of pupil; adrenaline may stimulate heart and induce glycogenolysis.
- **Depression**
  There is a decrease in the level of activity of specialised cells or physiological systems; e.g. general anaesthetics depress CNS; quinidine depresses the heart.

- **Replacement**

  There is replacement of deficient substances, either endogenous (insulin in diabetes mellitus, thyroxine in myxoedema) or exogenous (vitamin B_{12} in pernicious anaemia, iron in microcytic anaemias, vitamin C in beriberi.)

- **Chemotherapy**

  It involves selective targeting of invading microorganisms with minimal effect on the host cells; e.g. use of Rifampicin/Isoniazid in tuberculosis, use of quinine in malaria.

Mechanism of Drug Action

Following mechanisms operate in the manifestations of drug action:

- **Physical action**

  Some drugs act on the basis of a given physical property, e.g. adsorbent action by charcoal, kaolin; osmotic activity by osmotic purgatives and diuretics; bulk mass given by bulk laxatives like psyllium husk; radioopacity given by diagnostic contrast media.

- **Chemical action**

  Some drugs act by participating in a specific chemical reaction, e.g. gastric antacids neutralise gastric activity: aluminium hydroxide/magnesium hydroxide; chelating agents form complexes with metals: penicillamine with copper; dimercaprol with mercury; desferrioxamine with iron; acidifying agents like ammonium chloride; alkalinising agents like sodium bicarbonate and antioxidants like vitamin C, sylimarin, curcumin.

- **Action through enzymes**

  Enzymes can be important targets of drug action since many body functions are mediated through activity of certain enzymes. Enzyme induction and inhibition has been discussed under section 1.2.6 and 1.2.7 respectively. Enzyme stimulation also is a mechanism of drug action; e.g. adrenaline stimulates adrenaline cyclase while pyridoxine stimulates dopa decarboxylase.

- **Action through ion channels**

  A number of drugs influence transmembrane ion channels like sodium, potassium, calcium and chloride. They may open up or close such channels. The net effect depends on how specific channels are affected. Sodium or calcium channel blockers alter generation of action potentials. Potassium channel blockers or openers alter membrane repolarisation. Chloride channel openers induce hyperpolarisation. Irreversible blocker of sodium channel like tetrodotoxin is one of the most dangerous poison.

- **Action through receptors**

  Receptors for various neurotransmitters like acetyl choline, nor-adrenaline, adrenaline, serotonin (5-HT), dopamine etc. are discussed separately.

- **Action by replacement**

  Drugs can be used to replace deficient endogenous or exogenous factors e.g. treatment of anaemia. Replacement of deficient genes in the form of gene therapy has been used successfully in some genetic disorders. Some common disorders requiring gene therapy are listed below in table 2.1.

Table 2.1: Some common disorders requiring gene therapy

Sr. No.	Type of disorder	Names of diseases
1.	Immunodeficiency	Adenosine deaminase deficiency, X-linked combined immune deficiency, chronic granulomatous disease.
2.	Hepatic	Familial hypercholesterolemia, Haemophilia A.
3.	Hematologic	Sickle cell anaemia, Thalassemia.
4.	Lung	Cystic fibrosis, α-antitrypsin deficiency.
5.	Skeletal muscle	Duchenne muscular dystrophy, limb girdle muscular dystrophy.

- **Chemotherapy**

  Drugs can be used in antimicrobial and cancer chemotherapy by selective targeting of invading microorganisms or cancer cells, with minimal action on host cells.

2.1.2 Receptor Theories

There are three major theories for drug-receptor interaction. They are as follows:

(i) Occupation theory

Occupation theory advocates that effect of a drug is directly proportional to the number of receptors which are occupied. Further, it is argued that a drug effect caeses as a drug-receptor complex dissociates. The theory introduces towards: affinity and efficacy to indicate following meaning.

Affinity is the ability of a drug to combine with receptor to create a drug-receptor complex.

Efficacy is the ability of a drug-receptor complex to initiate a response.

(ii) Rate theory

In contrast to occupation theory, rate theory proposes that the activation of receptors is directly proportional to the number of encounters of a drug with its receptors per unit time. Pharmacological activity is directly proportional to the rates of dissociation and association and not on the number of receptors occupied. Thus, it is the rate at which drug-receptor complex is formed/dissociated which decides the quantum of response. In light of this theory; agonist, partial-agonist and antagonist can be identified as indicated below:

Agonist is a drug with fast association and fast dissociation. Partial agonist is a drug with an intermediate association and an intermediate dissociation. Antagonist is a drug with fast association and slow dissociation.

(iii) Induced-fit theory

According to induced-fit theory, as a drug approaches to a receptor, the receptor alters the conformation of its binding site to produce drug-receptor complex.

2.1.3 Classification of Receptors

Receptors are glycoproteins located in cell membranes which specifically recognise and bind to ligands/drugs. Drugs are smaller molecules which are capable of ligating themselves to the receptor protein. This binding initiates a conformational change in the receptor protein leading to a series of biochemical reactions inside the cell; it is termed as signal

transduction, often involving secondary messengers. Activity of secondary messengers is eventually translated into a biological response like muscle contraction, hormone secretion etc. Although drugs are of exogenous origin, receptors in human tissues have evolved to bind endogenous ligands like neurotransmitters, hormones and growth factors. Formation of drug-receptor complex is usually reversible and the proportion of receptors occupied is directly related to the concentration of the drug. Reversibility enables biological responses to be modulated and means that similar ligands may compete for access to the receptor. The term receptor is usually restricted to describe proteins whose only function is to bind a ligand, but it is sometimes used more widely to include other kinds of drug targets such as voltage sensitive ion channels, enzymes and transporter proteins.

There are five major types of receptors:

- G Protein-coupled receptors
- Ion-channel receptors
- Tyrosine kinase-linked receptors
- Nuclear hormone receptors
- Receptors with intrinsic enzymatic activity

2.1.4 Regulation of Receptors

Cells can increase (up regulate) or decrease (down regulate) the number of receptors to a given hormone or neurotransmitter to alter their sensitivity to different molecules. This is a locally acting feedback mechanism.

All living cells have the ability to receive the process signals which originate outside their membranes, which they do by means of receptors, usually found on a cell's surface embedded in the cell membrane. When such signals bind to a receptor, they effectively direct the cell to do an activity, such as dividing, dying or allowing substances to be created, or to enter or exit the cell. A cell's ability to respond to a chemical message depends on the presence of receptors tuned to that message. The more receptors a cell has that are tuned to the message, the more the cell will respond to it. Receptors are created, or expressed by the DNA of the cell, and they can be increased or up regulated when the signal is weak, or decreased/down regulated, when it is strong.

(i) Up Regulation

Up regulation involves increase in the number of receptors due to external stimulation. An example of up regulation is the response of liver cells exposed to molecules like dioxin. In this situation, the cells increase their production of cytochrome P 450 enzyme, which in turn increases their degradation of these molecules. Up regulation results in super-sensitized cells especially after repeated exposure to an antagonist drug or prolonged absence of the agonist.

(ii) Down Regulation

Down regulation involves decrease in the quantity of cellular component, such as RNA or protein, in response to an external stimulus. It happens when receptors have been chronically exposed to an excessive amount of neurotransmitters, whether endogenous or in the form of drugs. This results in ligand-induced desensitization or internalisation of that receptor. It is usually exhibited by various hormonal receptors. An example of insulin receptor down regulation can be cited here.

Elevated levels of insulin in the blood, trigger down regulation of the associated receptors. When insulin binds to its receptors on the surface of the cell, the hormone-receptor complex undergoes endocytosis and is subsequently attacked by intracellular lysosomal enzymes. Internalisation of the insulin molecule provides a pathway for the degradation of the hormone as well as for regulation of the number of sites which are available for binding on the cell surface. At high plasma concentrations, the number of surface receptors for insulin is gradually reduced by the accelerated rate of receptor internalisation and degradation brought about by increased hormonal binding. The rate of synthesis of new receptors within the endoplasmic reticulum and their insertion in the plasma membrane do not keep pace with their rate of destruction. Over the period of time, this self-induced loss of target cell receptors for insulin reduces the target cell's sensitivity to the elevated hormone concentration.

Due to elevated levels of blood glucose in an overweight individual, the β-cells in the pancreas must release more insulin to meet the demand, and return the blood to homeostatic levels. The near-constant increase in blood insulin levels results from an effort to match the increase in blood glucose, which will cause receptor sites on the liver cells to down regulate and decrease the number of receptors for insulin, increasing the subject's resistance by decreasing sensitivity to the hormone. There is also a hepatic decrease in sensitivity to insulin. This can be seen in continuing gluconeogenesis in the liver even when blood glucose levels are elevated. This is responsible for insulin resistance. Thus, insulin receptor down regulation helps in explaining Pathophysiology of diabetes.

Some receptor agonists may cause down regulation of their respective receptors, while most receptor antagonists temporarily up regulate their respective receptors. The disequilibrium caused by these changes often causes withdrawal when the long-term use of a drug is discontinued. However, use of certain receptor antagonists may damage receptors faster than they up regulate. Down regulation of receptors happens when receptors have been chronically exposed to an excessive amount of neurotransmitters. This results in ligand-induced desensitization. It is usually exhibited by various hormone receptors. Up regulation of receptors results in super-sensitized cells especially after repeated exposure to an antagonist or prolonged absence of agonist. Receptors are created, or expressed, by the DNA of the cell and they can be increased or up regulated, when the signal is weak or decreased or down regulated when the signal is strong.

2.1.5 Drug-Receptor Interaction

The idea that drug molecules interact at specific sites in the body is a relatively old concept. However, proof of the receptor concept lag behind theory. In 1965, Propranolol was the first β-adrenergic antagonist which entered into clinical practice to completely convince the scientific community that receptors truly exist.

The basic concept of drug-receptor interactions can be described by the "lock and key" model in which a receptor structure (the lock) has a region with a particular shaped pocket at which an appropriately shaped molecule (the key) can interact. See Fig. 2.1. The drug which interacts at the receptor binding site is known as ligand. In other words every drug is a ligand. It is to be appreciated that, receptors have been evolved the ages to provide

particular functions within the body; it is coincidence that, the ligand/drug interacts with the receptor. The purpose of existence of receptors is to interact with some normal endogenous component or common environmental material. Thus, drug molecules which interact at receptors either mimic or inhibit normal body compounds. Receptors themselves are normally categorised as protein structures, either a single protein or a complex comprised of multiple protein sub-units. The binding sites on the receptor complex where the drug interacts may only be a small portion of the molecule. The interaction of a drug molecule with its receptor can be represented in the manner as shown in Fig. 2.2, where D is the drug concentration, and R is the free receptor concentration, and DR is the concentration of receptor molecules occupied by drug molecules. The interaction of the drug at its binding site on the receptor complex is governed by two important concepts: affinity and intrinsic activity.

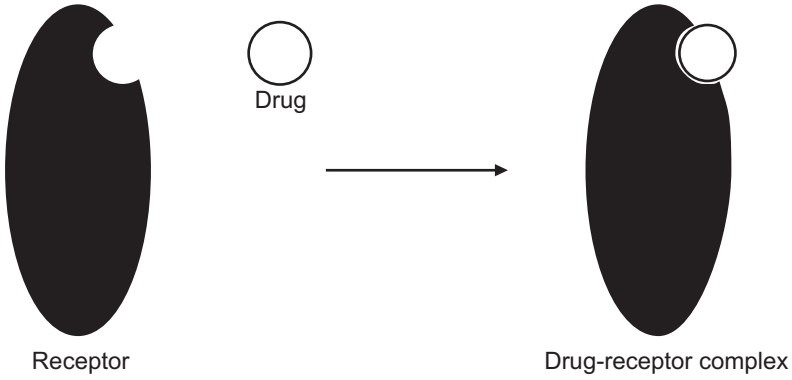


Fig. 2.1: Lock-key drug receptor interaction

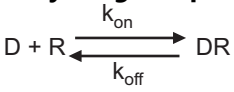


Fig. 2.2: Rate of binding and release

Affinity describes as how well a particular compound is drawn into and held at the binding site. Intrinsic activity is used to describe the effect which the drug has, when it interacts with the receptor site. A drug may have good affinity, but if it has no intrinsic activity, it will elicit no response even after binding to the receptor. On the other hand, a drug that has good intrinsic activity will elicit a strong response at the receptor zone if it has good affinity. Alternatively, if the affinity of a compound for the receptor site is low, even a high level of intrinsic activity will not elicit much of a response.

Let us have a look at equation mentioned in Fig. 2.2. At equilibrium, the dissociation constant (K_D) of a drug-receptor complex is equal to k_{off}/k_{on}. The equilibrium affinity constant (K_A) is the reciprocal of the equilibrium dissociation constant ($1/K_D$). Therefore, the smaller the equilibrium dissociation constant is, the greater the affinity of the drug for the receptor. This is useful while examining how well different drugs bind to a specific receptor complex. To understand how individual molecules, such as drug molecules move around receptor zone it is important to remember that, drug molecules are mixed with naturally available molecules around the cell moving in a random manner driven by Brownian motion. The interaction of a molecule with its receptor is primarily a matter of chance. The possibility that a particular type of compound will interact with a given receptor is based on the

number of molecules (concentration) located near the receptor site. The greater the concentration, the more likely is that, the random motion of a particular molecule will bring it close to a receptor site to interact. If a molecule is able to interact with the receptor site, it is said to have affinity for that site. The stronger it interacts, the greater is its affinity for that receptor site.

The concept of interaction at the receptor site is based mainly on drug's shape and chemical makeup. The receptor site may have particular chemical functional groups which interact at specific places. Most drugs may bind very briefly with the receptor site and are knocked out of the site by collisions with other molecules which are moving around in the surrounding area. Therefore, a drug may interact with the receptor zone very briefly. However, if the concentration of the drug molecules in the surrounding area is high, the likelihood of continued receptor-drug interaction increases. This idea is critical in understanding drug action. The greater the drug concentration at receptor zone, the more likely it is that a drug molecule will be occupying the receptor site at any given time. As the drug concentration goes down, the fraction of time the receptor is occupied also decreases.

The response generated from a receptor interaction can be plotted against the dose of a drug to produce the classic dose-response curve (DRC) which is so commonly known in pharmacology. (Fig. 2.3). Details of DRC are discussed under sub-section 2.1.12.

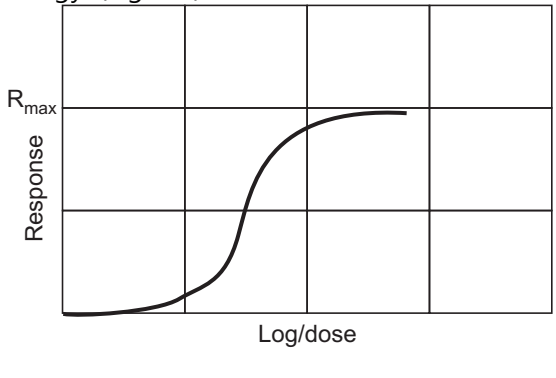


Fig. 2.3: Log dose – Response curve

2.1.6 Signal Transduction Mechanisms

Signal transduction is the process in which a chemical or physical signal is transmitted through a cell as a series of molecular events, most commonly protein phosphorylation catalysed by protein kinases, which ultimately results in a cellular response. Proteins responsible for detecting stimuli are called as receptors or sensors. The changes initiated by drug-binding/signal sensing in a receptor give rise to a signalling cascade, which is a chain of biochemical events along a signalling pathway. At molecular level responses include changes in transcription or translation in genes and post translational and conformational changes in proteins, as well as changes in their location. In multicellular organisms, signal transduction pathways have evolved to regulate cell communication in a wide variety of ways.

Each component of a signalling pathway is classified according to the role it plays with respect to initial stimulus. Ligands/drugs are called as first messengers, while receptors are signal transducers, which then activate primary effectors. Such effects are often linked to second messengers which can activate secondary effectors and so on. Depending on the efficiency of the nodes, a signal can be amplified, so that, one signalling molecule can

generate a response involving hundreds to millions of molecules. The transduction of biological signals is characterised by delay, noise, signal feedback, freed forward and interference, which can range from negligible to pathological state. With the advent of computational biology, the analysis of signalling pathways and networks has become an essential tool to understand cellular functions and disease, including signalling rewiring mechanisms underlined responses to acquired drug resistance. (Fig. 2.4).

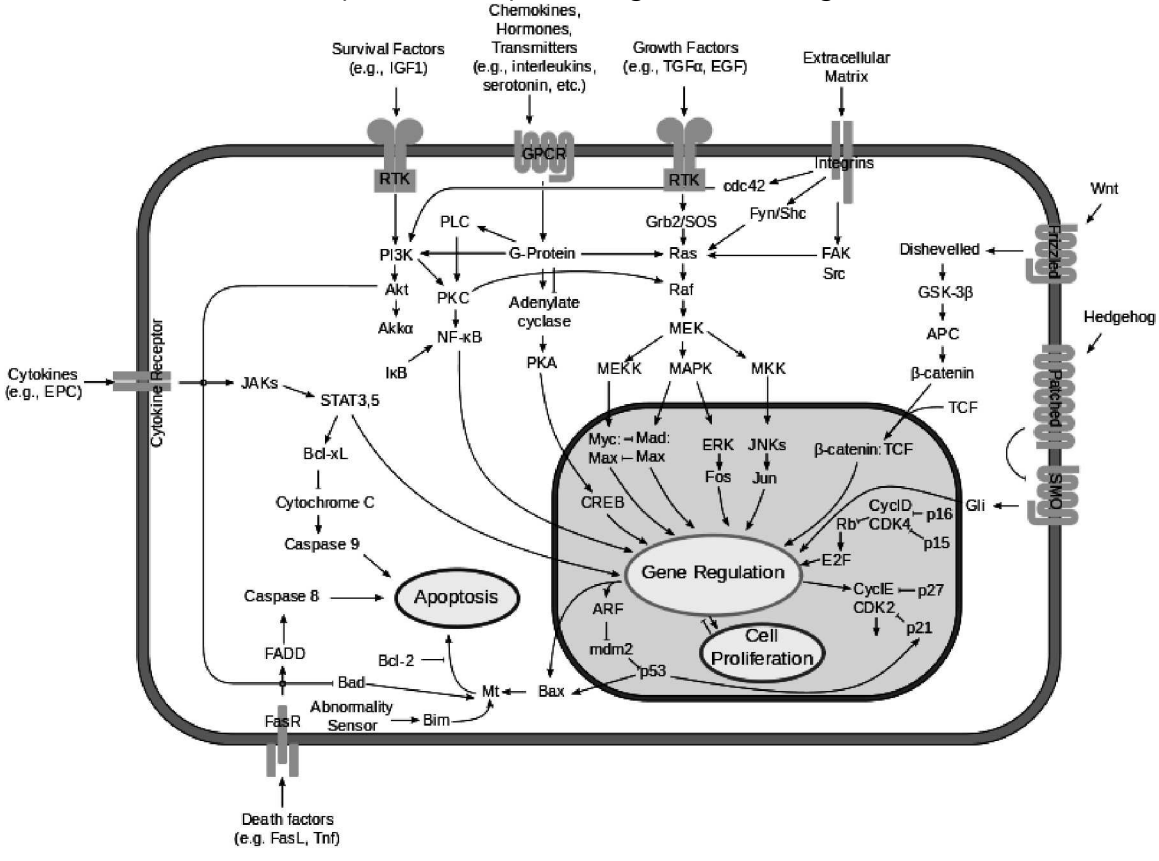


Fig. 2.4: Signal transduction pathways

Receptors related to signal transduction pathways can be divided into two major classes: intracellular and extracellular receptors.

Extracellular Receptors

Extracellular receptors are integral transmembrane proteins and make up most of the receptors. They are further subdivided into following subtypes:

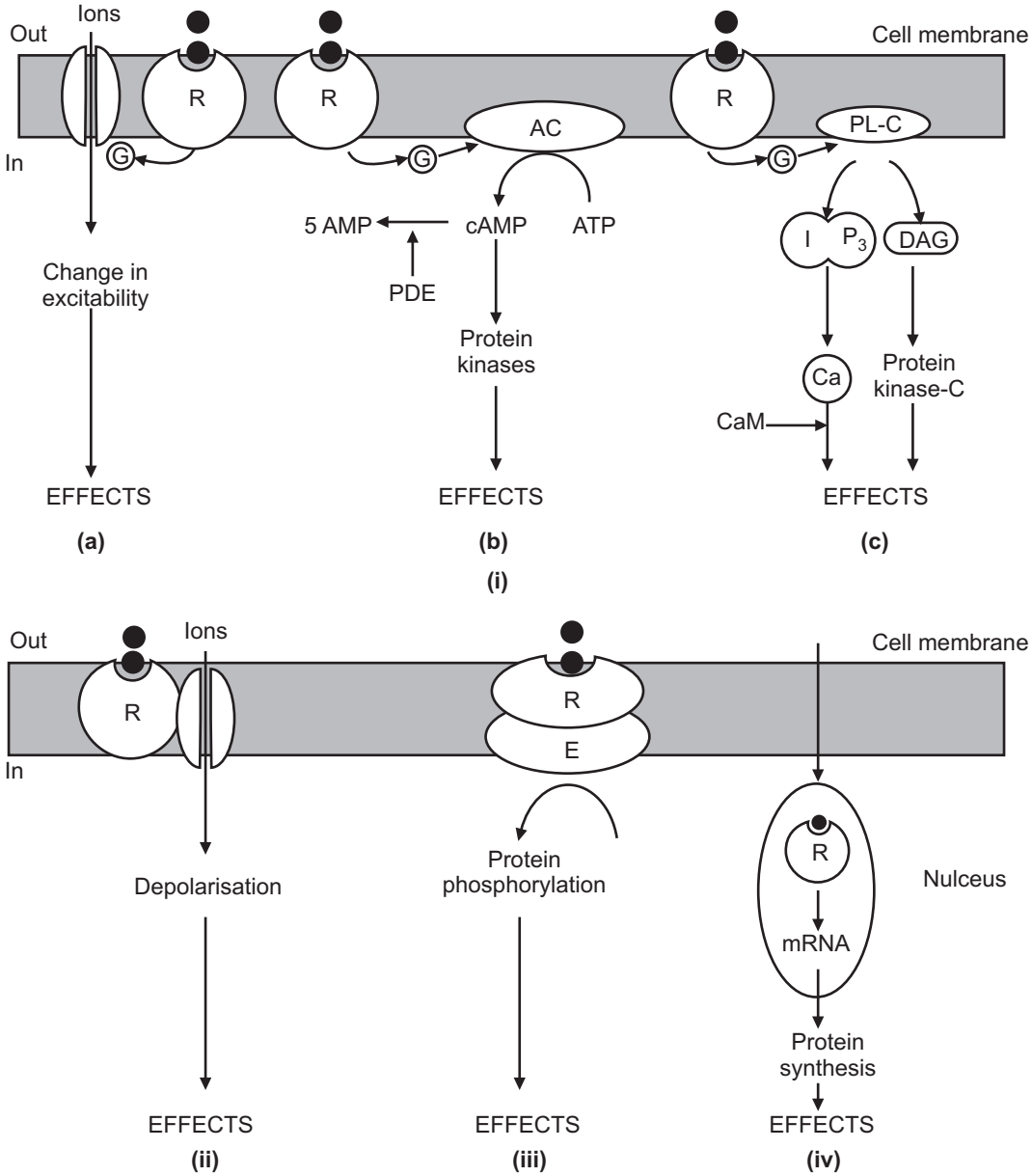
- G Protein-coupled receptors
- Tyrosine, Ser/Thr and Histidine-specific protein kinases
- Integrins
- Toll like receptors
- Ligand-gated ion channels
- Intracellular receptors

Intracellular receptors, such as nuclear receptors and cytoplasmic receptors are soluble proteins localised within their respective areas.

Secondary messengers include calcium, lipid messengers, nitric oxide and redox signalling.

Some of the receptors are discussed in detail in subsequent sections.

2.1.7 G-protein Coupled Receptors



(i) G-protein (G)-coupled receptors (R) – (a) Regulation of ion channels. (b) Adenylyl cyclase (AC)-cAMP system. PDE: phosphodiesterases. (c) Phospholipase-C (PL-C) Ca^{2+}/Phosphoinositide system. IP_3 Inositotriphosphate; DAG: Diacylgycerol; CaM: Calmodulin, (ii) Ligand-gated channel, (iii) Tyrosine kinase-linked receptors, (iv) Receptors that regulate gene expression

Fig. 2.5: Types of transmembrane signaling mechanisms

G-protein coupled receptors (GPCRs) represent the largest family of membrane proteins in the human genome. It is one of the richest sources of targets for new drugs for the pharmaceutical industry. There are seven transmembrane proteins in GPCRs; hence another common word for GPCRs is 7TM receptors.

Many extracellular ligands act by increasing the concentration of intracellular second messengers, e.g. cAMP, Ca^{++} or phosphoionositides. Receptor occupancy activates G-protein which changes the activity of effector element (enzyme or ion channel). Finally there is change in the concentration of second messenger.

Various receptors like muscarinic cholinergic, adrenergic, histamine H_2, serotonin (5HT), opiate and many peptide hormones (excluding insulin) belong to this family. Receptor occupancy by an appropriate ligand leads to activation of G-protein which in turn acts on target enzyme like adenyl cyclase/phospholipase C or an ion channel (Fig. 2.5).

G-proteins

Several varieties of G-proteins have been identified. The most common one are Gs and Gi. Gs and Gi stimulate or inhibit the enzyme adenyl cyclase respectively, thus producing opposite effects. Activation of adenyl cyclase increases concentration of cAMP while inhibition of the enzyme causes decrease in cAMP. β_1-adrenergic amines, histamine H_2 agonists, 5-HT_1 agonists and polypeptide hormones stimulate Gs protein. On the contrary, β_2-agonists, muscarinic M_2 and δ-opioid receptor agonists act on Gi.

It is known that, a ligand-receptor interaction lasts only for milliseconds. Once a G-protein is activated, it remains so for about 10 seconds, during which the original signal is highly amplified. Thus, in G-protein-receptor coupled system, occupancy of only a fraction of receptor population is enough to produce maximal tissue response.

Physiological Roles

Following physiological roles have been identified for GPCRs:

- The visual sense: The opsins are used in photoisomerisation reaction to translate electro-magentic radiation into cellular signals; e.g. rhodopsin uses conversion of 11-cis-retinal to all-trans-retinal for this purpose.
- The gustatory sense (taste): GPCRs in taste cells mediate release of gustducin in response to bitter - and sweet-tasting substances.
- The sense of smell: Receptors of the olfactory epithelium bind odorants (olfactory receptants) and pheromones (vomeronasal receptors).
- Behavioural and mood regulation: Receptors in the mammalian brain bind several neurotransmitters like serotonin, dopamine, GABA and glutamate.
- Regulation of immune system activity and inflammation: Chemokine receptors bind ligands which mediate inter-cellular communication between cells of the immune system; receptors such as histamine receptors bind inflammatory mediators and engage target cell types in the inflammatory response. GPCRs are also involved in immune modulation and directly involved in suppression of TLR-induced immune response from T-cells.

- Autonomic nervous system transmission: Both sympathetic and parasympathetic nervous systems are regulated by GPCR pathways, responsible for control of many automatic functions in the body like blood pressure, heart rate and digestive processes.
- A cell-density sensing: A novel GPCR role exists in regulating cell-density sensing.
- Homeostasis modulation: Water balance is controlled through GPCR sensing.
- GPCR system is also involved in growth and metastasis of some types of tumours.

Classification of GPCRs

GPCRs can be grouped into six classes based on sequence homology and functional similarity:

- Class A (or 1) (Rhodposin-like)
- Class B (or 2) (Secretin family)
- Class C (or 3) (Metabotropic glutamate/pheromone)
- Class D (or 4) (Fungal mating pheromone receptors)
- Class E (or 5) (Cyclic AMP receptors)
- Class F (or 6) (Frizzled/Smoothened)

GPCR Structure

GPCRs are integral membrane proteins possessing seven membrane-spanning domains or transmembrane helices. The extra-cellular parts of the receptor can be glycosylated. Some seven-transmembrane helix proteins (channel rhodopsin) that resemble GPCRs may contain ion channels, with their protein. In 2007, the first structure of human GPCR was resolved. Human β_2-adrenergic receptor GPCR structure is similar to bovine rhodopsin in terms of relative orientation of the seven-transmembrane helices. Structure-function relationship of GPCRs has been worked out. In addition, mechanism of action at molecular level is understood.

Second Messengers

There are four G-protein-coupled effector systems:

(i) Adenyl cyclase-cAMP system

The system has a wide variety of receptor population and produce diverse effects. The effects include ionotropic and chronotropic effects on heart, relaxation of smooth muscles, glycogenolysis, lipolysis. In addition, effects related to hormones like vasopressin, parathyroid hormone, ACTH, FSH, LH and TRH are mediated through the system. cAMP exerts most of these effects by stimulating cAMP – dependent protein kinases. The intracellular effects of cAMP are terminated by degradation of cAMP to 5-AMP by the enzyme phosphodiesterases (PDE). Methylxanthines like caffeine inhibit PDE and thus prolong the action of second messenger cAMP.

(ii) Phospholipase C-Ca^{++}/phosphoionositide system

Some of the agonists which trigger this pathway are Acetyl choline (ACh M_1), Catecholamines (α_1), 5-HT_2, TRH, Vasopressin (V_1) and Angiotensin. This system is more complex than the cAMP pathway due to presence of two second messengers (inositotriphosphate, IP_3 and diacylglycerol, DAG), and multiplicity of protein kinases.

(iii) cGMP system

cGMP, as a second messenger, has a signalling role only in few cell types. Receptor-linked-G-protein controls the enzyme guanylyl cyclase in a way similar to that of adenylyl cyclase. Activation of membrane-bound guanylyl cyclase leads to generation of cytosolic second messenger, cGMP which acts by stimulating a cGMP-dependent protein kinase. Increased cGMP concentration leads to relaxation of vascular smooth muscles. Ligands involved in this case are Acetyl choline, histamine, a peptide hormone-atrial natricuretic factor (ANF) and vascular endothelial nitric oxide. The system has also been detected in intestines.

(iv) Regulation of ion channels

G-protein coupled receptors can control some ion channels by mechanisms that do not seem to involve any second messenger. In this case, G-protein interacts directly with the channel; ACh M_1 receptors enhance permeability of potassium ions in cardiac muscle, and opiate analgesics open potassium channels reducing neuronal excitability.

2.1.8 Ion-channel Receptors

Ion channels are pore-forming membrane proteins which allow ions to pass through the channel pore. Their functions include establishing a resting membrane potential, shaping action potentials and other electrical signals by getting the flow of ions across the cell membrane, controlling the flow of ions across secretory and epithelial cells, and regulating cell volume. Ion channels are present in the membranes of all excitable cells. Ion channels are one of the two classes of ionophoric proteins, along with ion transporters including the sodium-potassium pump, sodium-calcium exchanger, and sodium-glucose transport proteins.

There are two distinctive features of ion channels which differentiate them from other types of transporter proteins:

- The rate of ion transported through the channel is very high; often 10^6 ions per second or higher.
- Ions pass through the channel down their electrochemical gradient, which is a function of ion concentration and membrane potential without the input of metabolic energy.

Ion channels are located within the membrane of all excitable cells and of many intracellular organelles. They are narrow, water-filled tunnels that only allow certain size and/or charge to pass through. Thus, they allow selective permeability. Some channels may be permeable to the passage of more than one type of ion, typically sharing a common charge: positive or negative. In many ion channels, passage through the pore is governed by a gate, which may be opened or closed in response to chemical or electrical signals, temperature, or mechanical force. Ion channels are integral membrane proteins, typically formed as assemblies of several individual proteins.

Biological Role

They are the important components of nervous system. Many toxins related to nervous system like venoms of spiders, scorpions, snakes, fish, bees, sea snails and others work by modulating ion channel conductance and/or kinetics. In addition, they are key components involving rapid changes in cells like cardiac, skeletal, smooth muscle contraction, epithelial transport of nutrients and ions, T-cell activation and pancreatic β-cell insulin release. Ion channels are also targets for new drugs.

Classification

Ion channels are classified on following parameters:

1. Gating

The classification based on what opens and closes the channels. There are three sub-types in this category:

(i) Voltage-gated: Voltage-gated ion channels open and close in response to membrane potential. Some of the examples are as follows:
- Voltage-gated sodium channels
- Voltage-gated calcium channels
- Voltage-gated potassium channels
- Transient receptor potential channels
- Hyperpolarisation- activated cyclic nucleotide-gated channels
- Voltage-gated proton channels

(ii) Ligand gated: They are also known as ionotropic receptors. Some of the examples are as follows:
- Cation-permeable nicotinic Acetyl choline receptor
- Glutamate-gated receptors
- Acid-sensing ion channels (ASICs)
- ATP-gated P2X receptors
- Anion-permeable GABA-gated $GABA_A$ receptor

(iii) Other gating: In this case, gating includes activation and inactivation by second messengers from inside of the cell membrane rather than outside the cell, as in the case of ligands. Some of the examples are as follows:
- Some potassium channels like inward-rectifier, calcium activated, two-pore-domain
- Channelrhodopsin opened by photons
- Mechanosensitive ion channels opened by stretch/pressure/shear/displacement
- Cyclic nucleotide-gated channels, activated by cAMP/cGMP
- Temperature related channels, opened by hot or cold temperature

- **Type of ions:**

These channels are opened by specific ions as indicated below:
- Potassium channels
- Sodium channels
- Calcium channels
- Proton channels
- Non-selective cation channels for sodium/potassium/calcium

- **Cellular organisation**

  Ion channels are classified based on their sub-cellular localisation. The plasma membrane accounts for about 2% of the total membrane of the cell, while intracellular organelles contain 98% of cell's membrane. The major intracellular compartments are endoplasmic reticulum, Golgi apparatus and mitochondria. On the basis of localisation, ion channels are classified as follows:
  - Plasma membrane channels
  - Intracellular channels: They are further sub-classified as endoplasmic reticulum channels and mitochondrial channels
- **Other:** The classification is based on number of pores and transient potentials. Most of the ion channels are single pore; however there are few two-pore channels. Transient receptor potential channels are also termed as TRP channels.

2. Structure

Channels differ with respect to the ion they let pass (sodium/potassium/chloride), the ways in which they may be regulated, the number of sub-units they are composed of and other aspects of the structure. An example of voltage-gated channels which underlie nerve impulse can be cited here. It consists of four sub-units with six transmembrane helices each. On activation, these helices move about and open the pore. Two of these six helices are separated by a loop that lines the pore and is the primary determinant of ion selectivity and conductance in this channel class. Pore can determine the selectivity of the channel. Gate can be formed either inside or outside the pore region. (Fig. 2.6).

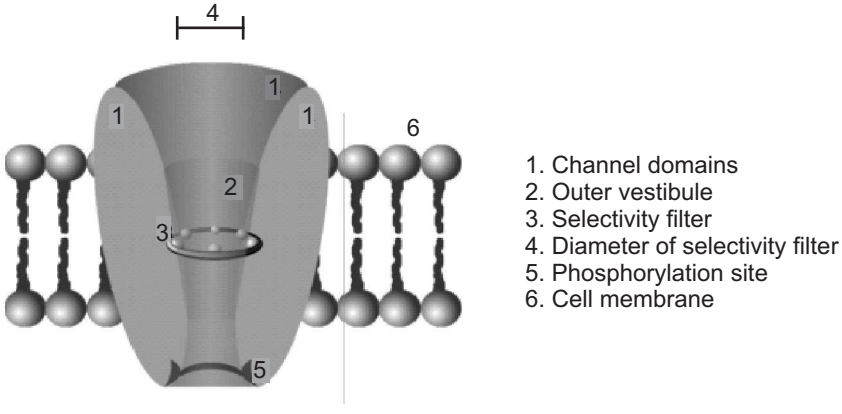


Fig. 2.6: Ion-channel diagram

Ion Channel Blockers

A variety of inorganic and organic molecules can modulate ion channel activity and conductance. Some examples are as follows:

- Tetrodotoxin (TTX): It blocks sodium channels
- Saxitoxin: It blocks voltage-dependent sodium channels
- Lidocaine and Novocaine block sodium ion channels
- Dendrotoxin blocks potassium channels
- Iberiotoxin blocks potassium channels
- Heteropodatoxin blocks potassium channels

3. Diseases

Various disorders which disrupt normal functioning of ion channels have disastrous consequences for the organism. Genetic and autoimmune disorders are known as channelopathies. Some of the examples are as follows:

- Shaker gene mutations cause defect in voltage-gated ion channels, slowing down repolarisation of the cell.
- Equine hyperkinetic periodic paralysis, human hyperkalaemic periodic paralysis (Hyper PP) are caused by a defect in voltage-dependent sodium channels.
- Generalised epilepsy with febrile seizures plus (GEFS +).
- Episodic ataxia (EA), provoked by stress, startle, or heavy exertion by exercise.
- Familial hemiplegic migraine (FHM).
- Long QT syndrome, due to defect in potassium channels.
- Brugada syndrome, a ventricular arrhythmia caused by defect in voltage-gated sodium channel.
- Cystic fibrosis, caused by defect in chloride channels.
- Some types of cancers like glioblastoma multiforme, caused by defect in potassium/chloride channels.

2.1.9 Trans-Membrane Linked Receptors

An enzyme linked-receptor, also known as catalytic receptor, is a transmembrane receptor, where the binding of an extracellular ligand causes enzymatic activity on the intracellular side. Hence, a catalytic receptor is an integral membrane protein possessing both enzymatic catalytic and receptor functions. They have two important domains: an extracellular-ligand binding domain and an intracellular domain, which has a catalytic function, and a transmembrane helix. The signalling molecule binds to the receptor on outside of the cell and causes a conformational change on the catalytic function located on the receptor inside the cell.

Some examples of the enzyme-linked receptor are as follows:

- Receptor tyrosine kinase, as in fibroblast growth factor receptor. Most enzyme-linked receptors are of this type.
- Serine/threonine-specific protein kinase, as in bone morphogenic protein
- Guanylate cyclise, as in atrial natriuretic factor receptor

Following major families of catalytic receptors are known:

- Erb (Epidermal growth factor receptor)
- GDNF (glial cell-derived) neurotrophic factor
- NPR (natriuretic peptide receptor)
- trk neurotrophin receptor
- Toll-like receptor (TLR)

Out of these five types, only in case of NPR, catalytic activity is involved with the enzyme gaunylyl cyclase (EC 4.6.1.2). In all other types, the enzyme involved is tyrosine kinase (EC 2.7.10.1). For every type of receptor, there are different members, genes and ligands.

2.1.10 JAK-STAT Binding Receptor

Janus kinase (JAK) is a family of intracellular nonreceptor tyrosine kinases which transduce cytokine-mediated signals via the JAK-STAT pathway. They were initially named as "just another kinase" 1 and 2. Later on, they were named as janus kinase. JAKs possess two near identical phosphate-transferring domains. One domain exhibits the kinase activity, while the other negatively regulates the kinase activity of the first.

1. Janus Kinase (JAK)

There are four family members of JAK:

- Janus kinase 1 (JAK 1)
- Janus kinase 2 (JAK 2)
- Janus kinase 3 (JAK 3)
- Tyrosine kinase 2 (TYK 2)

JAK 1 and JAK 2 are involved in type II interferon (interferon-gamma (γ)) signalling, while JAK 1 and TYK 2 are involved in type I interferon signalling.

Functions

Some members of the type I and type II cytokine receptor families possess no catalytic kinase activity; they rely on the JAK family of tyrosine kinases to phosphorylate and activate downstream proteins involved in their signal transduction pathways. The receptors exist as paired polypeptides, thus exhibiting two intracellular signal-transducing domains.

JAKs associate with a proline rich region in each intracellular region that is adjacent to cell membrane. After receptor associates with its respective cytokine/ligand, it goes through a conformational change, bringing the two JAKs close enough to phosphorylate each other. The JAK autophosphorylation induces a conformational change within itself, enabling it to transduce the intracellular signal by further phosphorylating and activating transcription factors. The activated factors dissociate from the receptor and form dimmers before translocating to the cell nucleus, where they regulate transcription of selected genes. Some examples of molecules using JAK/STAT signalling pathway are colony-stimulating factor, prolactin, growth factor and many cytokines.

Clinical Significance

JAK inhibitors are under development for treatment of psoriasis, rheumatoid arthritis, polycythemia vera, alopecia, essential thrombocytopenia, ulcerative colitis, myeloid metaplasia with myelofibrosis and vitiligo.

2. Stat Protein

Members of the signal transducer and activator of transcription (STAT) protein family are intracellular transcription factors which mediate many aspects of cellular immunity, proliferation, apoptosis and differentiation. They are primarily activated by membrane receptor-associated Janus kinases (JAK).

Dysregulation of JAK-STAT pathway is frequently observed in primary tumours and leads to increased angiogenesis which enhances the survival of tumours and immunosuppression. It is known that STAT proteins are involved in the development and function of the immune system and play a role in maintaining immune tolerance and tumour surveillance.

The first two stat proteins were identified in the interferon system. There are seven mammalian STAT family members that have been identified: STAT 1, STAT 2, STAT 3, STAT 4, STAT 5 (STAT 5A and STAT 5B) and STAT 6.

Activation

Extracellular binding of cytokines or growth factors induce activation of receptor-associated Janus kinases, which phosphorylate a specific tyrosine residue within the STAT protein promoting dimerisation. The phosphorylated dimer is then actively transported to the nucleus via an importin α/β ternary complex. Once STAT reaches the nucleus, it binds to a consensus DNA-recognition motif called as gamma-activated sites (GAS) in the promoter region of cytokine-inducible genes and activates transcription. The STAT protein can be dephosphorylated by nuclear phosphatases, which leads to inactivation of STAT and subsequent transport out of the nucleus.

JAK-STAT Signalling Pathway

The pathway transmits information from extracellular chemical signals to the nucleus resulting in DNA transcription and expression of genes involved in immunity, proliferation, differentiation, apoptosis and oncogenesis. The signalling cascade consists of three main components: a cell surface receptor, a Janus kinase (JAK) and two Signal Transducer and Activator of Transcription (STAT) proteins. Disrupted or dysregulated JAK-STAT functionality can result in immune deficiency syndromes and cancers.

Mechanism

The binding of various ligands, like cytokines, interferon, interleukin and growth factors to cell surface receptors, activate associated JAKs, increasing their kinase activity (Fig. 2.7). Activated JAKs then phosphorylate tyrosine residues on the receptor, creating binding sites for proteins possessing SH2 domains. SH2 domains containing STATs are recruited to the receptor where they are also tyrosine-phosphorylated by JAKs. These activated STATs form hetero- or homo- dimers and translocate to the cell nucleus where they induce transcription of target genes. STATs may also be tyrosine-phosphorylated directly by receptor tyrosine kinases, such as epidermal growth factor receptor, as well as by non-receptor (cytoplasmic) tyrosine kinases.

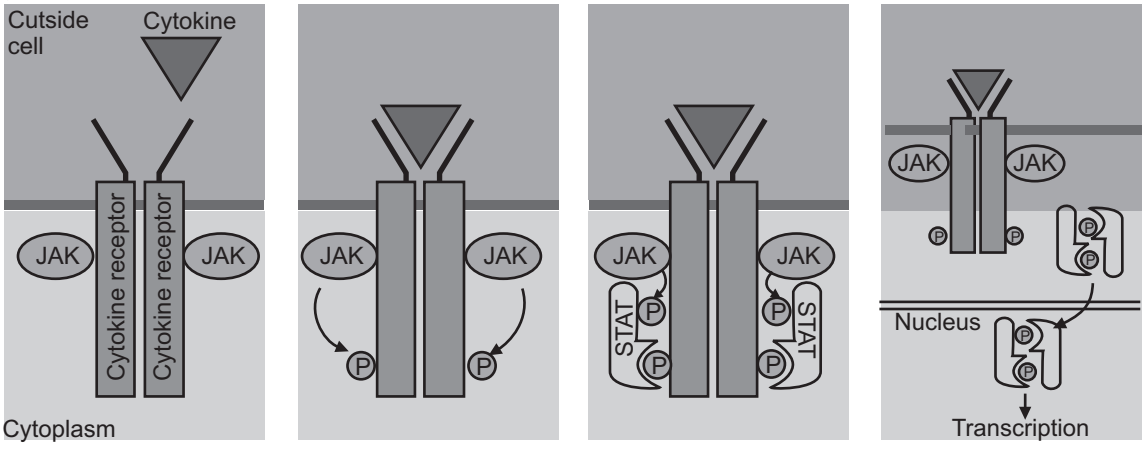


Fig. 2.7: Steps of JAK-STAT pathway

The pathway is negatively regulated on multiple levels. Protein tyrosine phosphatases remove phosphates from cytokine receptors and activated STATs. Suppressors of Cytokine Signalling (SOCS) inhibit STAT phosphorylation by binding and inhibiting JAKs or competing with STATs for phosphotyrosine binding sites on cytokine receptors. STATs are also negatively regulated by Protein Inhibitors of Activated STAT (PIAS), which act in the nucleus through several mechanisms.

Janus kinase inhibitor, a type of Janus kinases-blocking drugs are used for cancer therapy.

2.1.11 Receptors Regulating Transcription Factors

A transcription factor (TF) or sequence-specific DNA-binding factor is a protein which controls the rate of transcription of genetic information from DNA to mRNA, by binding to a specific DNA sequence. Their function is to regulate – turn on and off – genes in order to make sure that they are expressed in the right cell at the right time and in the right amount throughout the life of the cell and the organism. Groups of TFs function in a co-ordinated fashion to direct cell division, cell growth and cell death throughout life; cell migration and organisation (body plan) during embryonic development; and intermittently in response to signals from outside the cell, such as hormone. There are up to 2600 TFs in the human genome.

TFs work alone or with other proteins in a complex, by promoting (as an activator) or blocking (as a repressor) the recruitment of RNA polymerase to specific genes. RNA polymerase is the enzyme which performs transcription of genetic information from DNA to RNA.

A defining feature of TFs is that, they contain atleast one DNA-binding domain (DBD), which attaches to a specific sequence of DNA adjacent to the genes which they regulate. TFs are grouped in to classes based on their DBDs. Other proteins like co-activators, chromatin remodelers, histone acetyl transferases, histone deacetylases, kinases and methylases are also essential to gene regulation, but lack DBDs, and hence they are not TFs.

TFs are of interest in medicine because TF mutations can cause specific diseases, and medications can be targeted towards them.

Functions

TFs are one of the group of proteins which read and interpret the genetic blue print in the DNA. They bind to the DNA and help initiate a programme of increased or decreased gene transcription. They are of vital importance for many important cellular processes. Some of the important functions are listed below:

(i) Basal transcription regulation

An important class of transcription factors is called as general transcription factors (GTFs). Many of these GTFs do not actually bind DNA, but are a part of large transcription pre-initiation complex which interacts with RNA polymerase directly. The pre-initiation complex binds to promoter regions of DNA upstream to the gene that they regulate.

(ii) Differential enhancement of transcription

Other transcription factors differentially regulate the expression of various genes by binding to enhancer regions of DNA adjacent to regulatory genes. These transcription factors are critical to making sure that genes are expressed in the right cell at the right time and in the right amount.

- **Development**

  Many transcription factors in multicellular organisms are involved in development. Responding to stimuli, these transcription factors turn on/off the transcription of appropriate genes, which in turn, allows for changes in cell morphology or activities needed for cell fate determination and cellular differentiation; e.g. the Hox transcription factor family is responsible for proper body pattern formation in different organisms.

- **Response to intercellular signals**

  Cells can communicate with each other by releasing molecules which produce signalling cascades within another receptive cell. If the signal requires upregulation or downregulation of genes in the recipient cell, transcription factors will be downstreamed in the signalling cascade; e.g. estrogen signalling of a fairly short signalling cascade involves the estrogen receptor transcription factor.

- **Response to environment**

  Transcription factors can also be downstream of signalling cascades involved in environmental stimuli; e.g. heat shock factor (HSF) upregulates genes necessary for survival at higher temperatures.

- **Cell cycle control**

  Many transcription factors like proto-onco genes or tumour suppressors help regulating the cell cycle. They determine how large a cell will get and when it can divide into daughter cells; e.g. Myc onco gene has important roles in cell growth and apoptosis.

- **Pathogenesis**

  TFs can also be used to alter gene expression in a host cell to promote pathogenesis; e.g. transcription-activator like effectors (TAL effectors) are secreted by Xanthomonas bacteria. When injected into plants, these proteins can alter the nucleus of the plant cell, bind plant promoter sequences, and activate transcription of plant genes that aid in bacterial infection.

Clinical Significance

TFs are of clinical significance for following two reasons:

- Mutations can be associated with specific diseases
- They can be targets of medications

Disorders

Following disorders are related to TFs:

- Rett syndrome
- Diabetes
- Developmental verbal dyspraxia
- Autoimmune diseases
- Li-Fraumeni syndrome
- Breast cancer
- Multiple cancers

Drug Targets

Around 10% of currently prescribed drugs directly target the nuclear receptor class of transcription factors. Tamoxifen for breast cancer and Bicalutamide for prostate cancer are some of the examples. In addition, various types of anti-inflammatory and anabolic steroids are also from this category. TFs are often indirectly modulated through signalling cascades. TFs outside the nuclear receptor family are more difficult to target with small molecule therapeutics.

2.1.12 Dose-Response Relationship (DRR)

When the relation between drug dose (X-axis) and drug response (Y-axis) is plotted on a linear scale, the resulting curve is usually hyperbolic. Clinical responses plotted in this manner include change in heart rate, blood pressure, gastric pH or blood glucose. Non-clinical (biochemical) responses can also be plotted; e.g. enzyme activity, accumulation of intracellular second messenger, membrane potential or contraction of a muscle.

If the drug dose is plotted on a base 10 logarithmic scale, the generated curve is a sigmoidal dose-response curve (DRC). This representation is more useful because it expands the dose scale in the region where drug response is changing rapidly and compresses the scale at higher doses where large changes have little effect on response. In reality, it is ligand concentration (and resulting receptor occupation) which affects the response. The term DRC assumes that, the drug dose and ligand concentration are closely related.

Basic Principles of DRR

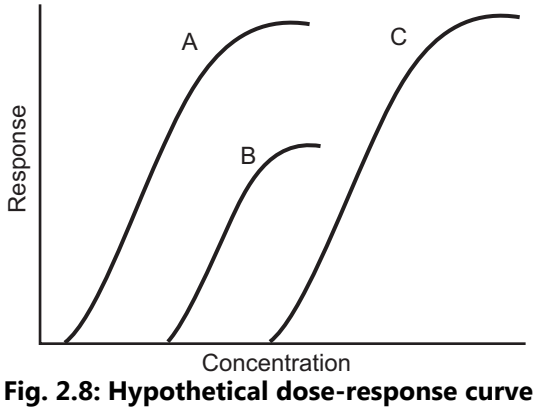


Fig. 2.8: Hypothetical dose-response curve

DRCs are a graphical representation of a specific functional reaction in a cell, tissue, or organism evoked by a range of doses of a given stimulus at a certain point of time. Stimuli

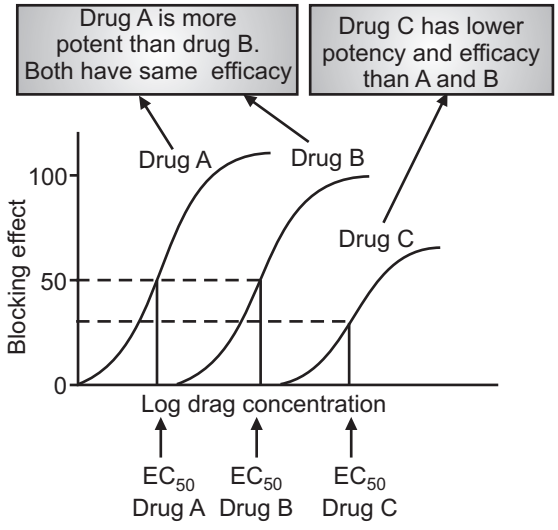
can be internal or external, physical or chemical. In basic pharmacology, DRCs are used to calculate binding affinities for receptor-ligand interactions. Fig. 2.8 shows a hypothetical DRC, highlighting some important parameters which can be drawn from it.

DRCs typically have dose on the X-axis and response on the Y-axis. Plotting the logarithm of concentration generally results in sigmoidal plots as shown in the Fig. 2.8. The main parameters which can be identified by DRCs are as follows:

- **Potency:** The position of the curve along X-axis (Curve A).
- **Maximal efficacy:** The greatest response attainable (Curve B).
- **Slope:** Change in response per unit dose (and half maximal dose) (Curve C).

DRCs are more likely to be evaluating responses to drugs. Drug dose response involves the principles of pharmacokinetics and pharmacodynamics and can be used to determine the required dose and frequency to achieve the desired response. Multiple factors can cause variation in DRCs: population differences, patient-related factors and measurement methodology. In view of biological variation, it is suggested to take repeated measurements under identical conditions to establish pharmacological profile of the drug being evaluated. The dose response relationship is important because the concentration of a drug at its site of action controls its effect.

Comparison between different types of DRCs is depicted in Fig. 2.9.



EC_{50} : Drug dose showing 50% of maximal response

Fig. 2.9: Variation in dose-response curves

The pharmacologic profiles of individual drugs can be differentiated by comparing their DRCs. In Fig. 2.9, drug A has greater biological activity per dosing unit and is therefore considered to be more potent than drugs B or C- shown by its left-shifted position on the X-axis. Drugs A and C have equal efficacy- indicated by their maximal attainable response (ceiling effect); however drug C is less potent than A because it needs higher concentration. Drug B is more potent than drug C, however its maximal efficacy is lower.

2.1.13 Therapeutic Index (TI)

TI is also referred to as therapeutic ratio. TI is a comparison of the amount of therapeutic agent that causes therapeutic effect to the amount that causes toxicity. In an established clinical setting of an approved drug, TI refers to the dose of drug which causes adverse effects at an incidence/severity not compatible with the targeted indication (e.g. toxic dose in 50% of subjects, TD50) to the dose which leads to the desired pharmacological effect (e.g. effective dose in 50% of subjects, ED50).

In early days of toxicology, TI was frequently determined in animals as lethal dose of a drug for 50% of the population (LD_{50}) divided by the minimum effective dose for 50% of the population (ED_{50}).

Thus in human beings, TI = TD_{50}/ED_{50}; in animals, TI = LD_{50}/ED_{50}

For many drugs, there are several types of toxicities which occur at sub-lethal doses in human beings. These toxicities often limit the maximum dose of a drug. For any drug, a higher TI is always preferable. Higher TI indicates more margin of safety. Generally, a drug with narrow therapeutic range (having little difference between toxic and therapeutic doses) may have its dosage adjusted according to measurements of the actual blood levels achieved in a person. An example of digoxin can be cited here. Its dose for CHF is 8-12 mcg/kg by IV route, and 10-15 mcg/kg by oral route. The therapeutic range is 1-2.5 nmol/L (0.5-2.0 ng/mL). It indicates that, when the serum concentration of digoxin exceeds to 2.0 ngm/ml, it can be toxic and lethal. Thus, digoxin is a drug with low TI.

The therapeutic index varies widely among substances. Amongst the opium pain killers, Remifentani has a therapeutic index of 33,000 : 1, while morphine has TI of 70 : 1. Diazepam has a TI of 100 : 1. Digoxin has TI of 2 : 1.

2.1.14 Combined Effects of Drugs

When two or more drugs are given together, there is a possibility that the effect may be additive or synergistic. When the total effect of two or more drugs given together is same as that of their individual administration, the effect is called as additive. Sometimes the effect is more than expected, i.e. more than additive; in such cases it is called as synergistic effect. The risk associated with benzodiazepines like diazepam increases significantly when taken with alcohol in comparison to opiates like morphine or stimulants like amphetamine being taken alone. This is expressed by the comment that benzodiazepines are synergistic with alcohol. The explanation for synergistic effect is provided by different mechanisms of actions exhibited by involved drugs. The opposite of synergy is termed as antagonism. Two drugs are antagonistic when their interaction causes a decrease in the effects of one or both of the drugs.

Both synergy and antagonism can occur during different phases of the interaction of the drug with an organism, with each effect having different name. When the synergy occurs at a cellular receptor level, it is termed as agonism, and the substances involved are termed as agonists. On the other hand, in case of antagonism, one of the substances may be agonist and another antagonist. Different responses of receptors to the action of a drug has resulted

in a number of classifications such as partial agonist, competitive/non-competitive agonist, etc. These concepts have fundamental applications in the phamacodynamics of these interactions. See section 1.1.7 for related discussion.

2.1.15 Factors Modifying Drug Action

Following factors or conditions pre-dispose or favour the appearance of drug interactions:

- **Old age**
  It is known that liver metabolism, kidney function, nerve transmission or functioning of bone marrow decreases with age. In addition, in old age there is a sensory decrease which increases the chances of errors being made in the administration of drugs.
- **Polypharmacy**
  More the number of drugs a patient takes, more are the chances amongst their interaction.
- **Genetic factors**
  Genes synthesise enzymes which metabolise drugs. Some races have genotypic variations which could decrease or increase the activity of these enzymes. The consequence of this effect predisposes the patients towards more drug-interactions. Genotypic variations in isozymes of cytochrome P450 is a classical example.
- **Hepatic/renal diseases**
  Drugs which are metabolised in liver and/or eliminated by kidneys can have pharmacokinetic alterations if liver and/or kidney is not functioning properly. In such cases serum concentrations of related drugs may increase, because of which the patients may show adverse reactions/interactions.
- **Serious diseases**
  For any reason, if dose of the drug is reduced, there is a likelihood that serious diseases could worsen.
- **Drug-dependent factors**
  Factors like narrow therapeutic index (e.g. digoxin), steep dose response curve, saturable hepatic metabolism as in case of phenytoin, can alter effects of drugs at different concentrations.

2.2 ADVERSE DRUG REACTIONS (ADRs)

Whenever a drug is given to treat a disease, it is also likely that the drug may cause additional responses in the body. A response caused by drug which is noxious and unintended and occurs at dises normally used in humans for the prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function is called as adverse reaction. There is also a term called as adverse event. The difference between ADR and adverse event is related to causality. Whenever an adverse event is characterised by the suspicion of a causal relationship between the drug and the occurrence i.e. judged as being atleast possibly related to treatment, then it is called as ADR. Study of ADRs is called as pharmacovigilance. See Section 2.4.4.

2.3 DRUG INTERACTIONS (PHARMACOKINETIC AND PHARMACODYNAMIC)

When more than one drug is administered to a patient, then there is a possibility of interaction between their effects. The cause may be pharmacodynamic or pharmacokinetic. Each one of them is discussed below.

2.3.1 Pharmacokinetic Drug Interactions

Drugs do differ in their absorption, transport, distribution, metabolism and/or excretion. These are called as pharmacokinetic factors. When more than one drug is given, it may alter pharmacokinetic factors of other drug(s). Thus, they are sub-classified as follows:

2.3.1.1 Absorption Interactions

Some drugs increase the speed with which a drug passes through the intestine. These drugs decrease gastric emptying time. Such drugs, e.g. domperidon are called as pro-kinetic drugs. Pro-kinetic drugs can reduce timing of a drug in GIT, resulting in lower concentration of co-administered drug. Some other drugs like atropine can reduce gastro-intestinal motility; such drugs may increase stay in GIT and therefore their absorption may increase.

Drugs can exist either in an ionised or in a non-ionised form depending on their pKa (pH at which the drug reaches equilibrium between its ionised and non-ionised form). The non-ionised forms of drugs are usually easier to absorb, provided they are small molecules. Ionisable drugs are usually less absorbed. Increasing absorption of a drug will increase its bioavailability. Thus, changing the drug's state from ionised to non-ionised form can be more useful for increasing its absorption. Change in pH, due to effect of drugs can alter absorption of other drugs. In addition, substances like antacid may decrease absorption of other drugs because of adsorption of other drugs on their surface.

Solubility of a drug is an important factor. Absorption of some drugs can be drastically reduced if they are administered together with food of high fat content.

Formation of non-absorbable complexes is yet another cause for reducing their absorption. Chelation with cations, binding with proteins and formation of large complexes are some of the mechanisms. The examples are as follows: tetracycline can chelate calcium ions; sucralfate binds with proteins; cholestyramine forms complexes with thyroxine/digoxin.

Action of enterocytes on P-glycoprotein is one more mechanism. Consumption of grape fruit juice increases bioavailability of drugs like verapamil.

2.3.1.2 Transport and Distribution Interactions

In this case, the main mechanism is competition for plasma protein transport. If two drugs compete for the same site on plasma albumin and if one drug has more affinity than the other drug, then one drug can replace the other leading to enhanced pharmacological effect of another drug. Phenylbutazone or sulphamethoxazole can displace warfarin leading to effects of warfarin.

2.3.1.3 Metabolism Interactions

Many drug interactions are due to alterations in drug metabolism. Cytochrome P450 is the classical example.

Cytochrome P450 (CYP 450)

CYP 450 is a very large family of haemoproteins, characterised by their enzymatic activity and their role in metabolism of various drugs. The most important enzymes are CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. Majority of these enzymes are involved in metabolism of steroids or drug hormones. As an illustration, drugs related to CYP1A2 are listed in table 2.2.

Certain drugs may act as substrate for a type of CYP450 enzyme. Some other drug may inhibit enzymatic action of CYP450. Inhibition of CYP450 will lead to reduced metabolism of the relevant drug. Some other drugs may induce the enzyme and increase its concentration. As a result of enzyme induction, metabolism of related drug will be enhanced. Both induction and/or inhibition of a type of CYP450 can lead to drug interaction.

Table 2.2: Drugs related to CYP1A2

Substrates	Inhibitors	Inducers
Caffeine	Omeprazole	Phenobarbital
Theophylline	Nicotine	Fluvoxamine
Phenacetin	Cimetidine	Venlafaxine
Clomipramine	Ciprofloxacin	Ticlopidine

Some food components also act as inducers or inhibitors of enzymatic activity. Some examples are shown in table 2.3.

Table 2.3: Foods which influence drug metabolism

Food	Mechanism	Drugs affected
Grape fruit juice	Enzymatic inhibition	• nifedipine, felodipine,nimodipine, amlodipine • cyclosporine, tacrolimus • terfenadine, astemizole • cisapride, pimozide • carbamazepine, saquinavir, midazolam, alprazolam, triazolam
Soya	Enzymatic inhibition	Clozapine, haloperidol, olanzapine, caffeine, NSAIDs, phenytoin, warfarin, zafirlukast
Garlic	Increases antiplatelet activity	Anticoagulants, NSAIDs, acetyl salicylic acid
Ginkgo biloba	Inhibitor of platelet aggregation	Warfarin, aspirin and NSAIDs
St John's wort	Enzyme inducer	Warfarin, digoxin, theophylline, cyclosporine, phenytoin and anti-retrovirals
Ephedra	Receptor agonist	MAO, CNS stimulants, ergotamines, xanthenes
Ginger	Inhibits enzyme	Anti-coagulants

2.3.1.4 Excretion Interactions

These are divided in to two excretory mechanisms: renal excretion and bile excretion.

1. Renal excretion

Only the free fraction of the drug which is dissolved in blood plasma can be removed through kidney. Hence, drugs which are tightly bound to proteins are not available for renal excretion. Creatinine clearance is used as a indicator for kidney functioning but it is only useful in cases where the drug is excreted in an unaltered form in the urine. During formation of urine, drugs pass through nephrons by filtration. Filtration depends on a number of factors including pH of urine. It is shown that, drugs which act as weak bases are increasingly excreted as the pH of urine becomes more acidic. Conversely, weak acids are increasingly excreted as urine becomes more alkaline. Usually, pH of urine is acidic in nature; however for excretion of weak acids, alkalinisers like sodium citrate are given orally to promote their excretion. Table 2.4 lists some of the weak acids and weak bases which are used as drugs.

Table 2.4 Drugs that act as weak acids or bases

Sr. No.	Weak acids	Weak bases
1.	Acetyl salicylic acid	Reserpine
2.	Furosemide	Amphetamine
3.	Ibuprofen	Procaine
4.	Levodopa	Ephedrine
5.	Acetazolamide	Atropine
6.	Sulfadiazine	Diazepam
7.	Ampicillin	Hydralazine
8.	Chlorothiazide	Pindolol
9.	Paracetamol	Propranolol
10.	Chloropropamide	Salbutamol
11.	Chromoglicic acid	Alprenolol
12.	Ethacrynic acid	Terbutaline
13.	Alpha methyldopa	Amiloride
14.	Pehnobarbital	Chlorphenalmine
15.	Warfarin	
16.	Theophylline	
17.	Phenytoin	

2. Bile excretion

Bile excretion involves use of metabolic energy in active transport across the epithelium of bile duct against concentration gradient. The transport system can be saturated if the plasma concentration of the drug is too high. Bile excretion of drugs occurs when their molecular weight is greater than 300 and they contain both polar and non-polar groups. The

glucuronidation of the drug in the kidney facilitates bile excretion. Substances with similar physico-chemical properties can block the receptor. A drug excreted in the bile duct can occasionally follow entero-hepatic circulation and may be reabsorbed by the intestine. In such cases it can lead to interaction with other drugs.

2.3.2 Pharmacodynamic Drug Interactions

The change in an organism's response on administration of a drug is an important factor in pharmacodynamic interactions. These changes are difficult to classify due to wide variety of modes of action and various underlying mechanisms. Whenever the interactions are based on biological response of a drug at the active site, it is considered in this category.

Pharmacodynamic interactions can occur on:

- **Pharmacological Receptors:**
  Whenever interactions between two or more drugs are directly related to the same receptor, they are considered in this category. Receptor interactions are further sub-classified as homodynamic and heterodynamic.

1. Homodynamic

If two or more drugs act on the same receptor, they are considered under this category. They are further sub-classified as: pure agonists; partial agonists or antagonists. Antagonists can be either of competitive or uncompetitive type

2. Heterodynamic

If two or more drugs act on different receptors, they are considered under this category.

(i) Signal transduction mechanisms: These mechanisms are molecular processes which commence after interaction of the drug with receptor. cAMP is signal transducing substance in the action of insulin.

(ii) Antagonistic physiological systems: When two or more drugs alter a physiological process by different mechanisms or through different mechanisms, the interaction falls in this category. The action of digoxin on cardiac fibres can lower levels of potassium. Diuretic like furosemide also causes lower levels of potassium because of its action on kidney. Lower potassium levels are termed as hypokalemia. Thus, hypokalemia caused by diuretics increase toxicity of digoxin.

2.4 DRUG DISCOVERY AND CLINICAL EVALUATION OF NEW DRUGS

2.4.1 Drug Discovery

Discovery of a new drug involves an elaborate process. It starts with synthesis of a large number of chemical compounds. Historically, drugs were discovered through identifying the active ingredient from traditional remedy or by chance discovery. Later, chemical libraries of synthetic small molecules, natural products or extracts were screened in intact cells or whole organisms to identify substances which have desirable therapeutic effect in the process of classical pharmacology. After sequencing of human genome which allow rapid cloning and synthesis of large quantities of synthetic proteins, high throughput screening of large compounds libraries against isolated biological targets has become another effort for new drug discovery.

Modern drug discovery involves identification of screening hits, medicinal chemistry and optimisation of those hits to increase the affinity, selectivity, efficacy of the potency, metabolic stability and oral bioavailability (Fig. 2.10). Once a compound which fulfils all these requirements has been identified, the process of drug development begins with clinical trials. Before starting a clinical trial safety of the drug is evaluated in experimental animals. This process is called as pre-clinical evaluation.

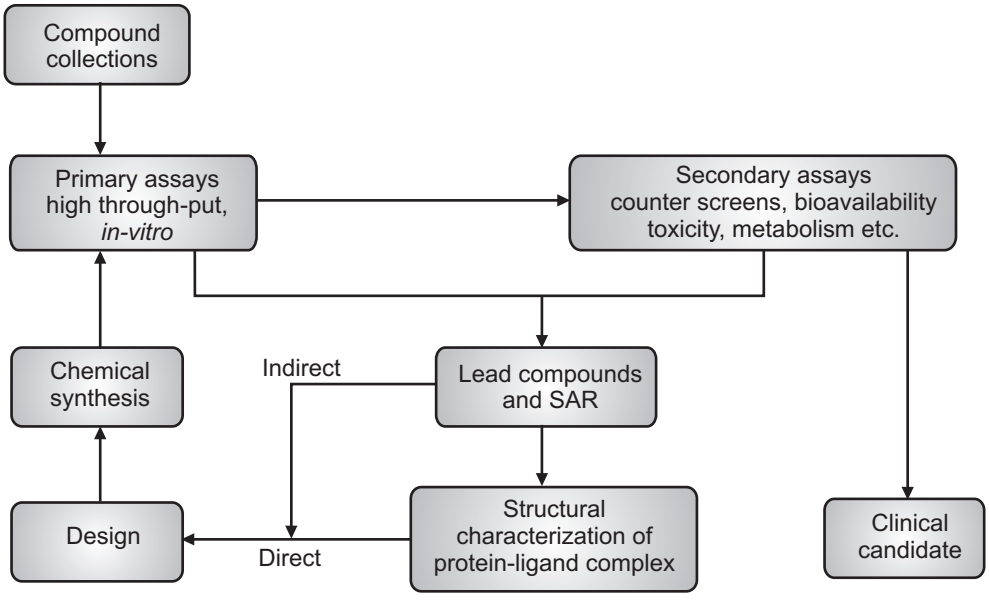


Fig. 2.10: Drug-discovery cycle

2.4.2 Pre-clinical Evaluation

The main goals of pre-clinical studies are to determine the safe dose for first-in-man study and assess a product's safety profile. On an average, only one in 5,000 compounds which enter drug discovery to the stage of clinical development becomes an approved drug.

Each class of product may undergo different types of pre-clinical research. Drugs may undergo pharmacodynamic (PD), pharmacokinetic (PK) and toxicological testing. This data allows researchers to estimate a safe starting dose of the drug for clinical trials in humans. While performing pre-clinical studies, Good Laboratory Practices (GLPs) are followed. Typically, both *in-vitro* and *in-vivo* tests are performed. Studies of a drug's toxicities include which organs are targeted by the drug. Three special types of toxicities are performed: they are carcinogenicity (tests for evaluating potential to cause cancer), mutagenecity (tests for evaluating mutagenic potential) and tetatogenecity (tests for evaluating potential damage to fetus during pregnancy of mother).

Animal Testing

Information collected from pre-clinical studies is vital for safe human testing. Typically, animal testing involves at least two species. The choice of species is based on animals which will give best correlation to human trials. Usually murine animals like mice/rats and canine animals like dogs are used for testing. In addition, primates like monkeys or porcine animals

like pigs may be used for pre-clinical testing. Differences in the gut, enzyme activity, circulatory system, or other considerations based on dosage form, site of activity or noxious metabolites help in selection of animal species. Canines like dog are good models for oral dosage form. Regulatory guidelines like those from USFDA, EMA, and other international and regional regulatory authorities require safety testing in at least two mammalian species like rabbit, including a non-rodent species, prior to human trials authorisation.

Animal testing also needs ethical considerations. Constitution of animal ethics committee and approval of test protocol by the animal ethics committee is necessary. In India, clearance from Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA) has provided elaborate guidelines on handling of animals, animal care, physical facilities in animal house, food, water for animals, sanitation and cleanliness and waste disposal. It is suggested that standard operating procedures (SOPs) for methods adopted to animal husbandry, maintenance, breeding, animal house microbial analysis and experimental records need to be maintained.

2.4.3 Phases of Clinical Trial

All new drugs are labelled as Investigational New Drugs (INDs) by UDFDA. All INDs undergo various stages of development. Clinical trials have been classically divided in to four phases as described below. In addition, phase 0 has been added in recent years.

2.4.3.1 Phase 0

Phase 0 has been added by USFDA from 2006 guidance on exploratory IND studies. Phase 0 trials are known as human micro-dosing studies and are designed to speed up the development of promising drugs or imaging agents by establishing very early on whether the drug behaves in human subjects as was expected from pre-clinical studies. Distinctive features of phase 0 trials include administration of sub-therapeutic doses to a small number of subjects (10-15) to gather preliminary data on pharmacokinetics of the drug.

Phase 0 study gives no data on safety or efficacy, being by definition a dose too low to cause any therapeutic effect. Based on information from phase 0 studies, a decision regarding progress of the drug in next phases is taken.

2.4.3.2 Phase I

Phase I trials were formerly called as first-in-humans studies. Normally, a small group of 2-100 healthy volunteers are recruited in phase I trial. These trials are conducted in a clinical trial clinic, where the subject can be observed by a full time staff. The subject who receives the drug is usually observed until several half-lives of the drug have passed. This phase is designed to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of a drug. Normally, phase I trials include dose-ranging, also called as dose escalation studies, so that the best and safest dose can be identified. Normally, phase I trials include dose-ranging, also called as dose escalation studies, so that the best and safest dose can be identified. The tested range of doses is usually a fraction of a dose which causes harm in animal testing. Although phase I trials are conducted on healthy volunteers, there are some circumstances when clinical patients are used for phase I. In such cases where treatment is

likely to make healthy individuals ill, patients of terminal cancer or HIV are used for the trial. In addition to terminal patients, patients who have been already tried and failed to improve on existing standard therapies may also participate in phase I trials. Volunteers are paid a variable inconvenience fee for their participation in phase I trial. In addition, their health insurance premium is paid by the sponsor of the trial. Before beginning phase I trial, the sponsor must submit an IND application to FDA detailing the preliminary data on the drug gathered from cellular models and animal studies.

Three types of studies are included in phase I trials: single ascending dose, multiple ascending dose and the effect of food.

2.4.3.3 Phase II

Once a dose range of doses is determined, the next goal is to evaluate whether the drug has any biological activity or effect in human beings. Phase II trials are performed on a relatively larger group as compared to phase I trials. Normally, 100-300 patients are included in phase II studies. Genetic testing is common, especially when there is evidence of variation in metabolic rate of the drug. When the development process for an IND fails, it is usually during phase II trials. Conveniently, phase II trials can be divided in to two sub-categories: phase II A and phase II B. Phase II A studies are pilot studies designed to demonstrate clinical efficacy or biological activity. It can be termed as "proof of the concept" studies. Phase II B studies find the optimum dose at which the drug shows the biological activity with minimal side effects. They are also termed as "definite dose-finding" studies. Occasionally, phase I and phase II may be combined to test both efficacy and toxicity.

Phase II studies historically have recorded lowest success rate. In 2010, the percentage of phase II trials that have proceeded to phase III was 18 %. During 2006-2015, only 37% of developmental drugs advanced from phase II to phase III.

2.4.3.4 Phase III

This phase is designed to assess the effectiveness of the IND. Phase III studies are randomised controlled multicentre trials on a large patient groups ranging from 300-3000. These studies are aimed at being the definitive assessment of effectiveness of the drug. Phase III trials are the most expensive, time-consuming and difficult trials to design and run, especially in chronic diseases. Phase III trials of chronic diseases often have a short follow-up period of evaluation, relative to the period of time during which intervention might be used in clinical practice. Phase III studies are also called as "pre-marketing phase". During this stage, sub-groups of patients like those having hepatic, renal or cardiac failure may also be exposed with appropriate modification in dosages. If proof about adequate safety is available, then paediatric and geriatric patients may also be included. In case of paediatric patients, a separate clinical study is suggested by regulatory authority.

It is expected that at least two successful phase III trials, demonstrating a drug's safety and efficacy are necessary in order to obtain approval from appropriate regulatory agencies like USFDA, EMA etc. Once a drug has proved satisfactory in phase III trials, the trial results are usually combined in to a large document containing a comprehensive description of the

methods and results of human and animal studies, manufacturing procedures, formulation details and shelf life. This collection of information makes up the regulatory submission which is provided for review to appropriate regulatory authorities in different countries. The regulatory authorities review the submission, and if found appropriate, give approval for marketing the drug to the sponsor.

By 2010, about 50% of the INDs fail during phase III trials or are rejected by national regulatory agencies. An estimate of phase II/III trials depends on various factors, therapeutic area being studied and types of clinical procedures as key drivers. It is indicated that, phase II studies may cost about $ 20 million (₹ 130 crores), and phase III studies $ 53 million (₹ 345 crores).

2.4.3.5 Phase IV

By the end of phase III studies, after review, regulatory authorities provide marketing permission to the sponsor. Thus, a phase IV trial is also known as post-marketing surveillance trial/confirmatory trial. Phase IV trials involve surveillance of safety and ongoing technical support of a drug. Phase IV studies may be required by regulatory authorities or may be undertaken by the supporting company for competitive or other reasons. The safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer time period than was possible during the phase I-III clinical trials. If an adverse drug effect is rare, then it may be detected only in phase IV studies. The minimum time period mandatory for phase IV clinical trial is of two years. During this period, if a serious adverse reaction is observed, then the use of drug may be appropriately restricted. If the adverse reaction is too serious, probably causing death, then the drug may be withdrawn from the market during phase IV studies.

The entire process of developing a new drug from pre-clinical research to marketing can take 12-18 years and may cost over $ 1 billion (₹ 6500 crores). The life of patent of a drug expires 20 years after its registration. The figures indicate big financial risks in developing a new drug.

A summary of different phases of trials is presented in table 2.5.

Table 2.5: Summary of trial phases

Sr. No.	Phase	Primary goal	Dose	Typical number of participants
1.	Pre-clinical	Testing of drug in animals to gather efficacy, toxicity and pharmacokinetics	Unrestricted	Not applicable (*in-vitro* and *in-vivo* only)
2.	Phase 0	Pharmacokinetics, oral bioavailability and half-life	Very small, sub-therapeutic	10 healthy volunteers

contd. …

3.	Phase I	Testing on healthy volunteers for dose-ranging	Sub-therapeutic with ascending doses	20-100 healthy volunteers (cancer patients for anti-cancer drugs)
4.	Phase II	Testing of drug on patients to assess efficacy and side effects	Therapeutic dose	100-300 patients with specific diseases
5.	Phase III	Testing on patients to assess efficacy, effectiveness and safety	Therapeutic dose	300-3000 patients of diverse sub-groups
6.	Phase IV	Post-marketing surveillance-watching drug use in public	Therapeutic dose	Anyone seeking treatment from physician

2.4.4 Pharmacovigilance

Pharmacovigilance is defined as, "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem".

In some countries, adverse drug reactions (ADRs) rank among the top ten leading causes of mortality. In order to prevent or reduce harm to patients and thus improve public health, mechanisms for evaluating and monitoring the safety of medicines in clinical use are vital. In practice, this means having in place a well-organised pharmacovigilance system, up to phase III of clinical development of INDs, maximum 5000 patients are exposed to the new drug. After marketing approval, the number of patients is unlimited. Hence, rare adverse reactions may be newly observed during post-marketing surveillance of the drug.

The principal aims of pharmacovigilance programme are as follows:

- To improve patient care and safety in relation to the use of medicines, and all medical and para-medical interventions.
- To improve public health and safety in relation to the use of medicines.
- To contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost effective) use.
- To promote understanding, education and clinical training in pharmacovigilance and its effective communication to health professionals and the public.

Several stake holders are involved in monitoring safety of medicines. Some of them are listed below:

- Government
- Pharmaceutical industries
- Hospitals and academia

- Medical and pharmaceutical associations
- Poisons and medicines information centres
- Health professionals like doctors, pharmacists, nurses
- Patients
- Consumers
- The media
- World Health Organisation (WHO)

WHO's International Drug Monitoring started in 1968. By 2016, 123 countries have joined the programme. WHO headquarters in Geneva is responsible for monitoring the programme. The centre is now known as Uppsala Monitoring Centre (UMC) with the support of Swedish Government.

Pharmacovigilance in India

The Central Drug Standard Control Organisation (CDSCO), New Delhi, under the control of Ministry of Health and Family Welfare, Government of India has initiated a nation-wide pharmacovigilance programme from July 2010. All Institute of Medical Sciences (AIIMS), New Delhi was the National Co-ordinating Centre (NCC) for monitoring ADRs. From April 2011, the Indian Pharmacopoeia Commission (IPC), Ghaziabad looks after administrative matters related to NCC. 22 ADR monitoring centres (AMCs) have been established throughout India.

The scope and objectives of the programme are indicated below:

- To create a nation-wide system for patient safety reporting.
- To identify and analyse new signals from the reported cases.
- To analyse the benefit-risk ratio of marketed medications.
- To generate evidence-based information on safety of medicines.
- To support regulatory agencies in the decision-making process on use of medications.
- To communicate the safety information on use of medicines to various stake holders to minimise the risk.
- To emerge as a national centre of excellence for pharmacovigilance activities.
- To collaborate with other national centres for the exchange of information and data management.
- To provide training and consultancy support to other national pharmacovigilance centres across globe.
- To identify and analyse new ADR signal from the reported cases.
- To promote rational use of medicines.

There are various regulatory controls over the pharmacovigilance system. The European Medical Agency (EMA) has published elaborate details of Good Pharmacovigilance Practices (GPvP). In addition, USFDA has also published several guidance statements related to pharmacovigilance. International Council for Harmonisation (ICH) and Council for International Organisations of Medical Sciences (CIOMS) have published several guidelines related to pharmacovigilance.

There are several pharmacovigilance methods followed in recording adverse events related to drugs. The methods are as follows:

(i) Passive surveillance

Passive surveillance involves collecting reports generated out of existing system.

- **Spontaneous reports:** A spontaneous report is an unsolicited communication by health-care professionals or consumers to a company, regulatory authority or other organisation which describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organised collection scheme.
- **Case series:** Series of case reports related to one or more adverse events can provide evidence of an association between a drug and an adverse event. They may be spontaneously reported.

(ii) Stimulated reporting

Several methods like online reporting of adverse events encourage and facilitate reporting by health professionals in specific situations like hospital settings. They are termed as stimulated reporting.

(iii) Active surveillance

Active surveillance seeks to ascertain completely the number of adverse events via a continuous pre-organised process.

- **Sentinel sites:** By reviewing medical records or interviewing patients and/or physicians in a sample of selected site, termed as sentinel sites, complete and accurate data on reported adverse events can be ensured.
- **Drug event monitoring:** In drug event monitoring, patients may be identified from electronic prescription data or automated health insurance claims.
- **Registries:** A registry is a list of patients presenting with the same characteristics; e.g. there can be a registry of diabetic patients.

(iv) Comparative observational studies

There are a number of observation study designs which are useful in validating signals from spontaneous reports or case series.

- **Cross-sectional study (Survey):** Data collected on a population of patients at a single point in time (or interval of time) regardless of exposure or disease status constitute a cross-sectional study.
- **Case- control study:** In case-control study, cases of disease (or events) are identified. Controls, or patients without the disease or event of interest, are then selected from the source population.
- **Cohort study:** In a cohort study, a population-at-risk for the disease (or event) is followed over time for the occurrence of the disease (or event). Information on exposure status is known throughout the follow-up period for each patient.

(v) Targeted clinical investigations

When significant risks are identified from pre-approval clinical trials, further clinical studies might be called for to evaluate the mechanism of action for the adverse reaction. Sometimes, potential risks or un-forcing benefits in special populations (paediatric, geriatric) might be identified from pre-approval clinical trials. To elucidate the benefit-risk profile of a drug outside of a traditional clinical trial setting, a special clinical trial may be conducted. All these trials are termed as targeted clinical investigations.

(vi) Descriptive studies

Descriptive studies are primarily used to obtain the background rate of outcome events and/or establish the prevalence of the use of drugs in specified populations.

- **Natural history of disease:** The science of epidemiology initially focussed on the natural history of disease, including characteristics of disease, patients and distribution of disease in selected populations, as well as estimating the incidence and prevalence of potential outcome of interest. Studies which examine specific aspects of adverse events, like the background incidence rate of or risk factors for the adverse event of interest, can be used to assist in putting spontaneous reports in to perspective.
- **Drug utilisation study (DUS):** DUS describe how a drug is marketed, prescribed, and used in a population, and how these factors influence outcomes, including clinical, social, and economic outcomes. These studies provide data on specific populations, like the elderly, children, or patients with hepatic or renal dysfunction, often stratified by age, gender, concomitant medication, and other characteristics.

All information about safety of medications has to be communicated to all stake holders in different ways. Available methods for communication messages are listed in table 2.6.

Table 2.6: Communicating messages about medicine safety

Sr. No	Vehicle	Issued by
1.	"Dear doctor" letters	Pharmaceutical manufacturers.
2.	Medicine alerts	National health authorities.
3.	Media statements	National health authorities/ pharmacovigi-lance centres.
4.	Patient information leaflets	Pharmaceutical manufacturers/National health authorities/Pharmacovigilance centres.
5.	News letters	National pharmacovigilance centres and WHO.
6.	Personal feed-back to reporters	National pharmacovigilance centres.

QUESTIONS

Long Answer Questions:

1. Comment on principles and mechanism of drug action.
2. Discuss theories of drug receptor interaction.
3. With suitable examples classify types of receptors.

4. How can you identify type of antagonism based on dose-response curve.
5. Discuss important features of G-protein coupled receptors.
6. Discuss important features of ion channel receptors.
7. Comment on clinical significance of ion channel receptors.
8. What is the importance of JAK-STAT binding receptor?
9. Comment on clinical significance and disorders related to transcription factors.
10. Discuss basic principles of dose-response relationship.
11. Discuss factors modifying drug action.
12. Present an overview of pharmacokinetic drug interactions with suitable examples.
13. With suitable examples comment on pharmacodynamic drug interactions.
14. Describe sequence of events in drug discovery.
15. What is the importance of pre-clinical drug evaluation.
16. Describe different phases of clinical trial.
17. Who are the stake holders in the process of pharmacovigilance.
18. What are different communication mechanisms for monitoring safety of drugs.

Small Answer Questions:

1. Write short notes on:
   - Signal transduction mechanisms
   - G-proteins
   - Classification of G-protein coupled receptors
   - Structure of G-protein coupled receptors
   - Ion channel receptors
   - Voltage-gated channels
   - Ligand-gated channels
   - Ion channel blockers
   - Trans-membrane receptors
   - JAK-STAT binding receptors
   - Janus kinase
   - STAT-protein
   - Transcription factors.
   - Therapeutic index
   - Pharmacokinetic drug interactions
   - Pharmacodynamic drug interactions
2. Define following terms:
   - Spontaneous reports
   - Stimulated reporting
   - Cross-sectional study
   - Case-control study
   - Cohert study
   - Drug utilisation study

■■■

Unit ... 3

PHARMACOLOGY OF PERIPHERAL NERVOUS SYSTEM

♦ LEARNING OBJECTIVES ♦

After completing this chapter, students should be able to understand:

- *Organisation and functions of ANS*
- *Neuro-humoral Transmission, Co-transmission, Various Neurotransmitters*
- *Pharmacology of Parasympathomimetics, Parasympatholytics*
- *Pharmacology of Sympathomimetics, Sympatholytics*
- *Pharmacology of Neuromuscular Blocking Agents, Skeletal Muscle Relaxants*
- *Pharmacology of Local Anaesthetic Agents*
- *Pharmacology of Drugs used in Myasthenia Gravis and Glaucoma*

3.1 INTRODUCTION

- The nervous system has an important role to communicate information from outside the body; process it and to take corrective action based on the received response. The input information is processed by sensory nervous system. The processing within is due to internal communication between cells and the output information is processed by motor nervous system. The unit of nervous system is a neuron which consists of a cell and its projections in the form of several small dendrons and a major extension called as axon or axis cylinder. Fig. 3.1 describes structure of a neuron.
- The nervous system can also be identified in two forms: central and peripheral. Central nervous system consists of the brain and the spinal cord; and peripheral nervous system consists of associated nerves and ganglia. Ganglia are structures containing a number of nerve cell bodies, typically linked by synapses and often forming a swelling on nerve fibre. Many drugs are known to act on peripheral nervous system (PNS). Before discussing drugs acting on PNS, knowledge about their structure and functions is necessary.

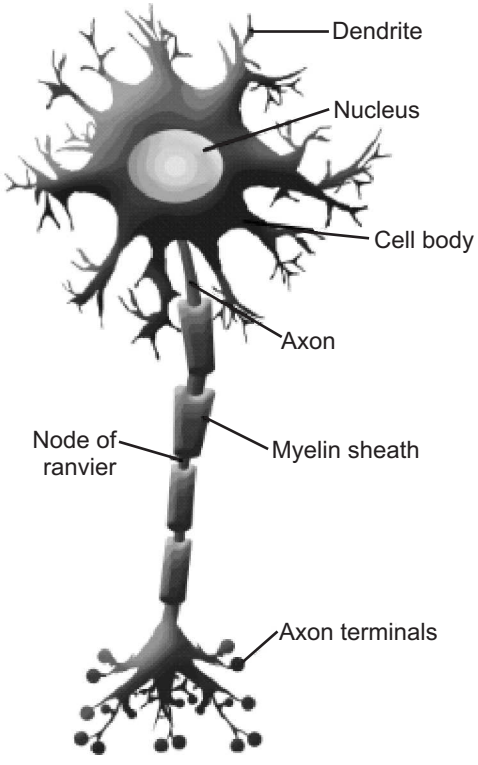


Fig. 3.1: Structure of neuron

3.2 ORGANISATION AND FUNCTIONS OF AUTONOMIC NERVOUS SYSTEM (ANS)

- In biological systems, structure and functions are correlated. In fact, structures get organised to perform specific functions. Thus, knowledge about structural features and associated functions is to be understood comprehensively.

3.2.1 Organisation of ANS

- Based on the part of the body which responds, the PNS is sub-divided in to Somatic Nervous System and Autonomic nervous system (ANS). Traditionally, the ANS and somatic nervous system are usually described as an output of efferent portion of PNS.

3.2.1.1 Somatic Nervous System

The somatic nervous system consists of two types of neurons: sensory and motor. Sensory neurons carry information from the skin and special sensory receptors to the CNS. Motor neurons conduct impulses from the CNS to skeletal muscles. Since the effect of motor neurons can be consciously controlled, the efferent part of somatic nervous system is primarily concerned with voluntary functions like locomotion, respiration, posture and deep tendon reflexes.

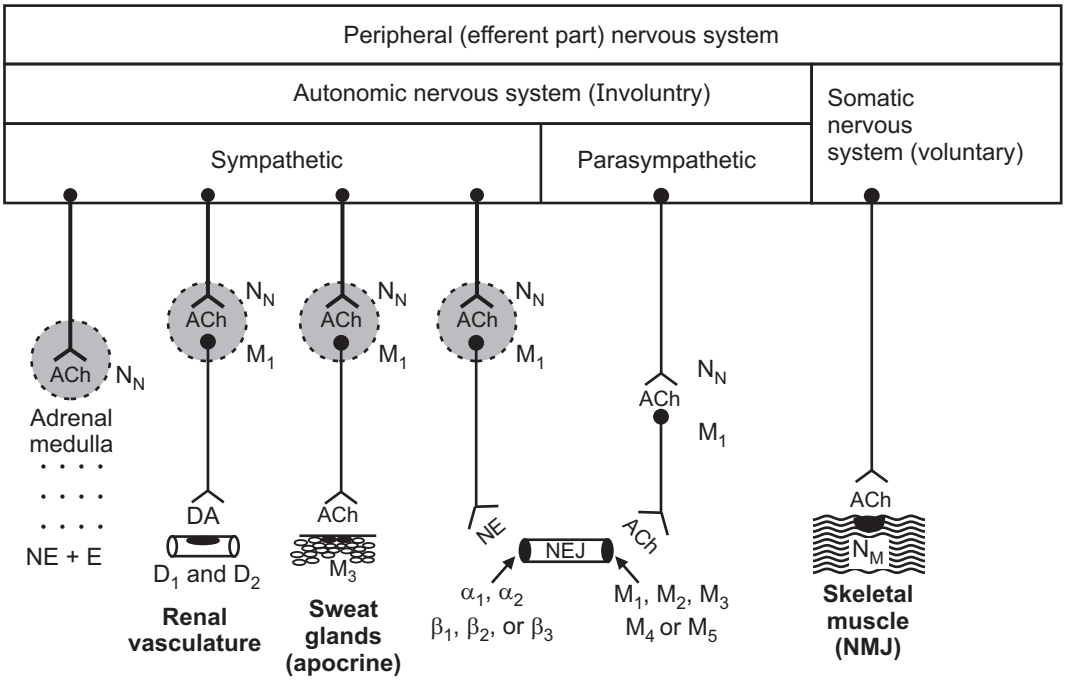
The axons of somatic motor neurons extend from the CNS and are myelinated. The neurotransmitter release by somatic nerves at the Neuromuscular Junction (NMJ) is acetyl choline (ACh).

3.2.1.2 Autonomic Nervous System (ANS)

The ANS consists of three main anatomical divisions:

- Parasympathetic Nervous System (PSNS) or (Cholinergic Division)
- Sympathetic Nervous System (SNS) or (Adrenergic Division)
- Enteric Nervous System (ENS)

In ANS, a nerve originating from brain/spinal cord first enters ganglia and then reaches the effector organ. The nerve-fibre coming up to ganglia is termed as pre-ganglionic fibre; while the nerve from ganglia to the effector organ is called as post-ganglionic fibre. In case of SNS, post-ganglionic fibres are usually long except in the case of adrenal medulla. Unlike this, in case of PSNS, pre-ganglionic fibres are relatively long and post-ganglionic fibres are relatively short. The somatic nervous system differs from both SNS and PSNS in not having ganglia before reaching the effector organ. Difference between sub-sections of nervous system is depicted in Fig. 3.2. Distribution of cholinergic and adrenergic neurons in PNS.



ACh – Acetylcholine; NE – Norepinephrine, E-Epinephrine, DA-Dopamine;

N_M – Nicotinic cholinergic receptor (muscular type) at neuromuscular junction (NMJ);

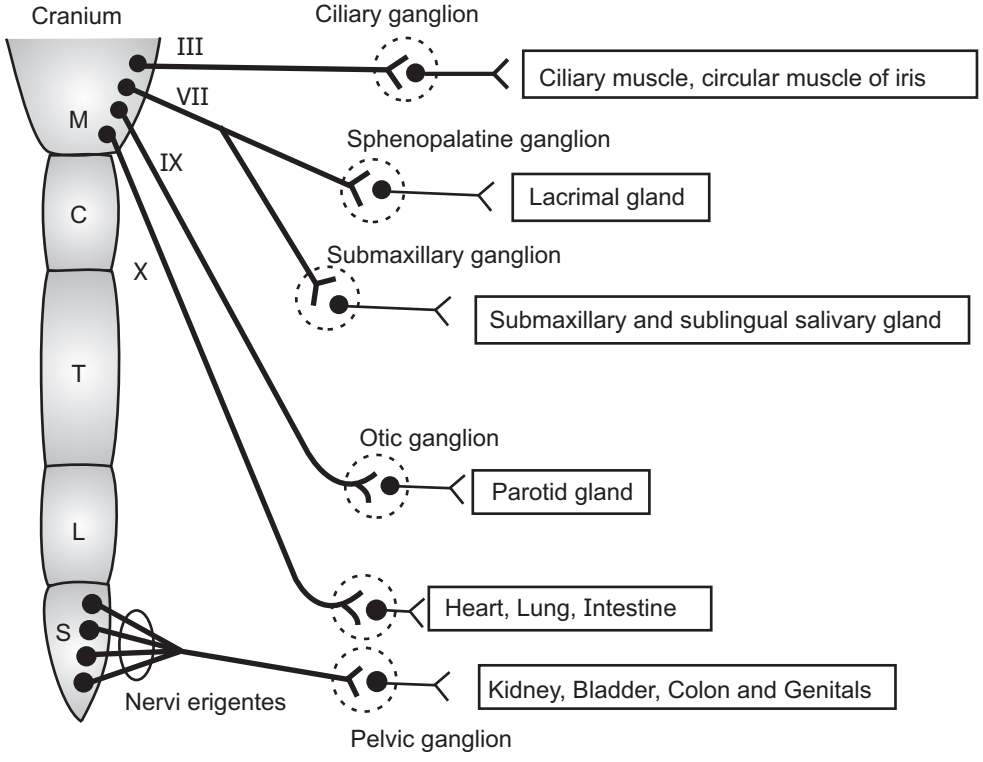
N_N – Nicotinic cholinergic receptor at ganglia (neuronal type); α_1, α_2, β_1, β_2, β_3 – Alpha and beta adrenergic receptor subtypes; M_1 to M_5 – Muscarnic cholinergic receptor subtypes; D_1 and D_2 – Dopamine receptor subtypes at renal vasculature; NEJ – Neuroeffector junction at the smooth muscle of the effector organ.

Fig. 3.2: Distribution of cholinergic and adrenergic neurons in PNS

The entire length of CNS including brain and spinal cord can be divided in to four following sub-sections:

- **Cranial:** related to brain,
- **Thorax:** related to upper part of spinal cord (up to diaphragm),
- **Lumbar:** related to lower part of spinal cord (next to diaphragm),
- **Sacral:** related to lowest tapering part of spinal cord.

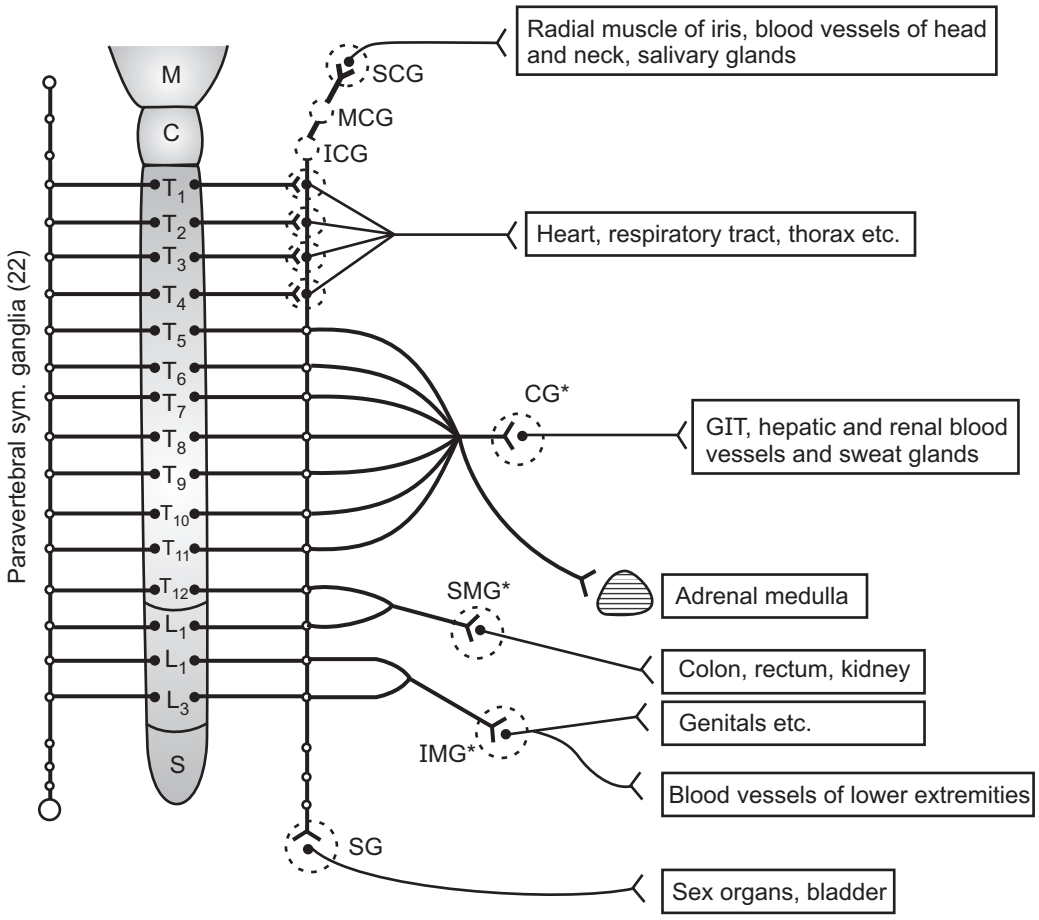
Out of these four parts, output of cranial and sacral region, called as cranio-sacral belongs to PSNS. The output of thoracic and lumbar region, called as thoracico-lumbar belongs to SNS. The origin of nerves related to PSNS and SNS and their connection to effector organs is depicted in Figs. 3.3 and 3.4.



Key: M–Medullary; C – Cervical; T-Thoracic; L-Lumbar; S-Sacral

myelinated preganglionic parasympathetic fibres. myelinated postganglionic parasympathetic fibres (to ciliary muscle). non-myelinated postganglionic parasympathetic fibres. Note that, preganglionic parasympathetic fibres are long while postganglionic parasympathetic fibres are short. Also, the parasympathetic ganglia related to III, VII, IX and pelvic nerves are lying close to effector organ while that related to X (vagus) nerves are embedded within the wall of the effector organ.

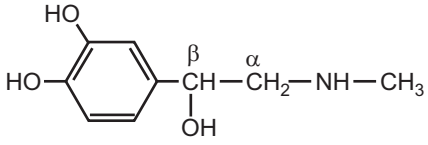
Fig. 3.3: Parasympathetic nervous system and its effector organs



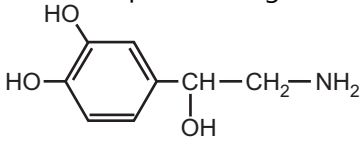
Key: preganglionic neuron; postganglionic neuron; * – prevertebral ganglia (not bilaterally paired); SCG – Superior cervical ganglia; MCG – Middle cervical ganglia; ICG – Inferior cervical ganglia; CG – Goeliac ganglia; SMG – Superior mesenteric ganglia; IMG – Inferior mesenteric ganglia; SG – Sacral ganglia; M – Medulla; C – Cervical; T – Thoracic; L – Lumbar; S – Sacral. Although paravertebral sympathetic ganglia (22) chain is bilaterally paired, yet for convenience, the innervation has been shown only on the right side of the figure.

Fig. 3.4: Sympathetic nervous system and its effect or organs

There is one more difference between PSNS and SNS. After stimulation of a nerve, a specialised chemical is secreted at the nerve ending. The chemical is responsible for transmission of information from nerve to effector organ. The specialised chemical is termed as neurotransmitter (NT). NT for PSNS and SNS are different. Acetyl choline (ACh) is the NT for PSNS. Nor-adrenaline/nor-epinephrine (NA) and adrenaline/epinephrine (A) are neurotransmitters of SNS. Structures of various NTs in ANS are depicted in Fig. 3.5.



(a) Structure of Adrenaline (Epinenphrine)



(b) Structure of Nor-adrenaline (Norepinephrine)

Fig. 3.5: Structure of ACh

3.2.2 Functions of ANS

In general, stimulation of SNS promotes catabolism; while stimulation of PSNS promotes anabolism. However at different organs, the effects are apparently contradictory. This is not true for every organ as observed in table 3.1. In reality, effects of stimulation of SNS and PSNS are complimentary to each other so that either of them may be activated depending on metabolic need of the body. Usually, SNS is called as the system of fight and flight indicating that, it is stimulated when the need of metabolic energy is very high. On the contrary, PSNS is stimulated after consumption of food so that anabolic activity leading to build up of energy is stimulated.

Table 3.1 lists gross effects of stimulation of ANS at the level of different organs.

Table 3.1: Summary and comparison of effects of ANS stimulation

Organ	Sympathetic stimulation	Parasympathetic stimulation
HEART		(Vagal fibres do not reach ventricles)
Rate	Increased; (Positive chronotropy)	Decreased; (Negative chronotropy)
Conductivity	Increased	Decreased (in SA node, atrium and AV node only)
Contractility	Increased (Both atrium and ventricle; positive ionotropy)	Decreased in atrium; no effect on ventricle
Cardiac output	Increased	Decreased
BLOOD VESSELS		
Arterioles of		
Coronary	Constriction; ultimate dilation due to other effects	No effect except erectile tissue-vasodilation; erection; salivary vaso-dilation
Skin	Constriction	-
Splanchnic	Constriction	-
Skeletal muscles	Dilation	-
Veins	Constriction/Dilation in some vessels	No effect
BRONCHIAL TREE		
Smooth muscles	Relaxation (broncho-dilatation)	Constriction (broncho-constriction)
Bronchial glands	Increased/decreased secretion	Increased secretion

contd. …

GASTRO-INTESTINAL TRACT		
General smooth muscles	Relaxation; decreased peristalisis	Contraction; increased peristalisis
Sphincters	Contraction	Relaxation
Exocrine glands	Variable (increase/decrease)	Increased secretion
IEYE	Dilation of pupils (mydriasis), ciliary relaxation	Constriction of pupil (miosis), ciliary constriction
SKIN		
Hair	Piloerection (raising of hair)	Variable
Sweat gland	Sweating	No effect
KIDNEY	Rennin production; renal vasoconstriction	Variable
UTERUS	Contraction in pregnant; relaxation in non-pregnant	Unpredictable
URINARY BLADDER	Contraction of sphincter; relaxation of detrusor; urinary retention	Evacuation of bladder
MALE SEX ORGAN	Contraction of vas and other ducts; ejaculation	Erection of penis
LIVER	Glycogenolysis	Variable

Receptors

The variation in actions of different neurotransmitters is primarily because of presence of different sub-types of receptors which execute the biological action. Receptors are located on the cell membrane of effector cells like smooth muscles/cardiac muscles/exocrine glands etc. Sub-types of PSNS and SNS are mentioned below:

PSNS

Acetyl choline is the neurotransmitter of PSNS. Hence, the receptors are called as cholinergic/cholinomimetic/cholinoceptive. There are two major varieties of the receptor: muscarinic (M) and Nicotinic (N).

Musarinic receptors are found on the cell membranes of effector cells of smooth or cardiac muscle, bronchial or gastrointestinal tract glands.

They are further sub-classified in to two sub-types: M_1 and M_2. M_1 receptors are present in the synapses of the brain. They are also present in enteric nervous system (ENS), especially in relation to parietal cells of stomach. M_2 receptors are present in other effector cell membranes of smooth or cardiac muscles, glands etc.

Nicotinic receptors are of two types: N_N and N_M. Nicotinic neuronal (N_N) are present in ANS ganglia while nicotinc muscular (N_M) are present in the neuromuscular junction and the skeletal muscle.

SNS

The neurotransmitters for SNS are adrenalin/nor-adrenalin/dopamine. There are two types of receptors for SNS: α and β. Further sub-types of α–receptors are α_1 and α_2 whereas sub-types of β are β_1 and β_2. α_1 receptors are found on smooth muscles of many arterioles, radial muscles of iris in eye, sphincters of gastrointestinal tract and urinary bladder, Arrectorus pilorum muscles of skin, vas deferns and seminal vesicle of male reproductive organs. α_2-receptors are scarcely located on skin and coronary arterioles. β_1 receptors are located in the myocardium and its conducting tissues (SA node, AV node, bundle of HIS). In kidney, they are responsible for increased production of renin. β_2-receptors are located on muscles of arterioles, vessels of lungs, veins, ciliary muscles of eye, bronchial muscles and glands, smooth muscles of gastrointestinal tract, uterus, detrusor muscle of urinary bladder and liver. Distribution of adrenergic receptors and their effects are summarised in table 3.2.

Table 3.2: Adrenergic receptors; their distribution and functions

Receptors	Distribution	Effects of stimulation
α_1	Most vascular smooth muscles	Vasoconstriction, raised peripheral resistance
α_1	Arrectorus pilorum	Piloerection
α_1	Dilator pupillae	Pupillary dilation
α_1	Liver (rat)	Glycogenolysis (rat)
α_2	Some CNS synapses	Stimulation causes inhibition of vasomotor centre and bradycardia
α_2	Platelets	Aggregation
α_2	Some vascular smooth muscles, not attached with nerve	Vasoconstriction
α_2	Adipose tissue	Inhibition of lipolysis
α_2	Pre-junctional membrane of post-ganglionic SNS and PSNS	Inhibition of release of neurotransmitter
β_1	Heart	Cardiac stimulation
β_1	Kidney	Stimulation of renin stimulation
β_1	Posterior pituitary	Stimulation of ADH secretion
β_1	Adipose tissue	Lipolysis
β_2	Bronchial smooth muscles	Dilatation
β_2	Smooth muscles of arterioles of skeletal muscles	Vasodilatation
β_2	Smooth muscles of uterus	Relaxation
β_2	Liver cells (human)	Glycogenolysis

3.3 NEURO-HUMORAL TRANSMISSION, CO-TRANSMISSION AND CLASSIFICATION OF NEUROTRANSMITTERS

The transmission of an impulse along a nerve fibre is an electrical phenomenon. Normally, a cell in resting condition is electronegative; indicating that extracellular charge is negative and intracellular charge is positive in nature. The difference in charge is along membrane of the cell. Whenever a cell is stimulated, the charge reverses at the point where transmission of an impulse is being forwarded. After some time, the cell restores electro-negativity. In contrast to this, at the nerve ending i.e. at synapses, the transmission is chemical in nature. A specialised chemical is secreted at the nerve ending. It is called as neurohumoral transmission. Certain chemicals support and augment action of neurotransmitters. They are called as co-transmitters.

3.3.1 Neuro-humoral Transmission and Co-transmission

Four processes occur in relation to nerve transmission in CNS. They are as follows:

(i) Neurotransmission

Neurotransmission occurs due to specialised chemicals called as neurotransmitters. They are synthesised in pre-synaptic neurons and are released in to synaptic cleft to rapidly stimulate or inhibit post-synaptic neurons or effector organs. The examples are: Acetyl choline, dopamine, nor-epinephrine/epinephrine, 5-hydroxytryptamine (serotonin), γ-amino butyric acid, glycine, glutamate, aspartate, endorphins, encephalins.

(ii) Neuromodulation

The chemicals causing neuromodulation are called as neuromodulators. They are released by neurons and astrocytes to produce slower pre-or post synaptic responses. Neuromodulation is related to long term changes in synaptic transmission, connectivity and efficacy following pathological damage as in epilepsy; or following physiological alterations in neuronal activity as in learning and memory. The examples of neuromodulators are: Carbon dioxide, adenosine, some purines, peptides, prostaglandins and nitric oxide.

(iii) Neuromediation

Neuromediation is caused by neuromediators, which are second messengers playing a crucial role in eliciting post-synaptic responses caused by neurotransmitters. The examples are: cAMP, cGMP and inositol phosphate.

Neuromodulators and neuromediators are termed as co-transmitting factors.

(iv) Mediation through neurotropic factors

Neurotropic factors are mainly released by CNS neurons, astrocytes and microglia. They act longer than neuromodulators to regulate the growth and morphology of neurons and control long term changes in brain like synaptic plasticity, remodelling, phenotype characteristics. They act by affecting gene transcription through tyrosine kinase-linked receptors. The examples are: Cytokines, chemokines, growth factors etc.

3.3.2 Classification of Neurotransmitters

Neurotransmitters can be classified in to four major classes as follows:

(i) Acetyl Choline (ACh)

Neurons producing acetyl choline are called as cholinergic neurons. They are present in cerebral cortex, ascending reticular axcting system, basal ganglia, limbic system, cerebellum and spinal cord. ACh modulates arousal, respiration, motor activity, vertigo and memory.

(ii) Amino acids

The central nervous system contains high concentrations of certain amino acids like glutamate, Gamma amino butyric acid (GABA). The dicarboxylic acids (glutamate and aspartate) produce excitation and monocarboxylic ω-amino acids (GABA, glycine, β-alanine and taurine) produce inhibition. It is interesting to note that inhibitor GABA is generated from excitant glutamic acid through the action of enzyme Glutamic-acid-decarboxylase (GAD).

(iii) Biogenic amines

Biogenic amine include dopamine, nor-epinephrine/epinephrine, 5-hydroxy tryptamine and histamine.

(iv) Peptides

Various peptides like vasopressin, oxytocin, tachykinins, neurotensin, vasoactive intestinal polypeptide (VIP), endogenous opioids like endorphins and encephalins, cholecystokinin, angiotensin II and neuropeptide Y perform various functions in different parts of the body. Some of them act as hormones.

Imbalance amongst various neurotransmitters and/or damage to the neurons or parts of CNS can lead to various disorders.

3.4 PARASYMPATHOMIMETICS, PARASYMPATHOLYTICS

Drugs related to autonomic nervous system (ANS) belong to two major divisions of ANS: PSNS and SNS. Each division is further sub-classified in to two types: those which mimic the actions of neurotransmitters or those which antagonise the actions of neurotransmitters. The drugs mimicking the actions of ACh are called as parasympathomimetics. The drugs blocking actions of ACh are termed as parasympatholytics. The drugs mimicking actions of nor-adrenalin/adrenalin are called as sympathomimietics. The drugs antagonising actions of nor-adrenalin/adrenalin are termed as sympatholytics.

3.4.1 Biosynthesis, Storage and Release of ACh

Acetyl choline, as such, is of no therapeutic use because of its ultra-short action. Its half life is of few seconds only due to rapid hydrolysis by the enzyme acetylcholinesterase. Chemically, ACh is the acetic ester of choline. See Fig. 3.6.

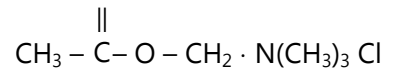


Fig. 3.6: Structure of acetylcholine chloride

Biosynthesis

The events related to biosynthesis of ACh along with sites of action of some drugs/toxins are summarised in Fig. 3.7. ACh is synthesised in the axon terminal by acetylation of choline with acetyl CoA (AcCoA). The reaction is catalysed by cytosolic enzyme named choline acetyl transferase (ChAT). Choline from extracellular fluid is actively transported inside the cytoplasm of cholinergic nerve terminal by a sodium-dependent transporter (CDT). The rate-limiting process in synthesis of ACh synthesis is transport of choline, the activity of which is regulated depending on the need of ACh being released. This process can be blocked by a group of drugs called hemicholiniums. (see Fig. 3.7)

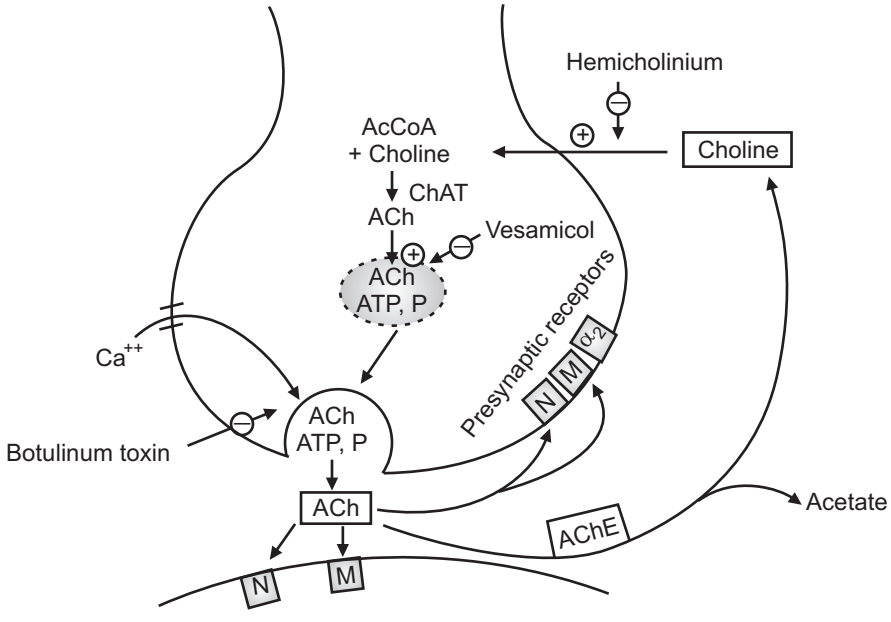


Fig. 3.7: Neurochemical events during synthesis, storage, release and degradation of ACh

AcCoA needed for biosynthesis of ACh is synthesised in the mitochondria from pyruvate by the action of enzyme pyruvate dehydrogenase (PDH). AcCoA is then transported out of the mitochondria in to the cytoplasm.

Storage

ACh, formed by the process discussed above, is actively transported in to vesicles by a transporter. This active vesicular uptake of ACh is selectively blocked by vesamicol (see Fig. 3.7). This results in slow development of neuromuscular block. ATP and peptides are also stored in the vesicles as co-transmitters.

Release

Arrival of an action potential at the nerve terminal causes an influx of calcium ions, which in turn triggers release of ACh by the process of exocytosis. This mechanism involves an interaction between the proteins associated with vesicles, called as synaptobrevin and the nerve ending membrane, called as syntaxin. The interaction results in fusion of vesicle and

nerve ending membrane, opening of a pore towards extracellular space and release of ACh. Botulinum toxin alters synaptobrevin to prevent release of ACh. Release of ACh, which requires nerve action potential through entry of calcium ions is prevented by local anaesthetics in a reversible manner. Tetrodotoxin binds to sodium channel irreversibly.

Metabolism

ACh is hydrolysed by the enzyme called as acetyl cholinesterase to choline and acetic acid. The hydrolysis terminates actions of ACh. It is the reason why duration of action of ACh is very less. (few seconds). Cholinesterase enzyme (ChE) is of two types:

(i) True Acetylcholine Esterase

It is a membrane bound enzyme located in the cholinergic synaptic cleft. It is specific only to ACh and methacholine. It does not hydrolyse other esters of choline. It is mainly located in neuronal membrane, cholinergic synaptic cleft and to a small extent in RBCs and placenta.

(ii) Plasma Choline Esterase (Pseudocholine esterase/Butyryl choline esterase)

It is synthesised in liver and found predominantly in plasma and intestine. It is not located in membrane. It hydrolyses other esters of choline also; e.g. succinyl choline, benzoyl choline and butyrl choline esters. There are genetic variants to this enzyme. Some persons, who have atypical pseudocholinesterase, show slow hydrolysis of succinyl choline, resulting in longer duration of action with prolonged apnoea after its use.

Actions of ACh are exhibited (see table 3.1; Effects of parasympathetic stimulation) through two types of receptors: Muscarinic and Nicotinic. The actions are outlined below.

Muscarinic Actions

There are three sub-types of muscarinic receptors: M_1, M_2 and M_3. M_1 receptors are located on sympathetic ganglia, gastric parietal cells and cerebral cortex. They mediate excitatory effects. M_2 receptors are located on myocardium, smooth muscles, pre-synaptic terminals of peripheral and central neurons. They exert inhibitory effects. M_3 receptors are located on glandular and visceral smooth muscles. Their activation results in excitatory effects, except for vasodilation due to release of nitric oxide from neighbouring endothelial cells.

Effects on Different Organs

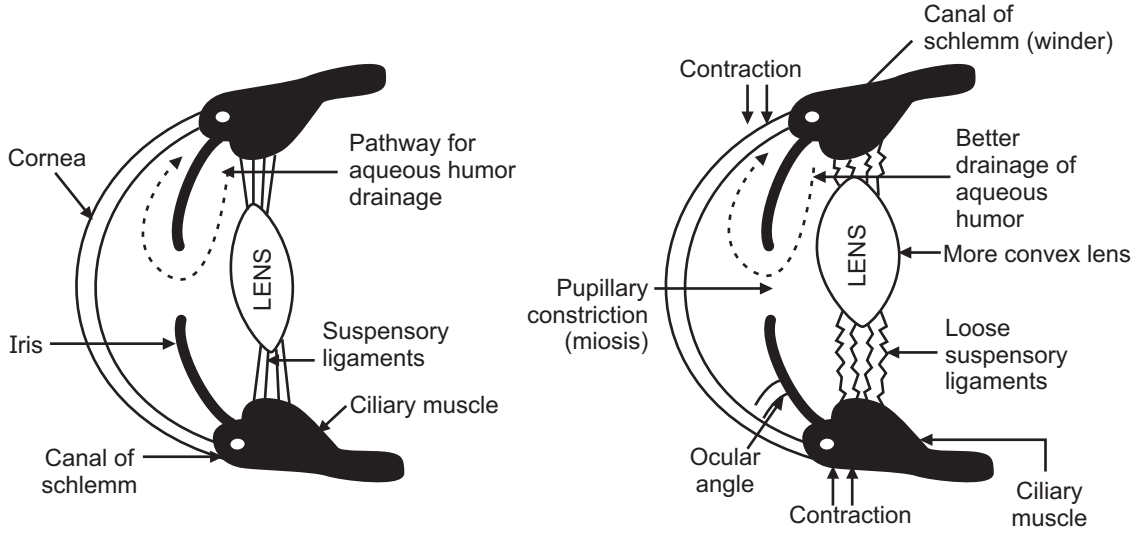
The codes MiSLUBD and DHR help us to remember the effects of stimulation of PSNS. The explanation for codes is as follows; Myosis (Mi), Salivation (S), Lacrimation (L), Urination (U), Bronchoconstriction (B), Defaecation (D), and Decrease in Heart Rate (DHR).

(i) Eye

Circular muscle of iris, ciliary muscle and lacrimal glands possess M_3 receptors. Radial muscle of iris and eyelid smooth muscle have no parasympathetic supply.

ACh causes contraction of circular muscle of iris and of the ciliary muscle. See Fig. 3.8. Contraction of circular muscle of iris causes myosis. Contraction of ciliary muscles makes the suspensory ligaments loose. As a result of this, the lens is made more convex resulting in reduction of focal length. The net result is accommodation of eye for near vision. In addition,

contraction of ciliary muscle, aided by stretching of pupil due to myosis, opens pores of the canal of Schlemm facilitating drainage of aqueous humour leading to reduction of intraocular pressure. (See Fig. 3.8). This action is particularly useful in patients of glaucoma, where intraocular pressure is increased due to accumulation of lacrimal fluid. Stimulation of M_3 receptors at lacrimal glands produces lacrimation, due to vasodilatation.



(a) Normal eye **(b) Eye after effect of ACh**

Fig. 3.8: Effect of released Acetylcholine on eye

(ii) Salivary glands

Salivary glands have M_3 receptors. Their stimulation produces watery saliva due to vasodilatation resulting from release of bradykinin.

(iii) Lungs

Smooth muscles of bronchii and mucus glands possess M_3 receptors. Stimulation of smooth muscles causes broncho-constriction. Stimulation of mucus glands causes increasd bronchial secretions. These effects together cause difficulty in breathing.

(iv) GIT

Smooth muscles of GIT, sphincters and gastric glands have M_3 receptors. However gastric parietal cells possess M_1 receptors. ACh causes activation of M_3 receptors causing increase in motility and tone of GIT smooth muscle, relaxation of sphincters and increased secretions from gastric glands, together leading to defaecation. Stimulation of M_1 receptors promotes secretion of gastric acid. All actions of ACh together help in the process of digestion and promote peristalisis.

(v) Heart

PSNS supply only up to SA node, atria and AV node. In contrast, the ventricular myocardium has no innervation of PSNS; however they have muscarinic receptors. At SA node, atria and AV node there are M_2 receptors, stimulation of which causes decrease in the heart rate. This is termed as negative chronotropy. In addition, there is decrease in force of

contraction which is termed as negative ionotropy. M_2 receptor activation at AVA node causes decrease in conduction velocity and increase in the refractory period. Thus, ACh causes decrease in activity of heart.

(vi) Blood vessels

Arteries have no PSNS innervations, but they have M_2 receptors. As a result, administration of external ACh causes a transient but a marked fall in blood pressure due to vasodilatation. However, this does not occur by stimulation of PSNS. The fall in blood pressure evokes baro-receptor reflex, resulting in compensatory sympathetic discharge at the heart. As a result, ACh administration by intra-venous route initially causes bradycardia, but after some timer it is followed by tachycardia. Systemic veins have neither PSNS innervations nor M_3 receptors.

(vii) Urinary bladder

Both the detrusor muscle and the sphincter have M_3 receptors. Their stimulation causes contraction of detrusor muscle and relaxation of sphincter, leading to urination due to effects on urinary bladder.

(viii) Pancreas

Acini cells in the pancreas have M_3 receptors and its activation causes increased secretion of pancreatic juice. There is no effect on β-cells of islets of Langerhans. Thus, there is no effect on secretion of insulin due to PSNS stimulation.

(ix) Male sex organs

Vascular bed of erectile tissue is dilated due to PSNS stimulation while venous sphincters are closed leading to erection of penis. The effect is mediated through M_3 receptors.

(x) Sweat glands

These glands have M_3 receptors. Activation of these receptors leads to increased sweating. The innervation is sympathetic in origin but cholinergic in character.

(xi) CNS

On CNS, there are complex stimulatory effects due to PSNS. Ataxia, behavioural disturbances and restlessness are mediated through nicotinic receptors; while tremors and convulsions are mediated through muscarinic receptors.

On liver and kidney there is no parasympathetic innervations; hence PSNS stimulation does not cause any effect on liver and kidney.

(xii) Nicotinic actions

Nicotinic receptors are present at neuromuscular junction (NMJ/N_M receptors), at all autonomic ganglia (N_N) receptors and in brain. Activation of N_M receptors results in contraction of skeletal muscles. Activation of N_N receptors provides the transmission of impulse through autonomic ganglia and firing of post-ganglionic neuron. In brain, the nicotinic receptors are located on pre-synaptic membrane and facilitate release of dopamine and glutamate.

Actions of ACh through nicotinic receptors need a special mention. The actions include:

- Stimulation of SNS as well as PSNS ganglia occurs through nicotinic (N_N) receptors, which ultimately results in discharge of ACh in case of PSNS and NE/E in case of SNS from the post-ganglionic neurons. Most organs have innervation of both PSNS and SNS. The net result is dependent on the fact that domination of either PSNS or SNS for that organ. Thus in case of blood vessels, which are dominated by SNS, activation of nicotinic receptor causes vasoconstriction. Unlike this, GIT is dominated by PSNS. Hence ACh increases the motility and secretions because of PSNS discharge. It is to be noted that all ganglionic transmissions (either PSNS or SNS) is mediated through nicotinic receptors of ACh.
- Stimulation of adrenal medulla leads to discharge epinephrine/adrenalin (E/A), because adrenal medulla is a modified ganglion where ACh serves as a neurotransmitter stimulating nicotinic (N_N) receptors present on it.
- Stimulation of nicotinic receptors at the neuromuscular junction (NMJ) results in spasm of the skeletal muscle. The action is mediated through N_M receptor. However, prolonged activation results in fasciculations followed by paralysis.

3.4.2 Parasympathomimetics

Parasympathomimetics are classified in two categories: (i) directly acting and (ii) indirectly acting. Those drugs which act by their interaction directly on receptors of ACh fall in this category. Unlike this, drugs which inhibit the enzyme cholinesterase and thereby increase the concentration of ACh fall in this category.

[I] Directly Acting Parasympathomimetics

As mentioned earlier, these drugs directly activate ACh receptor and therefore can cause ACh- like action even after denervation (loss of PSNS nerves). The prototype agent in this category is ACh. They are sub-classified under three categories as follows:

1. Acetyl choline (ACh): Prototype

ACh is not used clinically because of its ultra-short action (few seconds only)

2. Synthetic choline esters

Methacholine and carbechol are no longer used clinically.

- Methacholine
- Carbachol
- Bethanechol

Bethanechol is resistant to hydrolysis by true cholinesterase and pseudocholinesterase. Hence, it has relatively longer half-life. It mainly acts on muscarinic receptors, particularly at urinary bladder and GIT; but it has no action on nicotinic receptors.

Uses:

- It is useful to treat urinary retention. For acute retention, 2.5 mg is given sub-cutaneously. In chronic cases, 10-15 mg is given orally and is slowly withdrawn.
- It is useful to treat atony (loss of tone) of GIT, if there is no obstruction e.g. to expel gases from intestine before radiological examination. For this purpose, it is given orally in a dose of 10-20 mg three times a day.
- It is useful to treat dysfunction of salivary glands, xerostomia (reduced secretion of salivary glands).

Precautions:

It should not be given by intravenous route. Sudden rise in plasma concentration can cause cardiovascular collapse.

Contra-indications and undesirable effects:

- The contra-indications are as follows:
  - Hyperthyroidism
  - Bronchial asthma
  - Peptic ulcer
  - Myocardial infarction
- The undesirable effects include CNS stimulation, myosis, spasm of accommodation for distant vision, broncho-constriction, abdominal cramps, flushing, sweating and salivation.

Bethanechol is available as 25 mg tablet.

3. Natural alkaloids

- Muscarine
- Nicotine
- Arecoline
- Pilocarpine (Trade name: **PILOCAR, PILAGAN, PILOPRESS, LOCARP**)

Muscarine, nicotine and arecoline are not used clinically. Muscarine is obtained from poisonous mushroom *Amanita muscaria*. Nicotine is present in tobacco and Arecoline is the main alkaloid present in betel nuts.

Pilocarpine is the main alkaloid obtained from leaves of the shrub *Piolcarpus jaborandi*. It is a tertiary amine and crosses blood-brain barrier. It has a primary muscarinic action on M_3 receptors. It has also a mild nicotinic action on N_N receptors of ganglia. It is too toxic for systemic use. One of the important adverse reactions of systemic use of pilocarpine is pulmonary oedema. It has following therapeutic uses:

- **Ophthalmic use**

  As a 0.5-4% solution, it is instilled in to the eye, it is used for initial treatment of open angle glaucoma. It reduces intra-occular pressure within few minutes and lasts for 4-8 hours.

  It produces miosis and counteracts mydriasis produced by atropine.

  It breaks adhesion between the iris and the lens, as in iridocyclitis, as a local solution.

- **Salivary secretion**

  It promotes salivary secretion and acts as sialagogue. In oral dose of 5-10 mg, it can be used to stimulate salivary secretions in patients after laryngeal surgery and to treat xerostomia resulting after radiotherapy.

It is available as eye drops of 1%, 2% or 4%.

- Miscellaneous
  - Tremorine
  - Oxotremorine

    Tremorine and oxytremorine are synthetic tertiary amines. Oxotremorine is an active metabolite of tremorine. They are not used clinically. They are used as research tools to stimulate Parkinson-like symptoms in animal models.

- Cevimeline

  In a oral dose of 30 mg, it is used to treat xerostomia in patients undergoing cancer chemotherapy or those suffering from Sjogren syndrome. Adverse effects include decreased visual acuity in central field and diarrhoea.

[II] Indirectly Acting Parasympathomimetics:

These agents inhibit the enzyme acetyl cholinesterase (AChE), located in synaptic cleft. The enzyme is responsible for rapid hydrolysis of ACh. As a result, these drugs prolong the action and increase indirect availability of ACh at muscarinic and /or nicotinic receptors. These drugs do not show any activity on dennervated organs because there is no inherent release of ACh in them.

During degradation, ACh combines with AChE through electrostatic attraction at two points: anionic site and esteratic site. See Fig. 3.9. In structure of ACh, there is one quarternary ammonium and there is one ester. Quarternary ammonium binds to anionic site and ester binds to hydroxyl group of serine residue of AChE at the esteratic site. Initially, an enzyme-substrate complex (AChE-ACh) is formed. This is the first step of the reaction (step I). It is followed by cleavage of the ester linkage (O-CO-CH_3) with generation of choline. This is called as step II. In the last step III reaction, remaining acetylated enzyme (AChE) reacts with water to regenerate the active enzyme AChE. See Fig. 3.9.

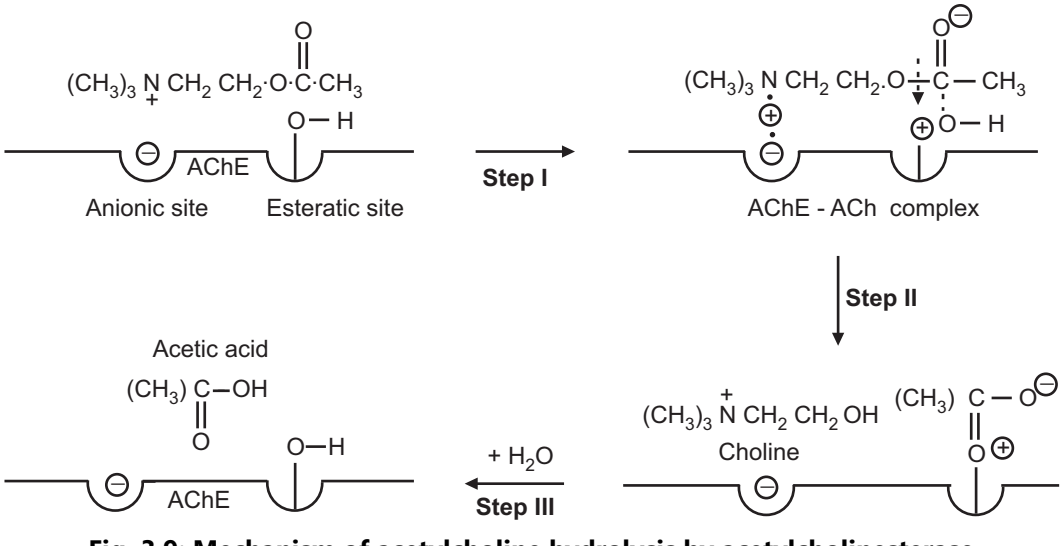


Fig. 3.9: Mechanism of acetylcholine hydrolysis by acetylcholinesterase

The reversible anticholinesterase drugs bear structural similarity with ACh. They combine with the anionic and the esteratic sites of ACh. This complex is less easily hydrolysed as compared to AChE-ACh complex. As a result, the enzyme is temporarily inhibited and prolongs the action of ACh. The action is due to slow recovery of AChE. Reversibility of anticholinesterase with AChE and its renal elimination after detachment of AChE account for its duration of action.

Following drugs belong to this category:

- Physostigmine **(ESERINE)**
- Neostigmine **(PROSTIGMINE, TILSTIGMIN, MYOSTIGMIN)**
- Pyridostigmine **(PIRIDO, DISTINON, MYESTIN)**
- Edrophonium
- Ambenonium
- Demecarium
- Rivastigmin
- Distigmin

Amongst these drugs, only physostigmin is a naturally occurring alkaloid. All other drugs are synthetic quarternary ammonium compounds. They exist in ionised form and do not cross blood-brain barrier. As a result, synthetic drugs have very limited action on CNS.

(i) Physostigmine (Eserine)

It is an alkaloid obtained from the dried ripe seeds of *Physostigma venenosum*. It is a tertiary amine; it is highly lipid soluble. It shows better absorption in the body and shows action even on CNS. It has marked muscarinic effects on M_1 and M_3 receptors and it also stimulates ganglia. However, its nicotinic effects on motor end plate (NMJ) are negligible. Because of its systemic toxicity, it is preferred for local use.

Uses:

- Ophthalmic uses of physostigmin resemble to uses of pilocarpine. It is used for following conditions:
  - For reversal of mydriasis
  - To prevent adhesions between pupil and lens
  - For the treatment of open angle glaucoma

  It is highly lipid soluble, relatively toxic and poorly tolerated. Its ophthalmic preparations are not used in India; however it is available as 0.25% and 0.5% eye drops elsewhere.
- Belladona (atropine) poisoning:
  - Physositgmine is a specific antidote for atropine (datura) poisoning or for poisoning by any other parasympatholytic/anticholinergic drug. It is useful for poisoning by tricyclicantidepressants, like imipramine which shows anticholinergic action as an adverse effect. Physostigmine, being a tertiary amine alkaloid passes blood-brain barrier and can antagonise central as well as peripheral toxicity of atropine. 2 mg of physostigmine is given either intravenously or intramuscularly. Parenteral preparation of physostigmine is not available in India.

(ii) Synthetic Quaternary Compounds

This group includes all reversible anticholinesterases under the category of indirectly acting parasympathomimetics. It includes:

- Neostigmine,
- Pyridostigmine,
- Erophonium,

- Ambienonium,
- Demecarium,
- Rivastigmine and
- Distigmine.

All synthetic compounds mentioned above are quartenary ammonium compounds. They are least absorbed and do not cross blood-brain barrier. These drugs are useful on neuromuscular junction as skeletal muscle relaxants. Low doses of these drugs prolong and intensify the actions of physiologically released ACh at motor end plate. It results in strengthening of muscles weakened by curare-like drugs or by a disease called as myasthenia gravis. In addition, these drugs possess dire weakened by curare-like drugs or by a disease called as myasthenia gravis. In addition, these drugs possess direct action at nicotinic receptors of NMJ (N_M) which also contributes to their effectiveness in treatment of myasthenia gravis.

Uses:

Their therapeutic uses are as follows:

- **Treatment of myasthenia gravis**
  It is discussed under Section 3.6.1.
- **Paralytic ileus and atony of urinary bladder**
  Reduced peristalisis in GIT can lead to paralytic ileus. Atony (loss of tone) of urinary bladder leads to urinary retention. These effects can be relieved by 0.5-1 mg sub-cutaneous dose of neostigmine. A longer acting drug, distigmine can be used in a dose of 5 mg orally every second day after neostigmine.
- **Glaucoma**
  0.25-0.5% solution of demecarium is applied topically, in the eye, twice a week. The drug has longer duration of action.
- **Post operative decurarization (treatment of curare poisoning)**
  0.5-1 mg intravenous neostigmine or 10 mg intravenous edrophonium, along with atropine, rapidly reverses muscle paralysis induced by d-tubocurarine given during anaesthesia.
- **Paroxysmal atrial and supra-ventricular tachycardia**
  Edrophonium is preferred; however it is now replaced by calcium channel blockers.
- **Treatment of snake bites (as accessory drug)**
  The classical treatment for poisoning by snake bite is use of anti-snake venom (ASV). The final cause of death by snake poisoning is respiratory paralysis. Hence reversible anticholinesterases can be used for a temporary reversal of respiratory paralysis.

Neostigmine is available as 15 mg tablet and 0.5 mg/ml injection. Pyridostigmine is available as 60 mg tablet.

Irreversible inhibitors of AChE

Irreversible AChE blockers are organo-phosphorous compounds. They phosphorylate esteratic site of AChE irreversibly by forming a covalent bond. They have no clinical use. They are known for their toxicological effects and their toxicity is treated by oximes.

3.4.3 Parasympatholytics

ACh has got two receptors: muscarinic and nicotinic. The drugs which block muscarinic receptors are discussed in this sub-section. In addition, drugs which block nicotinic (N_N) receptors are called as ganglion blockers, while drugs blocking synaptic transmission at NMJ are called as neuromuscular blocking drugs or skeletal muscle relaxants.

Classification and examples of muscarinic receptor antagonists are shown below:

1. **Natural alkaloids**

   Atropine (dl-hyoscyamine) and Scopalamine (l hyoscine)

2. **Semi-synthetic derivatives**

   Homatropine and its salts, Atropine methonitrate, Hyoscine methylbromide, Benztropine, Ipratropium bromide, Tiotropium bromide

3. **Synthetic derivatives**

   Eucatropine, Cyclopentolate, Tropicamide, Dicyclomine, Flavoxate, Oxybutinin, Pirenzepine, Telenzepine, Trihexyphenidyl, Procyclidine, Propantheline, Drotaverine, Oxyphenonium, Glycopyrrolate, Clinidium, Tolterodine, Pipenzolate, Valethamate

4. **Other drugs showing anti-muscarinic action**

   Anti-histamines: Diphenhydramine, Promethazine, Orphenadrine

   Anti-psychotics: Phenothiazines: Chlorpromazine, Thioridazine

   Butyrophenone: Haloperidol

   Tricyclic-antidepressants: Amitriptyline, Imipramine

Chemistry of Antimuscarinic Drugs (Parasympatholytics)

Atropine and Scopolamine are naturally existing alkaloids obtained from the family of solanaceae plants. Atropine is obtained from *Atropa belladonna* or from *Datura stramonium*. Naturally occurring atropine is l-hyoscyamine but is racemised immediately to di-hyoscyamine (commercial atropine). The anti-muscarinic activity resides only in l-hyoscyamine. Scopolamine is obtained from *Hyoscyamus niger* and also from *Scopolia carniolica*. Scopolamine is l-hyoscine and is several more potent than its d-isomer.

Chemically, both atropine and scopolamine are organic esters formed by combination of an aromatic acid-tropic acid - and an organic base which is either tropine (in atropime) or scopine (in scpolamine). Scopine differs from tropine in having an epoxide group (i.e. oxygen bridge) between carbon atoms C6 and C7. See Fig. 3.10.

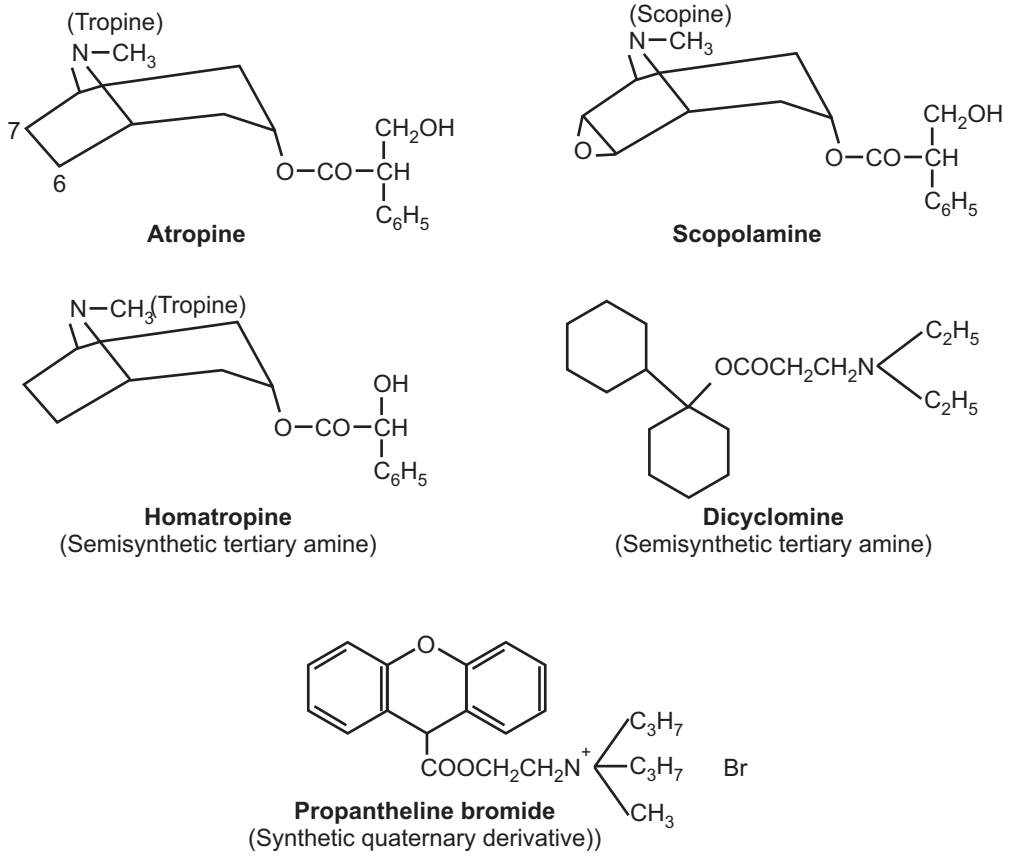


Fig. 3.10: Chemical structures of some antimuscarinic drugs (Parasympatholytics)

2. Semi-synthetic derivatives are obtained by combining natural organic base (tropine or scopine) with any organic acid (e.g. mandelic acid as in homatropine).
3. Synthetic derivatives do not have tropine/scopine portion in their chemical structure. Both semi-synthetic and synthetic derivatives are either tertiary amines or quartenary amine salts.

Pharmacology of Antimuscarinic Agents

Pharmacokinetics

- **Absorption**

  Atropine, scopolamine and other tertiary amines are well absorbed from GIT and can easily cross conjunctival membrane. If prepared in a suitable vehicle, the drugs can be absorbed by transdermal route (e.g. scopolamine transdermal patch). Quaternary amine salts are poorly absorbed and do not cross blood-brain barrier because of their poor lipid solubility.

- **Distribution**

  Except for quaternary compounds, other anti-muscarinic drugs get widely distributed in all compartments of body. Scopolamine is rapidly and fully distributed in CNS and has greater effects in CNS.

- **Metabolism**

  About 50% of atropine and 80% of scopolamine is metabolised in the liver as conjugates. Rabbits are resistant to action of atropine because they possess an enzyme called atropine esterase which degrades atropine at a faster rate.

- **Excretion**

  About 50% of atropine is excreted unchanged in urine. Half-life ($t_{1/2}$) is about 3 hours. Atropine effects decline rapidly in all organs except the eye, where the effects last for about 72 hours or even longer.

Pharmacodynamics

Atropine and related drugs compete with ACh or other muscarinic agonists on the muscarinic receptor (M_1, M_2, M_3). Thus, these drugs are competitive antagonists of ACh. The antagonism is reversible in nature. When atropine binds to muscarinic receptors, it blocks all actions of ACh (e.g. release of IP_3 from M_1 and M_3, activation and inhibition of adenylate cyclase from M_2 receptor activation). Both atropine and scopolamine are non-selective antagonists and block all (M_1, M_2, M_3) muscarinic receptors. From among synthetic drugs, selective antagonists for each of these sub-types of receptors are now available. Pirenzepine and Telenzepine block M_1 receptors. Tripitramine blocks M_2 receptors while Tolterodine blocks M_3 receptors.

The effectiveness of anti-muscarinic drugs varies according to the tissues. The sensitivity of tissues varies as follows: sweat, bronchial and salivary glands have highest sensitivity followed by heart and eye followed by urinary bladder and GIT, followed by gastric glands. The most likely determinant for sensitivity seems to be the extent of parasympathetic tone by which the particular organ is governed. Higher the tone, more will be the sensitivity of the organ.

Effects on different organs are described below:

1. Central Nervous System (CNS):

Atropine has no detectable CNS effects in low doses. In therapeutic doses, it has mild stimulant effect on medullary centres. In higher doses, it stimulates higher cerebral centres and in toxic doses it causes restlessness, irritability, disorientation, hallucinations and delirium. With still higher doses, the stimulation is followed by depression leading to circulatory collapse, paralysis, respiratory failure leading to death.

Scopolamine has greater permeability through blood-brain barrier. Scopolamine in low as well as therapeutic doses normally causes CNS depression. In therapeutic doses, it produces drowsiness, amnesia, fatigue, dreamless sleep and depression of vomiting centre (anti-emetic effect) by suppressing vestibular excitation. In toxic doses, scopolamine causes agitation, excitement and hallucinations. With still higher doses, the stimulation is followed by depression leading to coma and respiratory failure.

Therapeutic uses

- **Motion sickness**

Whenever the body is rotated or its equilibrium is disturbed, the vestibular apparatus sends nauseating signals to vomiting centre. ACh serves as an excitatory neurotransmitter in such emesis. It is called as motion sickness. Scopolamine in doses of 0.6-1.0 mg given sub-cutaneously is effective. Transdermal patches of scopolamine are also available. When applied on skin behind the ear, it provides 0.5 mg of scopolamine over a period of 3 days.

Hyoscine (scopolamine): **BELLOID, BUSCOPAN, HYOSPAN** *is available as 10 mg tablet, 20 mg/ml injection.*

- **Parkinson's disease**

Tremors and rigidity in Parkinson's disease is due to domination of cholinergic system over dopaminergic system in basal ganglia. Hence, muscarinic receptor antagonists are used to treat extra-pyrimidal side effects associated with anti-psychotic drug therapy. Centrally acting anti-cholinergic drugs like Benztropine (1-5 mg/day), Benzhexol (trihexyphenidyl, 2-10 mg/day), procyclidine (5-15 mg/day), Biperiden (2-10 mg/day) are given orally.

Trihexephenidyl: **PACITANE, PARKIN, PARKITANE** *is available as 2 mg tablet and Procyclidine:* **KEMADRIN, DINE** *is available as 5 mg tablet.*

- **Diagnosis of Alzheimer's disease (AD)**

Administering a low dose of short acting anti-muscarinic drug Tropicamide in eyes, causes marked dilation of the pupil due to changes in receptor sensitivity associated with AD. The observation is used to diagnose AD.

2. Eye:

Circular muscle of iris, ciliary muscle and lachrymal glands possess M_3 receptors. Atropine or other tertiary amine block M_3 receptors and produce mydriasis due to unopposed sympathetic dilator activity, caused by α_1-receptors located on radial muscle of iris. The wide pupillary dilatation causes photophobia. Blockade of M_3 receptors abolishes responses of cholinergic stimulation. As a result, suspensory ligaments get tightened, resulting in less convex lens and the eyes get set for distant vision. See Fig. 3.8. This is called as paralysis of accommodation or cycloplegia. It also weakens drainage of aqueous humour through canal of Schlemm. Hence, patients receiving large doses of atropine or tertiary amines complain of dry or sandy eyes.

Therapeutic uses

- **Mydriatic**

Opthalmoscopic examination of the retina is greatly facilitated by mydriasis. Accurate measurement of refractive error needs ciliary paralysis. Hence, anti-muscarinic drugs are given as eye drops during examination of retina. Drugs like Tropicamide, Eucatropine or Cyclopentolate are preferred for this purpose. The details are given in table 3.3.

Table 3.3 Characters of anti-muscarinic drugs for ophthalmic use

Sr. No.	Drug	% concentration	Mydriasis duration	Cycloplegia duration
1	Atropine	1	7-10 days	7-12 days
2	Scopolamine	0.5	3-7 days	3-7 days
3	Homatropine	1-2	1-3 days	1-3 days
4	Eucatropine	2-5	12-24 hours	-
5	Cyclopentolate	0.5-1	24 hours	6-18 hours
6	Tropicamide	0.5-1	6-8 hours	6-8 hours

- **To prevent adhesions in inflammatory conditions of eye**

Anti-muscarinic mydriatics can be alternated with myotics like Pilocarpine to prevent adhesions between the iris and anterior surface of the lens to treat conditions like iridocyclitis, iritis, uveitis. A longer acting drug like Homatropin with Pilocarpine is useful in this condition.

Tropicamide: **OPTIMIDE, TROMIDE, TMIDE** *and Cyclopentolate:* **CYCLATE, CYCLOGIK, DILATE** *are available as 1% eye drops; Homatropine:* **HOMIDE** *is available as 2% eye drops.*

3. CVS

Atropine in a dose of 0.4-0.6 mg by IM/SC route causes transient bradycardia initially. It is caused by blockade of presynaptic M_1 receptors causing release of ACh on SA node. However, additional doses of atropine cause tachycardia due to blockade of vagal effects on M_2 receptors on SA node. Atropine induced tachycardia is notable in teenagers because their vagal tone is high. Ventricles are less affected by atropine.

Although all blood vessels contain muscarinic receptors, they are devoid of parasympathetic innervation. Hence, atropine causes very little effect on blood pressure. Higher doses of atropine dilate cutaneous blood vessels, especially of the face. This is called as atropine flush. Atropine also induces fever but it is not associated with sweating.

Therapeutic uses

Adequate doses of atropine can abolish reflex vagal cardiac slowing or acysto. In some cases, atropine may reduce the degree of heart block. Atropine should be given cautiously to patients of sinus bradycardia, because low doses aggravate bradycardia. Higher doses causing tachycardia may extend the infarct by increasing oxygen demand.

4. Respiratory System

Both smooth muscle and secretory glands of pulmonary airway receive vagal parasympathetic innervation and have M_3 receptors. Atropine-like drugs inhibit secretions of nose, mouth, pharynx and bronchi causing dryness. These drugs reduce laryngospasm during general anaesthesia. Drying of mucus secretions and suppression of mucociliary clearance are the adverse effects of atropine-like drugs. Anticholinergic drugs like Ipratropium/Tiotropium/Oxitropium antagonise broncho-constriction induced by histamine, bradykinin and $PGF_{2\alpha}$. They block indirect effects of inflammatory mediators and have lesser drying effect on sputum. They do not inhibit mucociliary movements.

Bronchial asthma and chronic obstructive pulmonary disease (COPD)

Ipratropium-like drugs are preferred for COPD, because of advantages mentioned earlier. Ipratropium can be given as a nebulised broncho-dilator in acute attack of asthma along with β_2 adrenoceptor agonists like Salbutamol. Tiotropium has a longer duration of action than Ipratropium.

Ipratropium: **IPRAVENT, IPRATOP** *is available as 20 µg/puff metered dose inhaler. Tiotropium:* **TIATE, TIOVA** *is available as 18 µg rotocaps (1 rotocap/inhalation).*

- **Pre-anaesthetic medication**

Due to reduced bronchial secretions and to prevent excessive vagal effect on heart, drugs like atropine, scopolamine and glycopyrrolate are sometimes used as pre-anaesthetic agents. Non-irritating anaesthetic agents like Halothane/Enflurane have reduced use of atropine-like drugs. But, Scopolamine has an advantage because of its CNS depressant effects. Glycopyrrolate, in a dose of 0.1-0.3 mg IM causes less tachycardia and reduces bronchial and salivary secretions more effectively.

Glycopyrrolate: **GLYCOP, VAGOLATE** *is available as 0.2 mg/ml IV/IM injection. Atropine:* **ATROPINE SULPHATE, TROPINE** *is available as 0.6 mg/ml IM injection. Scopolamine is available as 10 mg tablet and 20 mg/ml IM injection. It is advised to give these drugs 30 minutes before aneathesia.*

5. GIT

Anti-muscarinic drugs can reduce basal secretions of gastric HCl by 40-50%. Basal secretions are blocked more effectively than that stimulated by food, alcohol or nicotine. Not only the volume of secretion but the total amount of H^+, HCO_3^-, pepsin and mucin are also reduced. The effects on salivary secretions are more marked. Due to dry mouth, swallowing and talking becomes difficult.

Anti-muscurinic drugs effectively reduce the tone and motility of GIT, right from stomach to colon. It results in prolongation of gastric emptying time, closure of sphincters, decrease in tone, amplitude and frequency of peristalitic movements. The drugs also increase transit time in the intestine. Some drugs can relax the gut in absence as well as presence of cholinoceptor stimulants. These drugs also relax bile duct and gall bladder.

Therapeutic uses

- **Peptic ulcer**

Anti-muscarinic drugs are non-selective muscarinic receptor blockers and exhibit adverse effects like blurred vision, dry mouth, constipation and urinary retention. Due to introduction of histamine H_2-receptor blockers like Ranitidine/Famotidine and proton pump inhibitors like Omeprazole/Pantoprazole, anti-cholinergic drugs are less preferred for treating peptic ulcers. Amongst anti-cholinergics, Propantheline and Glycopyrrolate do not cross blood-brain barrier and do not cause effects on CNS. Development of Pirenzepine and Telenzepine has renewed interest in use of anti-muscarinic agents for peptic ulcer; because they are comparable to Ranitidine. These drugs act by blocking M_1 receptors at paracrine cells and thereby prevent release of histamine.

- **Anti-spasmodics**

Semi-synthetic drugs like methyl-atropine and Hyoscine methylbromide, Tertiary amine derivatives like Dicyclomine and Quartenary ammonium compounds like Propanthelene, Oxyphenonium, Glycopyrrolate, Clidinium bromide and Pipenzulate methylbromide are used to treat hyper motility of the gut. The related conditions are intestinal colic, traveller's diarrhoea, irritable bowel syndrome, mild dysentery and diarrhoea associated with diverticulitis. The drugs can also be used for treating biliary colic.

Dicyclomine: **COLINET, CYCLOPAM**, *is available as 10 mg tablet, 10 mg/ml injection; it is also available as combination with paracetamol (dicyclomine 20 mg + paracetamol 20 mg) or with mefanamic acid (dicyclomine 10 mg + mefanamic:* **MEFTAL-SPAS** *acid 10 mg).* **PROBANTHINE** *is available as 15 mg tablet. Oxyphenonium is available as 5, 10 mg tablets. Clidinium is available as a combination product:* **ANTRENYL** *(clidinium bromide 2.5 mg + chlordiazepoxide:* **LIBRAX** *5 mg) tablet and Pipenzulate methylbromide is available as a combination product in the form of drops (pipenzulate 4 mg + phenobarbitone:* **PIPLAR** *6 mg/ml).*

- **To reduce excessive salivation**

Beladona alkaloids and synthetic tertiary amine derivatives like dicyclomine are effective in excessive salivation with heavy metal poisoning or Parkinsoniasm. Dose adjustment is necessary to avoid dryness of mouth.

6. Genito-urinary Tract

The smooth muscle of ureters and urinary bladder wall is relaxed by antimuscarinic drugs. As a result, voiding is slowed causing urinary retention. These drugs cross placental barrier; however the foetus is not affected.

Therapeutic uses

Dicyclomine (10-20 mg BD oral) and oxybutinine (5 mg BD oral) are used in the treatment of renal colic. Oxybutinine has selective action on M_3 receptors and is used to relieve bladder spasm after urologic surgery. It is also useful in reducing involuntary voiding in neurological disorders. When given orally, or instilled by catheter in to bladder, oxybutinine improves the bladder capacity. Valethamate (10 mg BD oral) is useful in delayed dilatation of cervix during delivery. Flavoxate (200 mg TDS oral) is useful in urinary incontinence and for suprapubic pain in cystitis and urethritis. Drotaverin (80 mg BD/TDS oral) acts on spastic sites by inhibiting phosphodiesterase IV enzyme and corrects cAMP and calcium ion imbalance to relieve smooth muscle spasm. Tolterodine (2 mg ND oral) and Fasoterodine are selective M_3 anti-muscarinic drugs for treating urinary incontinence in adults. Propaverine is one more drug with negligible CNS effects.

The anti-muscarinic drugs used to relieve bladder spasm should be used with caution in elderly patients having prostatic hyperplasia.

Drotaverine: **DOTARIN** *is available as 80 mg tablet. It is also available as a combination product (drotaverin 80 mg + mefanamic acid:* **BANALGAN-DM, DOTARIN-MF** *250 mg) in the form of tablet. Flavoxate:* **FLAVOSPAS** *is available as 200 mg tablet. Oxybutinine:*

OXYSPAS, CYSTRAN *is available as 2.5 mg and 5 mg tablet. Tolterodine:* **TOLTER-OD, FLOWCHEK** *is available as 2 mg or 4 mg tablet. Valethamate:* **EPIDOSIN** *is available as 8 mg tablet or 8 mg/ml injection.*

7. Sweat Glands

Thermoregulatory sweating (sweating to reduce elevated body temperature) is suppressed by atropine. Sweat glands have M_3 receptors and are innervated by cholinergic nerves which are sympathetic in origin. In adults, the skin may become dry and hot but the rise in body temperature, called as atropine fever, occurs only in toxic doses. In infants and children (below 5 years) even therapeutic doses may cause atropine fever.

Therapeutic uses

- Hyperhydrosis is sometimes treated with anti-muscarinic drugs like Darifenacin, which is a selective M_3 receptor blocker. These drugs are not much effective because apocrine glands are involved in sweating.

Miscellaneous uses

- Treatment of mushroom poisoning.
- Treatment of muscarinic side effects of neostigmine (used for treating myasthenia gravis).
- Treatment of organo-phosphorous poisoning, along with Pralidoxime.

Adverse effects and toxicity

The most common adverse effects are dryness of mouth, blurred vision and photophobia, constipation, urinary retention, decreased sweating and precipitation of glaucoma.

Atropine toxicity or poisoning usually results due to accidental or suicidal intentions. Oral doses above 80 mg are toxic. Infants and young children may show toxicity, even with 10 mg oral dose.

Symptoms of poisoning include dry skin, hyperpyrexia, flushing of face (red face), mydriasis, photophobia, dry mouth, slurred speech, difficulty in micturition, confusion, delirium, restlessness, hallucinations and tachycardia. It is followed by coma, cardiovascular collapse and respiratory paralysis. Scopolamine is more toxic than atropine.

The poisoning is treated with 2 mg (IV/IM) phyostigmine initially. The dose of physostigmine may be repeated later. Adverse effects on CNS can be controlled by small doses of diazepam, given intramuscularly.

Table 3.4 summarises therapeutic uses of anti-muscarinic drugs.

Table 3.4: Summary of therapeutic uses of anti-muscarinic drugs

Sr. No.	System	Clinical condition	Drugs used
1.	CNS	Motion sickness	Scopolamine (SC injection/transdermal)
2.	CNS	Parkinson's disease	Trihexyphenidyl, Benztropine, Procyclidine
3.	CNS	Diagnosis of Alzheimer's disease	Tropicamide (as eye drops)

contd. …

4.	CNS	Amnesia with twilight sleep	Scopolamine (with morphine; rare)
5.	Eye	As mydriatic	Tropicamide, Eucatropine, Cyclopentolate, Homatropine
6.	Eye	Iridocyclitis, iritis, uveitis	Homatropine (with Pilocarpine)
7.	CVS	To abolish reflex vagal cardiac slowing or asystole	Atropine (rare use)
8.	CVS	Second degree heart block as with digitalis toxicity	Atropine (rare use)
9.	Respiratory system	Bronchial asthma and chronic obstructive disease	Ipratropium (in nebulised form along with salbutamol); Tiotropium
10.	GIT	Pre-anaesthetic medication	Glycopyrrolate, Atropine, Scopolamine
11.	GIT	Peptic ulcer	Pyrenzepine, Telenzepine, Propantheline
12.	GIT	Anti-spasmodics	Dicyclomine, Clidinium bromide, Pipenzolate, Oxyphenonium, Glycopyrrolate
13.	GIT	To relieve excessive salivation	Dicyclomine
14.	Genito-urinary tract	Renal colic	Dicyclomine, Oxybutinin
15.	Genito-urinary tract	Delated dilatation of cervix during delivery	Valethamate
16.	Genito-urinary tract	Urinary incontinence	Flavoxate, Drotaverin, Tolterodine
17.	Genito-urinary tract	Nocturnal inuresis	Propaverine
18.	Sweat glands	Hyperhydrosis	Dicyclomine, Darifenacin

3.5 SYMPATHOMIMETICS AND SYMPATHOLYTICS

3.5.1 Endogenous Sympathomimetics

Sympathomimetics are categorised in two sub-types: Endogenous and synthetic. They are discussed below:

3.5.1.1 Endogenous

Nor-epinephrine/nor-adrenaline (NE/NA) is the major neurotransmitter of SNS. Epinephrine/adrenaline (E/A) is the primary hormone secreted by adrenal medulla. Nor-epinephrine is precursor of epinephrine. Dopamine (DA) is the precursor of nor-epinephrine. All these three (epinephrine, nor-epinephrine and dopamine) together are called as catecholamines.

Adrenergic Neurotransmitters (NE, E and DA)

The steps in biosynthesis of dopamine, nor-adrenaline and adrenaline are indicated in Fig. 3.11.

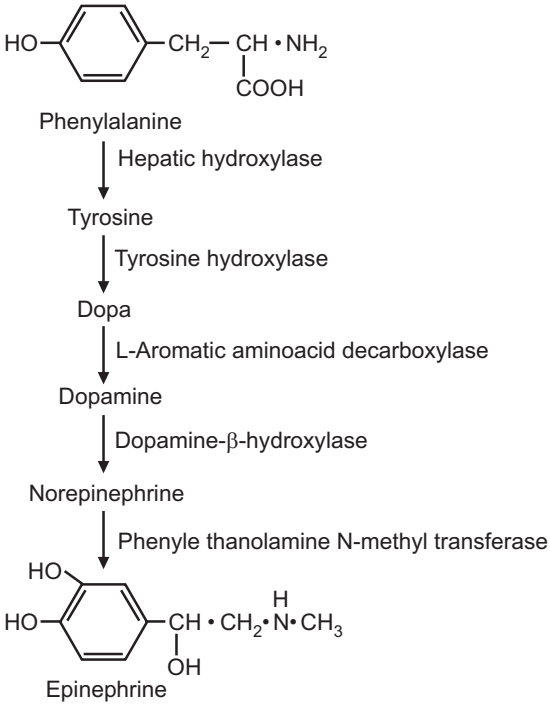


Fig. 3.11: Biosynthesis of catecholamines

Biosynthesis

Biosynthesis of catecholamines starts with the dietary amino acid L-phenyl alanine which is absorbed from GIT. In liver phenyl alanine gets oxidised by the enzyme phenyl alanine hydroxylase (hepatic hydroxylase) to form L-tyrosine. The circulating L-tyrosine is actively transported to the cytoplasm of nor-adrenergic neurons. Within the neuronal cytoplasm, L-tyrosine is hydroxylated by the enzyme tyrosine hydroxylase to l-dopa (dihydroxyphenyl alanine). **Conversion of tyrosine to dopa is the rate limiting step in the biosynthesis of nor-adrenaline.** Increase in cytoplasmic concentration in NE inhibits the activity of enzyme tyrosine hydroxylase through negative feedback mechanism, which in turn limits conversion of L-tyrosine to L-dopa. Thereafter L-dopa is converted to dopamine by cytoplasmic enzyme L-amino acid decarboxylase (dopa decarboxylase). In the dopaminergic neurons, within CNS, this is the last biosynthetic step. In SNS, dopamine is actively transported to storage vesicles of axon terminals, where it is oxidised to nor-epinephrine by the enzyme dopamine-β-hydroxylase, located in synaptic vesicles. NE is stored in synaptic vesicles and works as a neurotransmitter in SNS. The adrenal medulla has two distinct types of catecholamine containing cells: one for NE and another for E. An enzyme called phenyl ethanolamine-N-methyl transferase converts NE to E. After its synthesis, E re-enters the chromaffin granules where it is stored till its release. In adults, 80% of catecholamines are present as E in adrenal medulla, while remaining 20% is NE.

Storage

The endogenous NE, located in the nerve terminal is stored in the synaptic vesicles as a complex with ATP (4 molecules of ATP complex with 1 molecule of NE) along with a soluble binding protein called as chromogranin-A. Inside the storage vesicles, there is acidic pH which provides a positive charge on amino group of NE. This prevents outside diffusion through the vesicle membrane.

Release

The release occurs either due to action potential or due to a spontaneous effect.

(i) Action potential induced release

An action potential after reaching to the synaptic vesicles causes changes in membrane permeability. As a result sodium, calcium and chloride ions enter the synaptic vesicle while potassium ions come out. Influx of calcium ions disrupts the storage vesicle to release NE, ATP, chromogenin along with small amounts of dopamine β-hydroxylase enzyme in to synaptic cleft by the process of exocytosis.

(ii) Spontaneous release

The random migration of storage vesicles towards the end of neuron can result in spontaneous discharge of NE. This release is very small and the process is of less importance.

Action on Different Receptors

The liberated NE, then stimulates different post-synaptic adrenoceptors as mentioned below. Epinephrine (E) activates all five sub-types, while NE primarily activates all sub-types except β_2. Out of five sub-types, α_2 and β_2 receptors are located on pre-synaptic terminals. Other sub-types are located on post-synaptic sites. See Fig. 3.12.

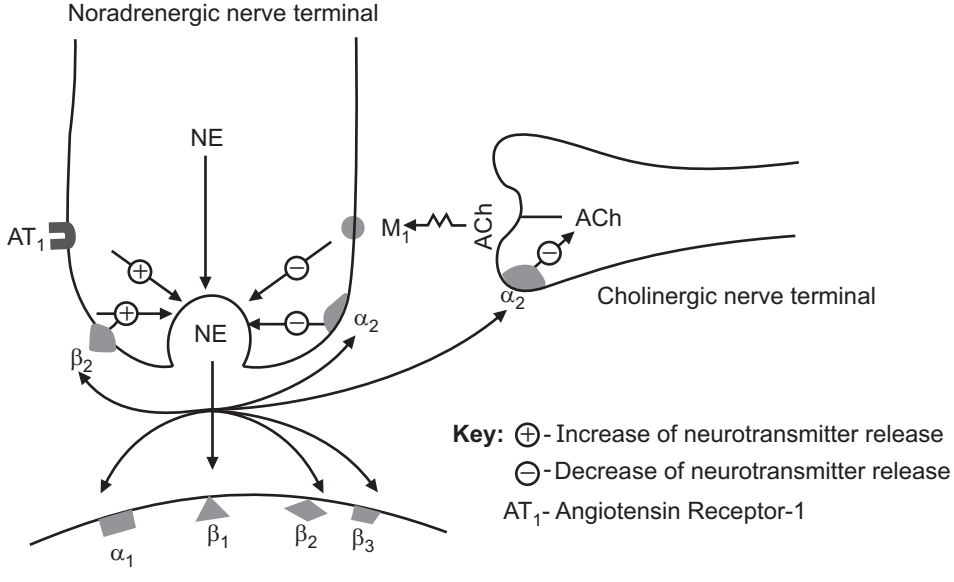


Fig. 3.12: Modulation of NE release indicating different receptors

(i) α_1-Receptors

These receptors are present post-synaptically and when activated produce excitatory effects in organs like vascular smooth muscles, salivary glands, bronchi, uterus, radial muscle of iris and liver cells. In the intestine, they produce inhibitory effects leading to relaxation.

(ii) α_2-Receptors

These receptors are located on pre-synaptic terminals of sympathetic post-ganglionic neurons. Stimulation of these receptors by NE decreases further release of NE. when these receptors are activated by NE, release of ACh is also decreased. In the brain stimulation of these receptors decrease sympathetic out flow.

(iii) β_1-Receptors

These are located post-synaptically. They are found primarily in heart where they produce positive ionotropic and positive chronotropic effect, after activation by NE or E. the receptors are also present in kidneys where they promote release of rennin. E exhibits moderate and NE exhibits strong actions on these receptors.

(iv) β_2-Receptors

These are present post-synaptically, primarily on bronchi, blood vessels supplying to skeletal muscle, coronary arteries, uterus, GIT and cardiac smooth muscle. Except in myocardium, their activation causes an inhibitory effect leading to relaxation of smooth muscles. E exhibits stronger affinity to these receptors. Comparatively, NE has very less affinity for them. The receptors have also been identified pre-synaptically on adrenergic nerve terminals. Activation of pre-synaptic β_2 receptors by NE/E, facilitates release of the neurotransmitter.

(v) β_3-Receptors

These receptors are present on adipocytes. Their activation promotes lipolysis (rise in blood free fatty acids) and thermogenesis (rise in temperature). NE has stronger action as compared to E on these receptors.

Responses of Effector Organs to Sympathetic Stimulation

As indicated in table 3.2, receptors related to neurotransmitters of SNS are located in different organs. As a result, stimulation of SNS results into different effects on various organs as indicated below:

(i) Eye

The radial papillary dilator muscle of iris contains α_1-receptors. Sympathetic stimulation or activation by sympathomimetic drugs like phenylephrine causes mydriasis. NE, if administered locally does not cause mydriasis because it does not cross conjunctival membrane. In contrast to atropine, phenylephrine causes an active mydriasis. Active mydriasis (more light) with no cycloplegia (no blurred vision) is one of the desired responses of SNS to prepare the body to fight or run away from emergency situations. Circular muscles of iris and lachrimal glands have no sympathetic innervation; and there are no tears at the time of emergency.

(ii) Salivary glands

Activation of SNS produces thick salivary secretions. Reduced salivary secretion is a consequence of reduced blood flow caused by vasoconstriction.

(iii) Lungs

Bronchial smooth muscles possess β_2-receptors and cause relaxation leading to bronchodilation. The blood vessels of mucus membrane of nasal and bronchial mucosa get constricted by E and hence SNS stimulation causes decongestion. Both bronchodilatation and mucosal vasoconstriction increase diameter of the lumen of respiratory tract and decrease bronchial resistance. Both these effects are desirable to meet emergency conditions. E also inhibits release of allergic mediators from the mast cells and help in reducing congestion in bronchial muscles.

(iv) Heart

Direct effects of SNS stimulation on the heart are primarily due to β_1-receptor. The effects lead to increase in heart rate due to activation of β_1-receptors at SA node, enhanced conduction and decrease in effective refractory period due to effect on β_1-receptors at AV node. It also increases automaticity by activation of Purkinje fibres and increased force of contraction due to effects on ventricular myocardium. All these effects help the body in preparing for fight or flight.

(v) Blood vessels

Vascular smooth muscle tone is controlled by presence of α_1 and β_2-receptors. While α_1-receptors increase arterial resistance, β_2-receptors promote smooth muscle relaxation. There are major differences in the types of receptors present in different vascular beds. The skin, mucosa, splanchnic and renal blood vessels have predominantly α_1-receptors. As a result, these muscles constrict because of SNS stimulation. Coronary arteries have predominantly β_2, α_2 and D_1 receptors and therefore exhibit vasodilatation. SNS stimulation increases myocardial contractility and increases its oxygen demand producing local hypoxia. This hypoxia in turn dilates the coronary arteries. The innervation to skeletal muscle blood vessels is sympathetic in origin but cholinergic in character. The overall effect of SNS stimulation is vasodilatation and reduced peripheral vascular resistance. Pulmonary blood vessels contain both α_1 and β_2 receptors with the net result of pulmonary vasoconstriction leading to decongestion. There is no change in cerebral vascular resistance and that of systemic veins.

Thus, SNS stimulation leads to coronary dilatation leading to increased blood supply to the heart. Skeletal muscle blood vessels get dilated to meet the demand of exercising muscles. Blood supply to brain is not altered. Veins are not affected; renal perfusion is not compromised. Pulmonary vasoconstriction leads to decongestion. This is accompanied by broncho-dilatation. All these effects help the body to adjust to the needs of fight and flight.

(vi) GIT

Smooth muscles of stomach and intestines have α_2- and β_2-receptors. Out of these, α_2-receptors are located pre-synaptically at cholinergic neurons; their stimulation reduces the tone as well as motility due to reduction in ACh. β_2-receptors are located on smooth

muscles and cause relaxation via hyperpolarisation. α_2-receptors also decrease salt and water influx in to lumen of intestine. Sphincters have α_1-receptors and get contracted by SNS stimulation. α_1 receptors located on GIT smooth muscle are inhibitory in nature. SNS stimulation causes relaxation of GIT smooth muscles. Thus, decrease in tone and motility of GIT, closure of sphincters and decrease in influx of salt and water in to the lumen of intestine, all together prepare the body for fight or flight.

(vii) GUT

SNS stimulation causes urinary retention by relaxing the detrusor muscle (β_2 effect) and contracting the trigone and sphincter of the urinary bladder (α_1 effect). The response of uterus varies with the state of gestation. Uterine muscles of non-pregnant uterus are contracted while muscles of pregnant uterus are relaxed. Ejaculation is facilitated by activation of α_1-receptors located in vas deferens, seminal vesicles and prostate.

(viii) Skin

Secretion of sweat from sweat glands located on palms, sole and fore-head is increased due to SNS stimulation. Piolmotor muscles are contracted leading to piloerection; which increases the perception to the surrounding and helps the body to cope up with situations of fight or flight.

Metabolic Effects

The major metabolic effects are increased blood concentration of glucose, lactic acid and free fatty acids. See Fig. 3.13 for illustration.

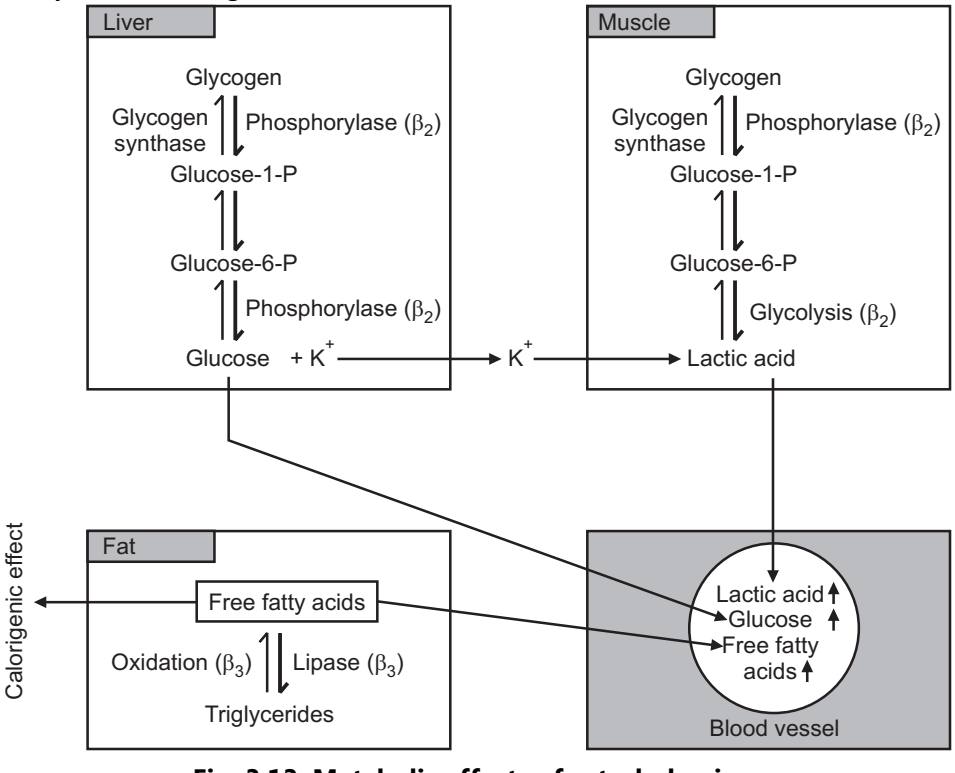


Fig. 3.13: Metabolic effects of catecholamines

In adipocytes, stimulation of β_2-receptors activate lipase enzyme which catalyses breakdown of triglycerides to free fatty acids in the fat cells. In liver, β_2 stimulation catalyses phosphorylase enzyme and thus promotes glycogenolysis and gluconeogenesis. Release of glucose from liver is accompanied by efflux of potassium ions. Later potassium ions released from liver are taken up by skeletal muscles. In skeletal muscles and heart, glycogenolysis and glycolysis produces lactic acid. This effect is mediated through β_2-receptors. The net result is hyperglycemia.

In pancreas, the prominent effect of SNS stimulation is on α_2-receptors of the pancreatic β-cells leads to reduction of insulin secretion. Simultaneously, there is increase in glucagon secretion from the pancreatic α-cells through activation of β_2-receptors. All these effects further contribute to hyperglycemia.

(ix) Skeletal muscles

There is facilitation of neuromuscular transmission by a pre-synaptic α-receptor action leading to increase in ACh at neuromuscular junction. Stimulation of β_2-receptor improves the blood flow to skeletal muscles. The net result is anti-fatigue effect during stressful conditions.

(x) CNS

Effects of CNS stimulation are not very important. However during stress, there may be anxiety, apprehension, arousal, restlessness and rarely tremors. These are the effects of stress.

(xi) Kidney

There is release of renin from the juxta glomerular apparatus in the kidney; the effect is mediated through β_1-receptors. In addition, there is increase in motility and tone of ureter; this effect is mediated through α_1-receptor.

Other Effects

Following additional effects are caused by SNS stimulation:

- Inhibition of histamine release from mast cells leading to low incidence of itching
- Inhibition of lymphocytic activity
- Uptake of potassium ions from extracellular fluid to intracellular fluid resulting in hypokalemia, which may precipitate cardiac arrhythmia due to stress.

Inactivation of NE and E

The actions of NE and E are terminated by following mechanisms:

- Active uptake in to nerve terminals (neuronal re-uptake; up to 80%) and then by re-uptake by storage vesicles (vesicular re-uptake) (uptake 1)
- Uptake in to post-synaptic non-neuronal cell membrane (uptake-2)
- Metabolic degradation by two enzymes: MAO and COMT

Both MAO and COMT are widely distributed throughout the body. They are located in intestines, liver, kidney and brain. However, only MAO is located in adrenergic neurons. COMT is mainly located in the cytoplasm. MAO converts catecholamines (NE, E, DA) in to corresponding carboxylic acids by oxidative deamination. See Fig. 3.14. COMT converts

catecholamines in to their O-methyl derivatives by O-methylation of one of the catechol-hydroxyl group. Due to action of MAO and COMT, the final metabolite of catecholamines (NE and E) is vanillyl mandelic acid (VMA). Dopamine, after interaction with MAO and COMT gets converted in to homovanillic acid (HVA).

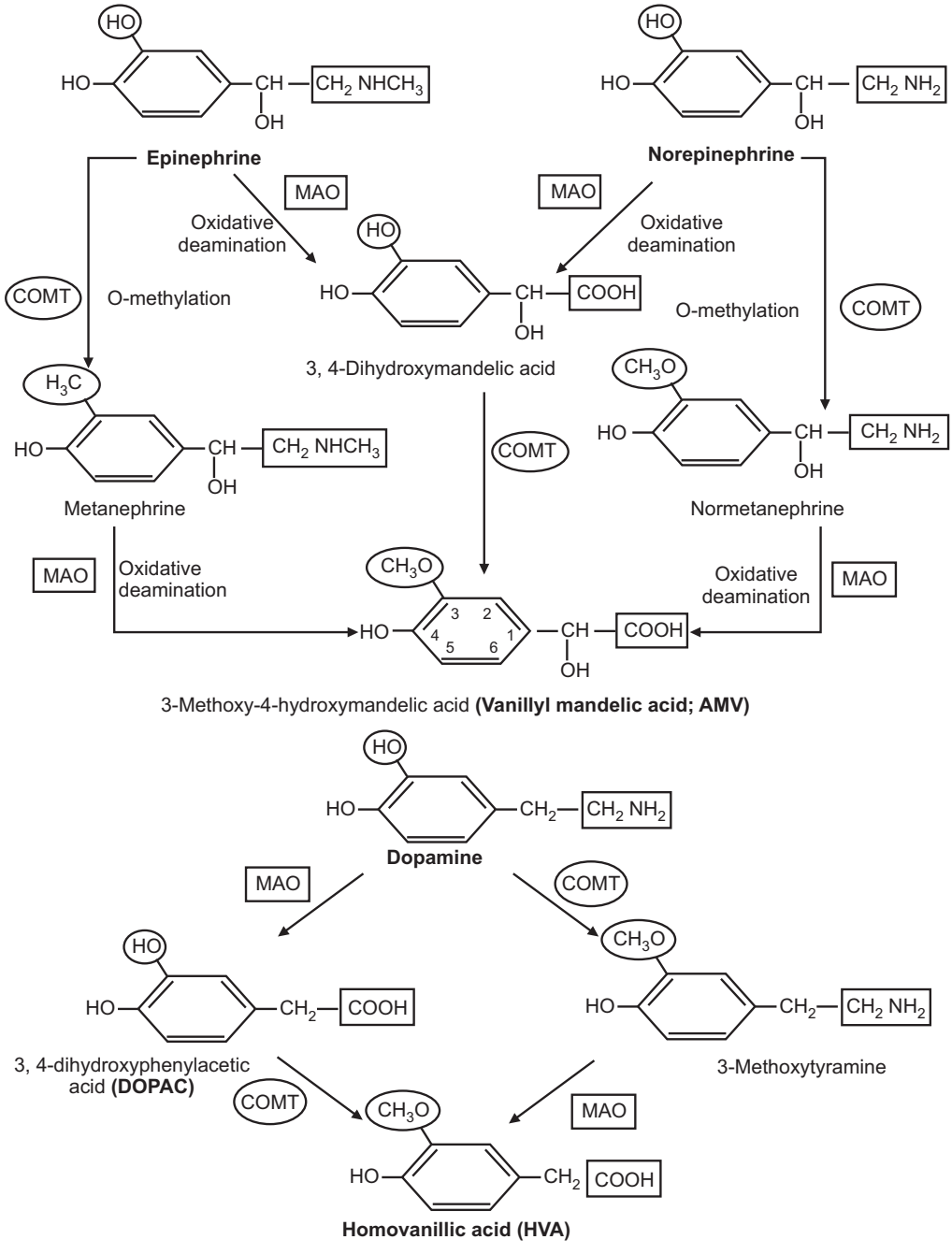


Fig. 3.14: Metabolism of catecholamines by COMT (Catecol-o-methyl transferase) and MAO (Monoaminotransferase)

These metabolites are excreted through urine as their sulphate or glucuronide water-soluble conjugates.

3.5.1.2 Synthetic Sympathomimetics

These drugs mimic the actions of endogenous catecholamines. They are classified in to three sub-groups as follows:

1. Directly acting sympathomimetics
2. Indirectly acting sympathomimetics
3. Mixed action sympathomimetics

3.5.1.2.1 Directly Acting Sympathomimetics

They have following characteristics:

- They act directly on pre-and/or post-synaptic α- and β- adrenergic receptors and produce various pharmacological effects.
- They can exhibit effects even after dennervation of post-ganglionic adrenergic neurons.
- Repeated doses of these drugs do not lead to tachyphylaxis.

These drugs can be primarily classified as catecholamines and non-catecholamines. Catecholamines are further sub-classified as endogenous and synthetic.

(i) Endogenous catecholamines

Drugs in this category have following characteristics:

- They have high potency.
- They are rapidly inactivated. Hence, they have a short duration of action. They are ineffective when given orally, because of being polar and inactivation by metabolising enzymes.
- They have poor penetration in to CNS. However, they produce anxiety, tremors and headache in high doses.

(a) Epinephrine (adrenaline)

80-90% of epinephrine (E) is secreted from adrenal medulla along with 10-20% NE. The relative affinity of E towards adrenoceptors is $\beta_2 > \beta_1 = \alpha_1 = \alpha_2$. However, at low doses β-effects predominate over α-effects. At high doses α effects are stronger.

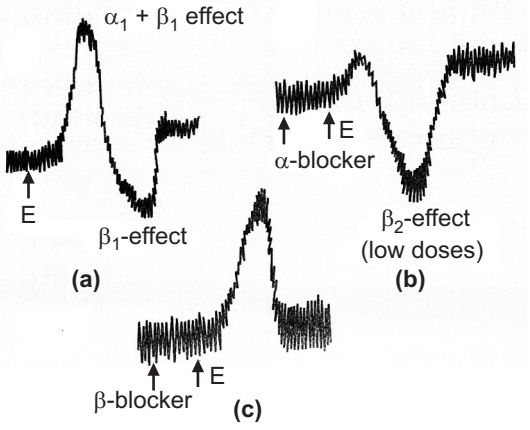
Cardiovascular effects

Epinephrine is a very potent vasoconstrictor and cardiac stimulant.

There is increase in heart rate and force of contraction which is followed by reflex bradycardia due to compensatory vagal discharge due to increase in blood pressure. The stroke volume increases leading to increase in cardiac output and rise in systolic BP. However, myocardium becomes more succeptible to arrhythmias.

E constricts aretrioles in skin, mucus membrane, viscera and renal beds; these effects are mediated through α-receptors. Dilatation predominates in skeletal muscle, liver and coronaries; these effects are mediated through β_2-receptors. Total peripheral resistance decreases. The cumulative effect is an increase in systolic BP coupled with slight decrease in diastolic BP.

Moderate doses of E produce biphasic response i.e. initial rise in BP (α_1 effect) followed by fall in BP (β_2-effect) later. The effects alter because of pre-treatment with respective blockers. Pre-treatment with α-blockers causes reduction in BP only; while pre-treatment with β-blocker causes increase in BP only. The effects are illustrated in Fig. 3.15.



(a) Normal effect of epinephrine on BP; (b) Dale's Vasomotor Reversal Phenomenon, (c) α-Effect (↑ BP) seen after β-blockade

Fig. 3.15: Effects of epinephrine altered by α/β blockers

Effects on smooth muscles

E causes powerful broncho-dilatation (β_2-effect) and decrease in bronchial secretions (α_1-effect). Cumulatively, there is decrease in bronchial resistance.

E causes relaxation of GIT muscles (α_2- and β-effects) along with constriction of sphincters (α_1-effect). These effects have no clinical significance.

On urinary tract E causes relaxation of detrusoe muscle (β_2-effect) along with contraction of trigone and sphincter (α_1-effect). As a result, micturition is hindered leading to urinary retention.

On non-pregnant human uterus, E causes constriction; while on pregnant human uterus it causes relaxation.

Metabolic effects

- Hyperglycemia due to glycogenolysis in liver (β_2) and skeletal muscle (α_1 and β_2).
- Increase in free fatty acids due to lipolysis in adipose tissue (α and β_3).
- Inhibition of insulin release (α_2).
- Caloriegenic effect; rise in basal metabolic rate and effects on CVS causing rise in temperature (β_3).

Miscellaneous effects

- Active mydriasis in eye due to contraction of radial muscle of iris (α_1).
- Thick salivary secretions (α_1).
- Piloerection and sweating of palms and soles (α_1).
- Inhibition of histamine release by stabilization of mast cells.
- Anxiety and tremors (CNS effect).

Therapeutic uses

- **Allergy (anaphylactic shock)**

  It is a drug of choice for type I hypersensitivity reactions like acute anaphylactic attack. It relieves broncho-spasm, angioneurotic edema of larynx, prevents release of histamine from mast cells and maintains BP in anaphylactic shock. It is given intra-muscularly as 0.3-0.5 ml; 1:1000 solution. In an anaphylactic shock, sub-cutaneous absorption of adrenaline is very low.

- **Bronchial asthma**

  It causes bronchodilatation and decongestion of bronchial mucosa. It is given sub-cutaneously 0.3-0.5 ml as 1: 1000 solution as aerosol.

- **Cardiac resuscitation**

  Intracardiac injection of 0.1 mg/ml adrenaline can be used to reverse sudden cardiac arrests caused by drowning and electrocution. Ventricular fibrillation is a contra-indication in this condition.

- **To prolong duration of local anaesthetic (LA) action**

  Adrenaline, because of its vasoconstricting effect, antagonises vasodilating effects of LA and retards their systemic absorption from the site of injection. As a result, not only duration of LA action is prolonged but their systemic toxicity is also decreased. It is given sub-cutaneously or intradermally in combination with any LA.

- **To control epistaxis (as a local hemostatic)**

  It is used to control bleeding as in epistaxis and in ENT surgery. It is used as a spray to have clear vision.

Adverse effects

- Increase in BP can lead to cerebral hemorrhage.
- Increase in cardiac work and contractility may lead to coronary insufficiency - it may precipitate angina, palpitation and even arrhythmia (in patients taking digitalis). Adrenaline may cause pulmonary edema.
- CNS side effects may include tremors, anxiety and headache.

Contra-indications and interactions

- **Hyperthyroidism:** Due to up-regulation of α-receptors on the vessels and β-receptors in heart, a patient with hyperthyroidism may become hyper-responsive to adrenaline. In such cases, dose of adrenalin should be reduced.
- Angina and hypertension.
- Tricyclic anti-depressants like Imipramine prevent re-uptake of E in to neurons. As a result, action of adrenaline may be excessively enhanced.
- Anaesthetics like Halothane increase the sensitivity of myocardium towards catecholamines.
- Inhibitors of MAO increase concentration and availability of adrenaline. Hence, its effects are excessively enhanced.

Adrenaline: **VASOCON** *is available as 1 mg/ml injection.*

(b) Nor-epinephrine (Nor-adrenaline) (NE/NA)

Endogenous NE is the l-isomer which is more potent than d-isomer. NE predominantly acts on α-receptors with relative receptor affinity as $\alpha_1 = \alpha_2 > \beta_1 >> \beta_2$. It also possesses significant β_3 actions.

Cardiovascular actions

NE raises both systolic and diastolic BP, due to cardiac stimulation (β_1) and rise in peripheral vascular resistance (α_1). Cardiac output is unchanged. Reflex bradycardia is caused, secondary to hypertension. The coronary blood flow increases due to rise in mean arterial pressure. NE has predominant α-action and does not exhibit Dale's vasomotor reversal.

Therapeutic uses

It is carefully used to treat cardiogenic shock, since the shock increases vascular resistance and decreases blood flow to vital organs. Dopamine is preferred in this condition, since it does not reduce blood flow to kidney. It is not suitable for sub-cutaneous, intra-muscular or undiluted IV injection because of possibility of necrosis at the site of action. Vasoconstriction is the cause of necrosis.

Adverse effects, precautions and contraindications

These are similar to that of adrenaline. Infusions of NE should be tapered off gradually to avoid sudden fall in BP. Extravasation in to sub-cutaneous tissue should be carefully watched to avoid tissue necrosis at the site of infusion.

NE: **ADRENOR, NODRESOL, NORAD, NOREPIRIN** *is available as 2 mg/2ml injection.*

(c) Dopamine

It is an endogenous catecholamine. When given parenterally, it does not cross blood-brain barrier and exhibits no effect on CNS. When given intravenously in therapeutic doses (2-5 µg/kg/min), it acts on D_1-receptors and causes dilatation of renal vessels resulting in increased GFR, renal blood flow, and excretion of sodium. At a dose of 5-10 µg/kg/min IV, it also stimulates β_1-receptors resulting in an increase in cardiac output but the total peripheral resistance and mean BP are unchanged due to simultaneous vasodilatation of renal and splanchnic vessels. In still higher doses of 10 µg/kg/min IV, it can cause vasoconstriction by activating α-receptors, thus nullifying beneficial effects of low doses of dopamine.

Therapeutic uses

It is used in conditions of low cardiac output with compromised renal functions, such as cardiogenic shock due to myocardial infarction, trauma or surgery. It is also used in the treatment of congestive heart failure, renal and liver failure. Dopamine is given as a infusion at a rate of 5-10 µg/kg/min. The BP, HR and urine flow should be continuously monitored for dose adjustment to get beneficial effects.

Adverse effects

They include nausea, vomiting, tachycardia, ectopic beats, hypertension (only in high doses) and cardiac arrhythmia (low incidence).

Dopamine: **DOPACARD, DOPAR, DOPASOL, DOPINGA** *is available as injection of 200 mg/5 ml ampule.*

(ii) Synthetic catecholamines

These are synthetic catecholamines containing two adjacent hydroxyl groups in the benzene nucleus.

(a) Isoprenaline

It predominantly stimulates β_1- and β_2-adrenoceptors. It has negligible α-receptor action. The structure of isoprenaline is shown in Fig. 3.16.

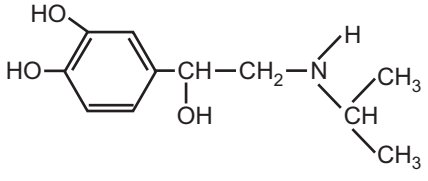


Fig. 3.16: Structure of isoprenaline

Pharmacological / Cardiovascular effects

It exerts positive ionotropic and chronotropic effect on heart causing an increase in cardiac output (β_1-effect). Due to cardiac stimulant action, it may slightly increase systolic BP but mean arterial pressure and diastolic BP are greatly reduced. It dilates the arterioles of skeletal muscle (β_2-effect) resulting in decreased peripheral resistance.

Isoprenaline relaxes bronchial as well as GIT smooth muscles. It relieves broncho-constriction mainly due to stimulation of β_2-receptor and partly due to inhibition of induced histamine release.

Pharmacokinetics

It is readily absorbed when given parenterally or as an aerosol. Compared to E and NE, it is taken up to a lesser extent by neurons. It is stable to MAO degradation; but it is metabolised by COMT present in liver and other tissues.

Therapeutic uses

It is used only in emergency situations to increase heart rate in patients with bradycardia or heart block, prior to insertion of an artificial pace maker.

Adverse effects

Its cardiac stimulant actions can lead to palpitations, sinus tachycardia or even serious arrhythmias.

Isoprenalilne: **ISOLIN, ISOPERIN, ISOSOL, NEO-EPININE** is available as 2 mg/ml injection and 20 mg sub-lingual tablet.

(b) Dipivefrine

It is a pro-drug for epinephrine with enhanced corneal permeability. 0.1% solution is used for the treatment of glaucoma. Ocular side effects may include photosensitivity and conjunctival hyperaemia.

It is available as 0.1% eyedrops: **PROPINE.**

(c) Dobutamine

It is used clinically as a racemic mixture of two enantiomers. The l-form is a potent agonist of α_1-receptor while d-form is a potent antagonist of α_1 and also powerful agonist of β_1-receptor. As a result, the net cardiovascular effects of dobutamine are mixed. On heart it has more selective ionotropic than chronotropic effects without any significant change in peripheral vascular resistance and BP.

It increases cardiac output and stroke volume without affecting heart rate, peripheral resistance or blood pressure. Its half-life is about 2 minutes; hence it is given as a IV infusion.

Therapeutic uses

It is used as IV infusion in a dose of 2-5 µg/kg/min to treat patients of heart failure associated with myocardial infarction, cardiac surgery and for short term management of acute congestive heart failure.

Adverse effects

There is a sharprise in BP and heart rate in patients with hypertension. Being an ionotropic agent, myocardial oxygen demand increases and hence angina may be precipitated or myocardial infarction may be aggrevated. Tolerance may develop on prolonged use. Since it increases AV conduction, it should be used with caution in atrial fibrillation.

It is available as 250 mg/5 ml vial as IV injection in the form of a drip: **DOBUTREX, DOBIER, DOBUCARD, KARDIA.**

(d) Dopexamine

It stimulates β_2 receptors and peripheral dopamine receptors and it inhibits neuronal uptake of NE. It results in an increased cardiac output, peripheral vasodilatation and an increase in renal and mesenteric blood flow. It is used to provide haemodynamic support in patients with congestive heart failure and shock. The most common side effect is tachycardia, transient hypotension and dyspnea. It should not be used in patients with phaeochromocytoma.

(e) Fenoldopam

It is a selective D_1-receptor agonist. It has no α- or β-agonist activity. It is a peripheral arteriolar dilator and causes vasodilatation ion coronary, renal and mesenteric arteries. It is useful in short term management of severe hypertension in patients with impaired renal functions where rapid reduction in BP is desired. Oral bioavilability of fenoldopam is poor; hence it is usually given by intravenous route.

Adverse effects include reflex tachycardia, increase in intra-occular pressure and headache. Hypokalemia may be caused due to diuretic action.

(iii) Non-catecholamines

The drugs having only one hydroxyl group and a substituted amine on the benzene nucleus are not catecholamines in nature. Still they show agonistic activity to α-receptor. Since there are two kinds of α-receptors, the drugs are discussed under the category of α_1-agonists and α_2-agonists.

1. α_1-agonist drugs

Phenylephrine and methoxamine are two prototype drugs in this category.

(a) Phenylephrine

It is a α_1-selective agonist. It lacks hydroxyl group on benzene; hence it is a non-catecholamine. It is not metabolised by COMT and hence has got a relatively longer duration of action. See Fig. 3.17. Activation of α_1-receptor results in increase in peripheral vascular resistance and BP; which is associated with reflex bradycardia. It is used as a nasal decongestant and a mydriatic. It may be useful in some patients of hypotension or shock.

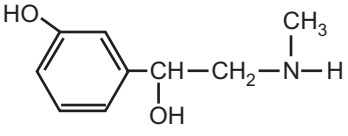


Fig. 3.17: Chemical structure of phenylephrine

It is available as 10% eye drops: **DROSYN** *and 0.20% nasal drops. In combination, it is available as 5% eye drops along with 0.8% Tropicamide:* **DROSYN-T**. *It is also available as nasal drops of 0.25% phenylephrine with 0.025% Naphazoline:* **FENOX**. *It is also available as a tablet having composition as 5 mg phenylephrine with 2 mg chlorpheneramine:* **COZYPLUS**, *500 mg paracetamol and 30 mg caeffine.*

(b) Methoxamine, Midodrine

It is similar to phenylephrine in pharmacological effects and uses. Midodrine is a pro-drug. Its active metabolite desglymidodrine has a selective α_1-receptor activity. It is used to treat postural hypotension. The adverse effect is hypertension in supine position; hence dosing at bed time should be avoided.

(c) Naphazoline, Oxymetazoline and Xylometazoline

These drugs are used as nasal decongestants in rhinorrhoea and to check epistaxis. They are predominantly α_1-agonists. Oxymetazoline has some α_2-agonist action and may cause hypotension.

Naphazoline is available as 0.1% nasal drop and 0.01% eye drops: **PRIVINE, OCUCEL, FENOX.**

Oxymetazoline is available as 0.05% and 0.5% nasal drops: **XYNOSE, SYNAREST.**

Xylometazoline is available as 0.1% nasal drops: **OTRIVIN.**

(d) Pseudoephedrine, Phenylpropanolamine

Pseudoephedrine is a stereo-isomer of ephedrine. Both drugs are used to treat nasal congestion. Because of possibility of haemorrhagic stroke in young women and hypertensives, local administration of Phenylpropanolamine has been banned.

Phenylpropanolamine is available as a tablet: **ALERID-COLD** *either as a combination product of 25 mg along with 5 mg Cetrizine and 500 mg Paracetamol; or 25 mg phenylpropanolamine along with 2.5 mg of Triprolidine:* **ACTIFED.**

Pseudoephedrine is available as a expectorant of 30 mg along with 2 mg Chlorphenyramine and 4 mg of Bromhexine/5 ml of product: **CHESTON.**

2. α_2-agonist drugs

α_2-receptors are located pre-synaptically on sympathetic post-ganglionic neuron and post-synaptically on blood vessels and brain. See Fig. 3.12. Stimulation of these receptors by NE or any α_2-agonists decreases further release of NE. In the brain, stimulation of α_2-receptors decrease central sympathetic outflow. Hence, they are primarily used for the treatment of hypertension. Many blood vessels possess post-synaptic α_2-receptors, which cause vasoconstriction on stimulation; hence their stimulation causes hypertension. Thus α_2-agonists like Clonidine, when given by IV infusion, may initially cause hypertension followed by a more prolonged hypertension due to decreased central sympathetic outflow.

(a) Clonidine

It belongs to imidazoline group chemically. After IV injection, it produces a transient rise in BP. However on oral administration, it produces only fall in BP. It causes the effect by following mechanisms:

- Is stimulates α_2-receptors present at vasomotor centre. As a result, central sympathetic outflow is reduced, resulting in fall in BP and heart rate.
- In addition, Clonidine also activates the pre-synaptic α_2-receptors present on post-ganglionic neurons and thus suppresses further release of NE from peripheral nerve endings.

The decreased central sympathetic discharge to the kidney also reduces renin release and decreases renal vascular resistance. Hence, clonidine is useful in hypertensive patients with poor renal functions.

Pharmacokinetics

It is well absorbed after oral administration with a bioavailability of 100%. A transdermal delivery patch permits continuous administration as an alternative to oral therapy. The patch releases drug at a constant rate for about a week. After removal of the patch, plasma concentration of the drug remains stable for 8 hours and then declines gradually in several days.

Therapeutic uses

- **Moderate hypertension**

It is given orally as 100 µg - 300 µg twice daily. It is usually given with a diuretic in order to avoid sodium and water retention. It has a limit of rebound hypertension after withdrawal. Hence, it is not used as a first line of therapy.

- **To control diarrhoea in diabetic patients with autonomic neuropathy**

Stimulation of α_2-receptors in GIT increases sodium and water retention, inhibits bicarbonate secretion and reduces intestinal motility by inhibiting release of ACh. However, oral clonidine causes orthostatic hypotension, limiting its utility.

- **Prophylaxis of migraine**

It reduces cerebral blood flow. Hence, earlier it was used for prophylaxis of migraine in doses of 25-75 µg. It is not preferred now for this indication.

- **Management of Nicotine, Alcohol and Opiate withdrawal**

It controls some of the adverse sympathetic effects associated with withdrawal of opiods, alcohol and smoking. It also decreases craving for these drugs.

- **Pre-anaesthetic medication**

Due to its sedative, anxieolytic and analgesic effects it is used before surgery to provide hemodynamic stability. **Dexmedetomidine** is a selective α_2-agonist which is used as a pre-anaesthetic medication. It reduces bronchial secretions in addition to other effects mentioned earlier. It is used in ICU for patients requiring mechanical ventilation for longer period. It reduces need for frequent opiod use in cancer patients for controlling pain.

- **Menopausal hot flushes**

Transdermal patches of Clonidine are used for treating menopausal hot flushes.

Adverse effects

Major adverse effects are as follows:

- Rebound hypertension after abrupt withdrawal
- Dry mouth
- Sedation
- Nasal stuffiness
- Constipation
- Impotence
- Contact dermatitis, when used as a trans-dermal patch

It is available as tablet of 150 µg: **ARKAMIN, CATAPRESS.**

Moxonidine and Rilmenidine are congeners of Clonidine with longer plasma half-life. Rebound hypertension is less common with them.

Apraclonidine and Brimonidine are selective α_2-agonists used for treatment of glaucoma. They are primarily used to prevent acute rise in intra-occular pressure. They do not cross blood-brain barrier and have least systemic side effects. They reduce formation of aqueous humor.

(b) α-methyldopa

It is a centrally acting anti-hypertensive drug. It exerts its action through a metabolite, α-methyl NE. It has two major advantages:

- It reduces renal vascular resistance. Hence, it is useful in hypertensive patients with renal insufficiency.
- It reduces ventricular hypertrophy. It is well tolerated by patients with diastolic dysfunction in whom it reduces left ventricular mass.

Due to potential adverse reactions, immunological and hepato-toxicity, it is no longer a drug of choice for long term management except for hypertension during pregnancy. It is safe both for mother as well as fetus.

Adverse reactions

It causes sedation, dryness of mouth, involuntary movements, gynaecomastia in males and galactorrhoea in females due to interference with dopaminergic suppression of prolactin release. Hepato-toxicity is associated with fever. It also causes hepatic dysfunction. It is advised that methyldopa should be avoided in patients with hepatic disease. It can cause haemolytic anaemia and Coombs test.

It is available as 250 mg tablet: **EMDOPA, ALFADOPA, ALDOPAM.**

Guanfacine and Guanabenz are similar to Clonidine in mechanism of action and adverse effects. These drugs are rarely used because of lack of advantage over Clonidine.

(iv) Non-catecholamine β_2-selective agonists

These drugs have preferential affinity for β_2-receptors. They are administered by inhalation, in the form of aerosol, leading to effective activation of β_2-receptors in bronchi. There is less potential to stimulate β_2-receptors in skeletal muscle which can cause palpitation and tremors when administered orally. They activate β_2-receptors located on airway smooth muscle and enhance the release of cAMP by activating the enzyme adenylyl cyclise. The mast cells also have β_2-receptors which respond to them.

They exert following actions:

- Relax airway smooth muscle.
- Inhibit the release of broncho-constricting mediators from mast cells.
- Inhibit micro-vascular leakage.
- Increase the muco-ciliary transport by increasing the ciliary activity.

The drugs under this category are as follows:

(a) Salbutamol

It is a fairly selective β_2-agonist with relaxant effects on smooth muscles of bronchi and uterus. It has minimal cardiac stimulant effects. It is not metabolised by COMT and exhibits longer duration of action as compared to isoprenaline. For immediate relief of asthma, it is given by oral inhalation from a metered dose inhaler (100 µg/dose). It can also be given orally (2-4 mg TDS), intra-muscularly or by slow intravenous injection. Sustained release tablets are also available. Inhalation causes fewer side effects in comparison to systemic administration. It can also be used for the arrest of uncomplicated pre-mature labour between 24-34 weeks of gestation by giving an intravenous infusion.

It is associated with nausea and vomiting with a risk of developing pulmonary edema. Other side effects are tremors in hands, palpitation, headache and hypokalemia (after large doses).

It is available as 2 mg, 4 mg tablet, 100 µg metered dose inhaler, 2 mg/5 ml syrup; 4 mg, 8 mg controlled release tablet: **ASTHALIN, VENTORLIN, DERIHALER.**

(b) Metaproterenol (orciprenaline)

It has lesser β_2 selective action than salbutamol and terbutaline. It is resistant to methylation by COMT. Its side effects are similar to that of salbutamol.

It is available as 10 mg tablet or 10 mg/5 ml syrup: **ALUPENT.**

(c) Terbutaline

It is a resorcinol derivative. It is not metabolised by COMT and hence has a longer duration of action. It is effective when given orally, sub-cutaneously or by inhalation. It is used to relieve acute broncho-spasm in asthma, as a metered dose aerosol whenever required. As with other β_2-agonists, tolerance may develop towards it, if used regularly. With oral doses, onset of action is slow. It can also be used for treatment of COPD. It is also used in the treatment of unresponsive urticaria along with Ketotifen. Its inhaled powder formulations should be avoided, as they may harm tooth enamel and cause tooth erosion. Its side effects are similar to that of salbutamol. Oral dose is 2.5-5 mg BD/TDS; 250 µg by inhalation, as and when required.

It is available as 2.5 mg, 5 mg tablet; 1.5 mg/5ml syrup and 250 µg/puff metered dose inhaler: **BRICANYL.**

(d) Bambuterol

It is a prodrug of Tebutaline. It is slowly metabolised (24 hours). It has only limited use in chronic asthma. Oral dose is 10-20 mg once a day in the evening.

It is available as tablet of 10, 20 mg and a syrup of 1 mg/ml: **BETADAY, BAMBUDIL, ROBUROL.**

(e) Salmeterol

It has prolonged duration of action (12 hours) but a slow onset of action. It is ineffective in acute attacks of asthma. It is preferred for management of nocturnal asthma. Dose is 25-100 µg by inhalation twice a day. It has an anti-inflammatory action also.

It is available as inhalation with a dose of 25 µg/puff: **SALMETER, SEROBID.**

(f) Formoterol

It has quicker onset of action (within 5 min) with a longer duration of action (12 hours). It is preferred to prevent nocturnal attacks of asthma, prophylaxis of exercise-induced bronchospasm and COPD. It has an anti-inflammatory action also. Dose is 12-24 µg by inhalation twice a day.

It is available as inhalation with a dose of 12 µg/puff: **FORATEC.**

(g) Pirbuterol

It has properties similar to Salbutamol. Following inhalation, it exerts its effects within 10 minutes, which lasts for about 5 hours.

(h) Clenbuterol

It increases the rate and force of contraction of skeletal muscle to a varying extent. It possesses anabolic properties and therefore used illicitly by sports person to improve performance.

3.5.1.2.2 Indirectly Acting Sympathomimetics

They have following characteristics:

- They do not have direct stimulant effect on adrenoceptors. They are taken up by neuronal membranes; they displace NE from their stores. The displaced NE causes pharmacological actions.
- Dennervation of post-ganglionic adrenergic neuron prevents their action.
- Repeated dosing at short intervals leads to tachyphylaxis due to depletion of stores of NE.

These drugs are more lipid soluble than NE or E. Hence, they have better penetration in CNS and are better absorbed by GIT.

Their common characteristics are, to replace catecholamines from the storage site. They cross blood-brain barrier and have notable effects on CNS. Drugs in this category are as follows:

(a) Tyramine

It is not used clinically. It is found in cheese, beef, wine, beer, banana, yeast and yoghurt. It is metabolised by MAO present in liver, GIT and other parts of body. If the patient is taking any inhibitor of MAO, then any substance containing Tyramine can precipitate serious hypertensive crisis by profusely releasing NE from storage sites.

(b) Amphetamine

It has a powerful CNS stimulant action in addition to peripheral α- and β-adrenoceptor effects.

Mechanism of action

It enters the nerve ending by active transport and displace DA and NE from storage vesicles by altering pH. To some extent, they also inhibit DA metabolism by inhibiting MAO-B in nerve ending. As a result, concentration of intra-neuronal DA increases. It reverses the direction of transport mechanism resulting in release of DA by reverse transport in addition to exocytosis. In totality, total DA concentration in the synaptic cleft increases.

Pharmacokinetics

It is well absorbed after oral administration and penetrates blood-brain barrier. A sizable portion of un-metabolised drug is excreted through urine. By acidifying urine with ascorbic acid or ammonium chloride reduces re-absorption of Amphetamine and enhances its clearance.

CNS effects

d-isomer of Amphetamine, called as Dextro-amphetamine is 3-4 times more potent than l-isomer in exhibiting CNS stimulant effects. It stimulates cortical region and reticular activating system. It also stimulates the medullary respiratory centre, lessens CNS depression by other drugs and produces wakefulness, alertness and decreased sense of fatigue. The need for sleep may be postponed but cannot be avoided indefinitely. The performance of simple mental tasks is improved but it is of no advantage because of increase in number of errors. Physical performance in athletes is improved and the drug is often abused for the purpose.

If Amphetamine is taken repeatedly over a period of few days, a state of Amphetamine psychosis develops which closely resembles schizophrenia and is associated with paranoid ideas along with auditory and tactile hallucinations. Higher doses can lead to aggressiveness and violent behaviour; death may occur due to violence, accident, murder or even suicide.

CVS effects

The l-isomer is more potent than d-isomer on CVS. Amphetamine raises both systolic and diastolic BP and produces tachycardia followed by bradycardia. In large doses, arrhythmia may occur.

Effects on smooth muscle

Sphincter of urinary bladder constricts resulting in difficulty for micturition. It causes relaxation of gut and increases tone of uterus.

Other effects

It suppresses appetite by depressing lateral hypothalamic feeding centre. Tolerance to appetite suppression develops rapidly. It is not advised to use this drug for appetite suppression.

Therapeutic uses

It is used for following indications:

- **Narcolepsy**

  Amphetamine in small doses improves narcolepsy and prevents attacks of day time sleep. It is advised that the drug should not be given after 4.00 pm, because it will disturb the nocturnal sleep resulting in compulsions to have day time sleep.

- **Attention Deficit Hyperactivity Disorder (ADHD)**

  This syndrome is observed in children. It is characterised by impulsiveness, impaired inter-personal relationship, excitability and difficulty in sustaining attention resulting in loss of academic achievements. Surprisingly, some children with ADHD respond well to low doses of Amphetamine.

Adverse effects

Following types of adverse effects are observed:

- Restlessness, tremors, hyperactive reflexes, irritability, insomnia, euphoria, hallucinations and sweating. High doses cause psychosis. These adverse effects are related to CNS.
- Palpitation, headache and arrhythmia.
- Dry mouth, metallic taste, anorexia, abdominal cramps and difficulty in micturition.
- Dependence and tolerance: Psychological dependence develops after prolonged use. Tolerance develops to its appetite suppressant effect but not for narcolepsy. Withdrawal effects include CNS depression, insomnia and tremors.

Treatment of toxicity

Amphetamine toxicity can be treated by acidification of urine by ammonium chloride or ascorbic acid, it prevents re-absorbtion of Amphetamine from renal tubule and promote excretion. Diazepam may be given to limit adverse effects on CNS.

(c) Methamphetamine

It is closely related to Amphetamine in chemical structure. Low doses have predominantly CNS stimulant effects without significant peripheral actions. It has a high potential for abuse.

(d) Methylphenidate

It is also related chemically to Amphetamine. It is a mild CNS stimulant; but it has more prominent action on mental functions. It is more effective than Amphetamine in treating narcolepsy and ADHD. Abuse potential is similar to that of Amphetamine. In large doses, it produces convulsions. It is contra-indicated in patients with glaucoma. Its d-isomer, dexmethylphenedate is better tolerated and preferred for use in ADHD.

(e) Pamoline

It is structurally similar to methylphenetate. It has prominent CNS stimulant effects with minimal effects on CVS. It has a longer plasma half-life. Hence, it is used in treatment of ADHD. Its prolonged use is associated with dependence and hepatic damage.

(f) Modafanil

It is not an analog of Amphetamine. It blocks uptake of both NE and DA. It is used to treat narcolepsy. It does not produce insomnia, but improves wakefulness. It has no abuse potential.

3.5.1.2.3 Mixed Action Sympathomimetics

As in case of indirectly acting sympathomimetics, these drugs act by replacement of stores of NE. In addition, they have a direct action on α- and β-receptors (like NE and E).

Following drugs are considered under this category:

(a) Ephedrine

It is a non-catecholamine alkaloid obtained from *Ephedra vulgaris*. Its racemic form is used clinically. It has a direct action on both α- and β-receptors. In addition, it enhances release of NE from sympathetic neuron. It is not destroyed by MAO and COMT and therefore it has longer duration of action than E and NE. It crosses blood-brain barrier and has a powerful stimulant action on CNS. It increases heart rate, cardiac output and BP. Activation of β_2-receptors in lungs promotes broncho-dilation. Stimulation of α_1-receptor produces mydriasis without cycloplegia. It is used to treat hypotension, subsequent to spinal anaesthesia. It can be used orally to treat mild chronic asthma; but selective β_2-agonists are preferred for this purpose. Adverse effects include hypertension, (when given parenterally) insomnia and tachycardia. Repeated doses at short intervals produce tachyphylaxis.

(b) Pseudoephedrine

It is a stereo-isomer of ephedrine and is used as a nasal decongestant in oral formulation.

(c) Mephentermine

Its pharmacological actions are similar to that of ephedrine. Its use is restricted to maintain BP in hypertensive states e.g. following spinal anaesthesia by giving slow injection. Adverse effects include CNS stimulation, hallucinations and convulsions (only in overdosage). The oral dose is 10-20 mg twice a day or as an IV infusion of 15-60 mg in 5% glucose.

It is available as 10 mg tablet or 15 mg/ml injection: **MEPHENTINE.**

3.5.2 Sympatholytics

Sympatholytics are also termed as adrenergic receptor antagonists. They abolish (lyse) the response to stimulation of sympathetic nerves. They are devoid of any intrinsic activity on adrenoceptors but they exert their actions by blocking the interaction of catecholamines or other sympathomimetics with adrenergic receptors; which are of three types: Alpha (α), Beta (β), and Dopamine (D). The drugs which block D-receptors peripherally are of no clinical significance; while those which block D receptors centrally are of clinical importance. The α and β adrenoceptors have been classified in to five categories: α_1, α_2, β_1, β_2, and β_3. Blockers related to these receptors, which are of clinical importance are discussed below.

3.5.2.1 α-Adrenergic Blockers

On the basis of their selectivity and mode of action, α-adrenoceptor antagonists can be classified as mentioned below. See Fig. 3.18.

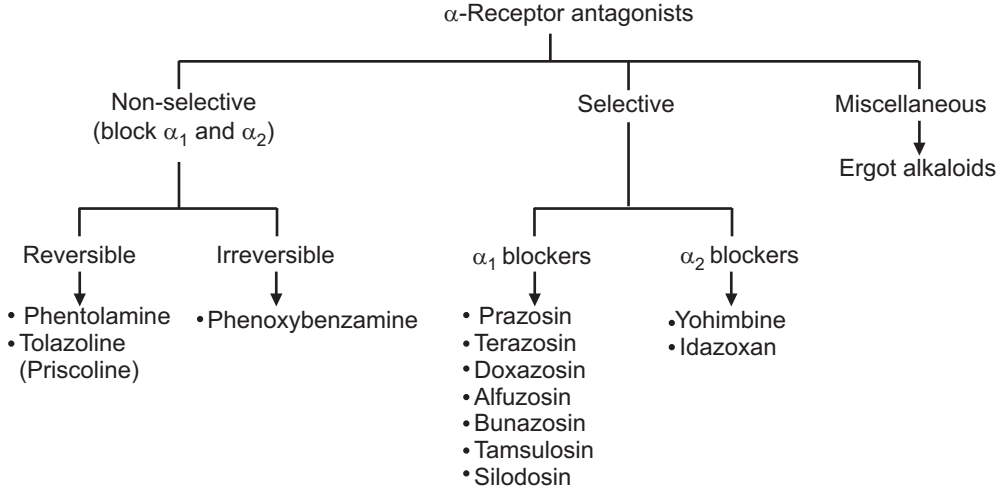


Fig. 3.18: Classification of α-blockers

(i) Reversible non-selective α-blockers

These drugs are competitive antagonists at α-adrenergic receptors and have similar affinities for α_1- and α_2-receptors. Two drugs viz. Phentolamine and Tolazoline deserve discussion in this category.

(a) Phentolamine

Cardiovascular effects

Blockade of vasoconstrictor α_1-receptors in the periphery by Phentolamine leads to vasodilatation, decrease in peripheral vascular resistance leading to hypotension. The resultant fall in BP stimulates baroreceptor reflex causing sympathetic discharge. Since α_1-receptors are blocked, the sympathetic discharge stimulates β_1-receptors on the heart producing tachycardia. Being non-selective, it also blocks pre-synaptic α_2-receptors limiting neuronal release of NE to produce more tachycardia and palpitation. The patients may suffer from events of postural hypotension. In absence of efficient peripheral vasoconstriction in erect posture, there is a peripheral pooling of blood leading to cerebral hypoxia, vertigo and fainting, which are important features of postural hypotension.

Other effects

Following effects are observed with Phentolamine:

- Nasal stuffiness results due to vasodilatation and congestion of nasal mucosa.
- Myosis, due to loss of tone of radial muscles of iris and unopposed contraction of circular muscle.
- Improved urine flow rates due to relaxation of smooth muscles of urinary bladder neck and prostate.
- Failure of ejaculation and impotence due to inhibition of contractions of vas deferens and ejaculatory ducts.
- Nausea, vomiting and diarrhoea due to partial inhibition of relaxant sympathetic influences on GIT, and increase in gastric secretions due to agonistic action on histamine H_2 receptors.

Pharmacokinetics

It is poorly absorbed from GIT. It is administered intravenously. It has an immediate onset and shorter duration of action.

Therapeutic uses

- For diagnosis and management of Phaeochromocytoma.
- For peripheral vascular disorders: It is used to treat Raynaud's syndrome and frostbite.
- To prevent dermal necrosis: It is used sub-cutaneously to prevent dermal necrosis after incidental extravasation of NE from intravenous infusion.
- To prevent hypertensive crisis following abrupt withdrawal of Clonidine and those resulting from ingestion of tyramine-containing food with MAO inhibitors.

It is available as 10 mg/ml injection: **FENTANOR, FENTOSOL.**

(b) Tolazoline

It is similar to Phentolamine; but it is less potent. It is better absorbed from GIT. It is rarely used.

(ii) Irreversible non-selective α-blockers

The only drug in this category is Phenoxybenzamine.

(a) Phenoxybenzamine

It binds covalently to α_1- and α_2-receptors causing irreversible blockade of the receptors with a longer duration of action (20-48 hours). It inhibits reuptake of released NE by adrenergic nerve terminals. It also crosses blood-brain barrier. It causes vasodilatation, progressive decrease in peripheral resistance and tachycardia. Cardiovascular effects of overdose of Phenoxybenzamine cannot be reversed by catecholamines due to covalent binding with the receptors, making it the drug a choice for Phaeochromocytoma. It causes marked postural hypotension due to impairment of compensatory vasoconstrictor responses. Tolerance to it develops later. Other toxic effects include reversible inhibition of ejaculation, salt and water retention, cardiac arrhythmia, sedation, fatigue and nausea.

Therapeutic uses

- Treatment of Phaeochromocytoma in an intravenous dose of 1 mg/kg, controls severe hypertension during surgery for Phaeochromocytoma.
- To treat peripheral vascular disease like Raynaud's syndrome and frostbite. It is used in a oral dose of 10 mg three times a day.

It is available as 10 mg capsule or 50 mg/ml injection: **FENOXENE.**

(iii) Reversible, selective α_1-blockers

The primary drug in this category is Prazosin. Few derivatives of Prazosin are also available.

(a) Prazosin

It is a selective α_1-receptor antagonist. It causes peripheral vasodilatation and a fall in arterial pressure with lesser tachycardia probably because of lack of α_2-receptor blocking actions, limiting release of NE. It also decreases cardiac preload and it suppresses sympathetic outflow from CNS.

It is a potent inhibitor of the enzyme cyclic phosphodiesterase leading to increase in cAMP. It also causes rise in the concentration of HDL and decrease in LDL and triglycerides. Being an α_1-selective antagonist, it relaxes smooth muscles of urinary bladder neck, prostate capsule and prostatic urethra leading to improvement of urine flow in cases of benign prostatic hypertrophy.

Pharmacokinetics

It is well absorbed after oral administraton. Its plasma half-life is about 4 hours.

Therapeutic uses

- Treatment of hypertension: Titration of dose is needed to limit postural hypotension. Initially, a dose of 1 mg may be given orally at bed time.
- In the treatment of benign prostatic hyperplagia (BPH). Oral dose of 1-5 mg twice daily is useful.
- In patients of Raynaud's disease, calcium channel blockers are preferred over Prazosin.

Adverse effects

- The major adverse effect is postural hypotension (Syncopal attack).
- Impotence, nasal congestion, GIT upset, sodium and water retention are additional adverse reactions.

It is available as tablet of 1 mg, 2 mg or 5 mg: **MINIPRESS, PRAZOPRESS.**

(b) Terazosin and Doxazosin

Both are α_1-blockers like Prazosin but have longer duration of action. Both are well absorbed after oral administration. Plasma half-life of Tetrazosin is 12 hours; and that of Doxasosin is 20 hours. One daily dose is preferred for treatment of hypertension and BPH. Terazosin in a dose of 2-5 mg or Doxazosin in a dose of 1-4 mg, once daily is useful to improve urine flow. It may be combined with another drug Finasteride, which inhibits conversion of testosterone to dihydrotestosterone. The combination is useful in reducing progress of BPH.

Terazosin: **HYTRIN, TERAPRESS, TERALFA, OLYSTER** *is available as tablet of 1 mg, 2 mg, 5 mg; Doxasosin:* **DOXACARD, DURACARD** *is available as tablet of 1 mg, 2 mg and 4 mg*

(c) Bunazosin and Alfuzosin

Both are orally effective α_1-blockers similar to Prazosin. Alfuzosin is given in a dose of 2.5 mg three times a day. It has a shorter half-life of 4 hours and hence needs frequent administration. It should be avoided in patients with hepatic impairment, due to extensive metabolism by liver. Bunazosin has slightly longer half-life. Both drugs are used to treat BPH.

Alfuzosin: **ALFOO, FUAL, AFFUSIN, PROFUZO** *is available as 10 mg extended release tablet.*

(d) Tamsulosin and Silodosin

These are selective α_1-blockers. Tamsulosin is more effective for BPH than for hypertension. It has a plasma half-life of 8 hours and better bioavailability than Prazosin. Abnormal ejaculation and intra-operative floppy iris syndrome (which causes problems during cataract surgery) are major adverse reactions. Silodosin is a weaker but long acting analog of Tamsulosin.

Tamsulosin: **CONTIFLO-OD, URIPRO, VELTAM, URIMAX** is available as 0.2 mg, 0.4 mg tablet.

(iv) α_2-receptor blockers

The only drug in this category is Yohimbine.

(a) Yohimbine

It is a natural alkaloid available from *Pausinystalia yohimbe*. It is lipid soluble. It crosses blood-brain barrier. It has antagonistic action to 5-HT. It can be used to treat autonomic insufficiency by promoting NE release by blocking pre-synaptic α_2-receptor. It can also be used to treat male sexual dysfunction and to treat diabetic neuropathy and postural hypotension. It can abruptly reverse anti-hypertensive effect of clonidine, which is a notable drug interaction. Its clinical role needs to be established.

(v) Miscellaneous non-selective α-blockers

Ergot alkaloids fall in this category.

(a) Ergot alkaloids

Alkaloids from ergot like Ergotamine and Dihydroergotamine exhibit complex pharmacological actions. They block both α_1- and α_2-receptors. In addition, they act as partial agonists to α-receptors and 5-HT_2 receptors. Some of them are Oxytocics and dopamine receptor agonists. Methysergide, a synthetic compound is related to ergot alkaloids. It is a potent 5-HT antagonist and was used for migraine prophylaxis. Ergonovine/Ergometrine is an ergot alkaloid. Its derivatives methyl-ergonovine and dihydroergonovine are used for their uterine relaxant (tocolytic) action.

3.5.2.2 β-Adrenergic Blockers

These drugs block β_1- or β_2-receptors and antagonise effects of catecholamines which are mediated through the receptors. In addition, some of these drugs also exert membrane-stabilising effect leading to local anaesthetic action. Some of them have intrinsic sympathomimetic activity. Based on their selectivity towards receptors, they can be classified as shown in Fig. 3.19.

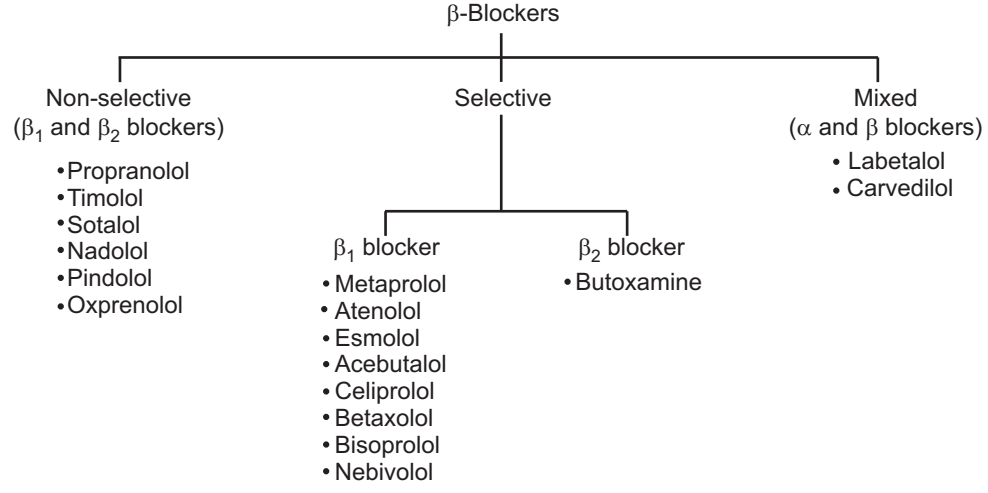


Fig. 3.19: Classification of β-blockers

(i) Non-selective β-blockers

Propranolol is the prototype drug in this category. Hence, it is discussed in detail. In addition, Timolol, Sotalol and Nadolol are derivatives of Propranolol.

(a) Propranolol

It is a non-selective β-antagonist. It is primarily used to treat hypertension and ischaemic heart disease. It has little effect on normal resting heart, but exhibits profound action when the sympathetic drive to the heart if high, as during physical exercise or stress.

Cardiovascular effects

It causes decrease in heart rate, myocardial contractility, conduction velocity and cardiac output. Because of decrease in the work-load by heart, the myocardial oxygen demand is also reduced. The automaticity of heart is suppressed because of the inhibition of latent pace makers. Subsequently there is fall in blood pressure. The total peripheral vascular resistance tends to rise initially because the vasoconstricting α_1-adrenoceptor response is no longer opposed by dilator effects on β_2-receptors. Further, asreflex vasoconstriction is preserved, postural hypotension is not very troublesome. Patients with hypertension show a gradual fall in BP after chronic use of Propranolol. In addition to β_1-receptor blockade, it shows following additional effects.

- Decrease in renin release, further reducing production of angiotensin II and aldosterone from adrenal cortex.
- Decrease in central sympathetic outflow.

- Chronic decrease in cardiac output.
- Blockade of facilitatory effect of pre-synaptic β_2-receptors on release of NE.

Cardiovascular effects of Propranolol can be overcome by Isoprenaline; however it cannot counteract cardiac stimulant action of Digoxin, calcium ions, Theophylline and Glucagon, which indicates its selective action on β-receptors only.

Plasma lipid profile is worsened after long-term use of Propranolol:

- Total triglycerides and LDL tend to increase.
- HDL cholesterol levels fall.

It has a membrane stabilising (local anaesthetic) action and direct cardiac depressant (quinidine like) actions. However, it does not contribute to anti-arrhythmic effects in usual doses.

Respiratory effects

In asthmatic patients, Propranolol can cause severe bronchoconstriction. This is because of its non-specific effect. Cardio-selective β_1-blockers are less prone for it.

Metabolic effects

Propranolol inhibits stress-induced or adrenaline-induced glycogenolysis, which acts as a safety device during episodes of hypoglycaemia, especially in insulin-induced hypo-glycaemia in diabetic patients. The drug also blocks adrenergically induced lipolysis and has an adverse effect on lipid profile. It also masks sympathetic manifestations of hypoglycaemia like palpitations, tremors, sweating etc.

CNS effects

Besides decreasing central sympathetic outflow, which contributes to anti-hypertensive effects, Propranolol also produces sedation, lethargy and disturbances in sleep after long-term use. It suppresses performance anxiety e.g. anxiety prior to examination; but this is due to peripheral action. In high doses it causes anti-psychotic effects; but they are not clinically useful due to adverse cardiovascular effects.

Ocular effects

Propranolol decreases formation of aqueous humour and thus decreases intra-occular pressure, especially in patients of glaucoma. Still it is not preferred for this clinical purpose because it is less potent and its local anaesthetic action is undesirable.

Miscellaneous effects

- Propranolol increases synthesis and release of prostaglandins in selected vascular beds, as the hypotensive effect of the drug can be reversed by aspirin-like drugs which cause analgesic effects by virtue of effects on prostaglandin synthesis.
- It prevents platelet aggregation and promotes fibrinolysis to some extent.
- It reduces portal vein pressure in patients with cirrhosis.

Pharmacokinetics

It is completely absorbed when given orally, but has low bioavailability because of extensive first-pass metabolism. It is highly lipid soluble and crosses blood-brain barrier. It

has shorter plasma half-life (4-6 hours). It exists in two isomeric forms. l-propranolol is 80-100 times more potent than d-propranolol in blocking β-adrenoceptors. d-propranolol exhibits more quinidine-like and membrane stabilising effects as compared to l-form. Commercial preparations are in racemic forms. Sustained-release preparations of Propranolol are available.

Therapeutic uses

Key word to remember therapeutic uses is **2H-2A-MI**. 2H refers to Hypertension and Heart failure; 2A refers to Angina and Arrhythmias and MI refers to Myocardial infarction.

- **Essential hypertension**

  Singularly or in combination with a diuretic or α-adrenergic blocker, Propranolol is used primarily to reduce elevated blood pressure. When used alone, fall in BP is gradual and without postural hypotension. The oral dose is 20-40 mg three times a day or 80 mg sustained release tablet once a day.

- **Congestive heart failure (CHF)**

  When introduced gradually with slow advancing doses over time and maintained for a long term, Propranolol retards progression of CHF and prolongs life. The benefit arises from antagonism of damaging effects of cardiac β_1-receptor over-activity, which promotes unfavourable re-modelling of myocardium.

- **Angina pectoris**

  As Propranolol decreases overload on heart, diminishes myocardial oxygen demand and increases exercise tolerance, it benefits patients having angina of effort. The drug should be given continuously and not merely when there is an attack.

- **Cardiac arrhythmia**

  Propranolol is effective in all supra-ventricular tachycardias associated with high levels of circulating catecholamines. The condition occurs in digitalis toxicity, phaeochromo-cytoma, thyrotoxicosis or with general anaesthetics like halothane. The ventricular ectopic beats are also controlled. The effects are due to increase in refractory period of AV node and direct membrane stabilising effect. The drug also reduces drive to cardiac pace-makers.

- **Myocardial infarction**

  Propranolol significantly decreases incidence, recurrence and mortality in cases of myocardial infarction after long term use. The benefit increases due to prevention of platelet aggregation and promotion of fibrinolysis. The drug also prevents sudden ventricular fibrillation due to second attack of myocardial infarction.

Other uses

Key word to remember other effects are **MAGH-Paw-EVB**. MAGH refers to Migraine, Anxiety, Glaucoma and Hyperthyroidism. Paw refers to Phaeochromocytoma, Alcohol withdrawal. EVB refers to Esophageal Variceal Bleeding.

- **Migraine**

  It is useful in prophylaxis of migraine. The dose is 20 mg three times a day.

- **Anxiety-provoking situations**

  It can be used in situations like examination, interview etc. It blocks symptoms of anxiety like palpitation, tremors and sweating. The oral dose is 10-20 mg twice/thrice a day.

- **Glaucoma**

  Other selective blockers like Timolol and Betaxolol are preferred for this purpose.

- **Hyperthyroidism**

  The drug reduces unpleasant symptoms of sympathetic over-activity. It reduces tachycardia, irregular cardiac rhythm, tremors, sweating and elevated basal metabolic rate (BMR). The oral dose is 20 mg twice a day.

- **Phaeochromocytoma**

  The drug is given along with α-blockers during surgery for removal of adrenal tumour. It antagonises β-agonistic effects of circulating catecholamines. The oral dose is 20 mg three times a day, three days before surgery.

- **Alcohol withdrawal**

  It is useful by reducing central sympathetic over-activity during the phase of withdrawal of alcohol. The oral dose is 20 mg twice/thrice a day.

- **Esophageal variceal bleeding**

  The drug reduces cardiac output and induces splanchnic vasoconstriction leading to reduction of bleeding from esophageal varices. Portal pressure is reduced by 40%. The oral dose is 10-20 mg twice a day.

Adverse effects and complications

Key word to remember is **2B-2C-2H-RH & ALP**. 2B refers to Broncho-constriction, Bardycardia. 2C refers to Cold extremities, CNS side effects. 2H refers to heart failure and hypoglycemia. RH refers to Rebound Hypertension and ALP refers to Adverse Lipid Profile.

- **Broncho-constriction**

  In patients with asthma and chronic obstructive lung disease, the effect can be life threatening.

- **Bradycardia**

  The drug can cause life threatening bradyarrhythmias and heart block.

- **Cold extremities**

  It is due to cutaneous vasodilatation. The drug is contra-indicated in Raynaud's disease.

- **CNS side effects**

  The effects include sleep disturbances, bad dreams, depression and sexual dysfunction (only in males).

- **Heart failure**

  AV nodal depression can lead to AV dissociation and can precipitate heart block. It is contraindicated in heart failure.

- **Hypoglycaemia**

  It is contra-indicated in patients receiving insulin and oral hypoglycaemic drugs. It is due to possibility of hypoglycaemic coma.

- **Rebound hypertension**

  Withdrawal of β-blockers should be slow; otherwise it may cause re-bound hypertension.

- **Adverse lipid profile**

  LDL-cholesterol tends to increase while HDL-cholesterol levels fail due to β-blockers.

Drug interactions

The drug interactions are sub-classified as pharmacokinetic and pharmacodynamic.

(i) Pharmacokinetic drug interactions

- Aluminium salts, cholestyramine and colestipol decrease absorption of β-blockers.
- Cimetidine and Hydralazine may increase bioavailability of β-blockers.
- β-blockers impair clearance of lignocaine and may increase bioavailability of lignocaine.

(ii) Pharmacodynamic drug interactions

- Digitalis and Verapamil cause additive depression of SA node and AV conduction leading to cardiac arrest.
- Indomethacin and Aspirin (other NSAIDs) can antagonise anti-hypertensive effects of β-blockers.
- Hypertensive patients receiving Propranolol are very sensitive to pressor responses of adrenaline.

Propranolol is available as tablets of 10 mg, 40 mg, 80 mg or slow release 40 mg, 80 mg. It is also available as 120 mg time-release capsule: **INDERAL, CIPLAR, BETACAP-TR.**

(b) Timolol

Timolol is orally absorbed. It shows moderate first-pass metabolism. It crosses blood-brain barrier. It's uses and side effects are similar to that of propranolol.

Therapeutic uses

It is used as eye drops to decrease raised intra-occular pressure, in case of wide angle glaucoma. It is devoid of membrane stabilising activity. From ocular formulations, some amount may be absorbed systemically to exhibit side effects.

It is available as 0.25% or 0.5% eye drops: **OCUPRES, GLUCOMOL, IOTIM, TIMOLET.** *Other β-blockers used for the same purpose are Betaxolol:* **OPTIPRESS, BULOL, IOBET, OCUBETA** *and Levobunolol:* **BETAGAN** *both as 0.5% eye drops.*

(c) Sotalol

Sotalol has low lipid solubility. It shows lesser CNS effects and has negligible first-pass metabolism. Its uses and side effects are similar to that of propranolol. It has potassium channel blocking activity and anti-arrhythmic activity also. Its oral dose is 80-320 mg twice a day.

It is available as 40 mg or 80 mg tablet: **SOTAGARD, SOLET.**

(d) Nadolol

Nadolol has longer plasma half-life (20 hours). It does not cross blood-brain barrier. It has least first-pass metabolism. Its dose is 40 mg once daily. Its effects are similar to that of propranolol.

It is available as 40 mg tablet.

(ii) Cardio-selective β_1-blockers

These drugs are more selective towards heart and exert lesser side effects on respiratory system. Their selectivity is in comparison to Propranolol. The examples in this category are Metoprolol, Atenolol, Blisoprolol, Nebivolol, Esmolol and Betaxolol.

Advantages over non-selective β-blockers

- They are safer in asthmatic patients in comparison to Propranolol.
- They are safer in diabetes since they cause less inhibition of glycogenolysis during hypoglycaemia. Tachycardia in response to hypoglycaemia is blocked.
- They are safer in patients with peripheral vascular disease since they do not cause β_2-blockade.
- They have less adverse effects on lipid profile.

Disadvantages

- They cause rebound hypertension after abrupt withdrawal.
- They are ineffective in controlling essential tremors.

Following drugs are discussed in this category:

(a) Metoprolol

It is completely absorbed after oral administration. Due to first-pass metabolism, its bioavailability is low. Its plasma half-life is 4 hours. For treating hypertension, usual dose is 50-100 mg daily. Extended release formulations are available for once daily administration. Its uses are similar to that of Propranolol.

It is available as a tablet with 25 mg, 50 mg or 100 mg content. It is also available as 1 mg/ml injection: **BETALOC, METOLAR, LOPRESOR.**

(b) Atenolol

It does not cross blood-brain barrier. It has relatively longer half-life in comparison to Metaprolol. It can be given once daily in dose of 25-50 mg. Its uses are similar to that of Metoprolol.

It is available as 25 mg, 50 mg or 100 mg tablets: **BETACARD, TENORMIN.**

(c) Bisoprolol

It is commonly used for hypertension and angina. Its dose is 2.5-10 mg once daily. When used with ACE inhibitors, it lowers mortality in chronic heart failure.

It is available as 2.5 mg, 5 mg or 10 mg tablets: **ZAVESTA, CORBIS, BISELECT.**

(d) Nebivolol

It enhances production and release of Nitric Oxide (NO) in addition to β-blockade. It lowers arterial blood pressure and reduces peripheral vascular resistance. It is used for treating hypertension. Usual oral dose is 5-10 mg once daily.

It is available as 2.5 or 5 mg tablet: **NEBICARD, NUBETA, NODON, NEBISTAR.**

(e) Esmolol

It is an ultra-short acting β_1-antagonist. It has a plasma half-life of 8-10 minutes. It is given intravenously in conditions to terminate supra-ventricular tachycardia, episodes of atrial fibrillation and to control heart rate and blood pressure during surgery or in critically ill patients in whom the drug can be withdrawn immediately. Adverse effects include bradycardia, hypotension and heart failure.

It is available as 10 mg/ml injection: **CARDESMO, NEOTACH, MINIBLOCK.**

(f) Betaxolol

It is less effective than Timolol because 80% of β-receptors on ciliary body epithelium are of β_2 sub-type. It is better tolerated. It has no membrane stabilising (local anaesthetic) effect. It has cyto-protective action on retinal neurons. It is safer in asthmatic and diabetic patients. Oral formulations are used for hypertension and angina. It facilitates drainage of aqueous humour.

It is available in the form of eye drops.

(iii) Non-selective β-blockers with intrinsic sympathomimetic activity

Drugs under this category possess some intrinsic sympathomimetic activity on β_1 and β_2 receptors in addition to non-selective β-blockade. Drugs under this category are: Pindolol and Oxprenolol. Their advantages and disadvantages are mentioned below:

Advantages:

- They cause lesser bradycardia and myocardial depression. Hence, they are more useful in patients prone to bradycardia or with low cardiac reserve as in cases of congestive heart failure.
- They are relatively better in patients of asthma because of β_2-agonistic action.
- Rebound hypertension after withdrawal is less likely.
- Lipid profile is less worsened in comparison to Propranolol.

Disadvantages:

- These drugs cannot be used in migraine prophylaxis since β_2 agonistic activity dilates cerebral blood vessels.
- It is less suitable for secondary prophylaxis of myocardial infarction.

(a) Pindolol and Oxprenolol

Daily doses are 10 mg for Pindolol, once daily and 20 mg twice or thrice a day for Oxprenolol.

Pindolol: **VISKEN** *is available as 10 mg, 15 mg tablet and Oxprenolol:* **TRASICOR** *is available as 40 mg and 80 mg tablet.*

(iv) Selective β_1-blockers with intrinsic sympathomimetic activity

Drugs under this category offer combined advantages of Pindolol and Atenolol. They also have membrane stabilising action. Drugs under this category are Acebutolol and Celiprolol.

(a) Acebutolol

It is well absorbed orally. It undergoes first-pass metabolism and is converted to an active metabolite, called diacetolol which has a longer half-life (10-12 hours). It is given as a single oral dose of 400 mg/day. It is used for treating ventricular arrhythmia.

It is available as 200 mg or 400 mg tablet: **SECTRAL.**

(b) Celeprolol

It is well absorbed with a bioavailability of 75%. It has partial agonistic action on β_2-receptors. It also causes some direct vasodilatation by releasing nitric oxide (NO). It is preferred for hypertensive patients with asthma in a oral dose of 200-400 mg once a day.

It is available as 100 mg or 200 mg tablet: **CELIPRES.**

(v) Mixed (α + β) antagonists

Drugs under this category block α- and β- receptors. The examples are Labetalol and Carvedilol.

(a) Labetalol

It acts as a competitive antagonist at both α_1- and β-adrenergic receptors. It exhibits optical isomerism and has four diastereomers. The racemic mixure exhibits following activities:

- Selective blockade of α_1-adrenergic receptors,
- Blockade of β_1-receptors,
- Blockade of β_2-receptors, and
- Partial agonistic activity at β_2-receptors.

The α_1- and β_1-blocking actions of Labetolol lead to fall in BP. The intrinsic sympathomimetic activity (ISA) at β_2-receptors may contribute to peripheral vasodilatation and bronchodilatation. Heart rate remains unaffected. It is orally effective but it has only 30% bioavailability due to first-pass metabolism. Plasma half-life is 4-5 hours. It is used to treat hypertension of elderly people. It is also useful in phaeochromocytoma for controlling rebound hypertension after Clonidine withdrawal. Postural hypertension and hepatotoxicity are main adverse reactions. Usual oral dose is 100 mg once a day which is increased to 200 mg twice daily for 7-10 days.

It is available as 50 mg or 100 mg or 200 mg tablets: **NORMADATE, LABESOL.**

(b) Carvedilol

It is orally effective. It undergoes significant first-pass effect with 30% bioavailability. It has a half-life of 6-8 hours. It is a β_1-, β_2- and α_1-adrenoceptor blocker. Its β_1- and β_2- receptor blocking actions are more prominent than α_1- actions. It also inhibits free radical-induced lipid peroxidation and also inhibits mitogenesis of vascular smooth muscle. It also blocks L-type voltage-gated calcium channels. All these effects lead to cardio-protective action in patients with congestive heart failure. It is used to treat essential hypertension. Along with conventional therapy it is also useful to reduce mortality in myocardial infarction. Adjustment of dosage is not necessary. For hypertension/angina, usual oral dose is 6.25 mg twice a day which is increased to 12.5 mg if needed.

It is available as 6.25 mg or 12.5 mg or 25 mg tablet: **ORICAR, CONPRESS, CEVAS, CARVIMED, CARDIVAS.**

3.6 NEURO-MUSCULAR BLOCKING AGENTS AND SKELETAL MUSCLE RELAXANTS (PERIPHERAL)

There is a need of skeletal muscle relaxants to facilitate surgery. Hence, these drugs are used along with surgical anaesthesia. They relax skeletal muscles, particularly of abdominal wall and lower limbs so that operative manipulations become easier. This situation minimises the risk of respiratory and cardiovascular depression and also reduce post anaesthetic recovery period because in presence of skeletal muscle relaxants, a lighter anaesthesia is sufficient. The drugs block post-synaptic actions of ACh at motor end plate. Some muscle relaxants simply reduce spasticity in few painful conditions like chronic back pain and myalgia. On the basis of their site and mechanism of action, skeletal muscle relaxants are broadly classified as neuromuscular blocking agents and peripheral muscle relaxants.

3.6.1 Neuromuscular Blocking Agents

Whenever a nerve joins a muscle, there is no anatomical continuity between them. There is a small gap between a nerve and a muscle. It is called as neuromuscular junction (NMJ). These drugs act at NMJ. At NMJ, ACh works as a neurotransmitter through nicotinic receptors. Hence, drugs blocking nicotinic actions of ACh perform as neuromuscular blocking agents.

They are sub-classified in to two sub-categories: Non-depolarising blockers (competitive blockers) and Depolarising blockers (persistent depolarisers).

(i) Non-depolarising Blockers

The first NMJ blocker was curare, which native hunters of South America were using for paralysing an animal before hunting. Curare was a plant extract and d-Tubocurarine (d-TC) was isolated and used in clinical practice from 1940s. Structure of d-TC and related derivative are depicted in Fig. 3.20. There are several derivatives of d-TC. Some are long acting e.g. Metocurine, Doxacurium, Pancuronium and Pipecuronium and some others are short acting e.g. Atracurium, Cis-atracurium, Mivacurium, Vecuronium, Rocuronium and Rapacuronium. See table 3.5 and 3.6. Their common features are presented below:

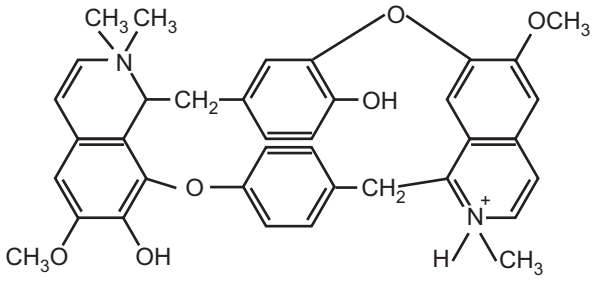


Fig. 3.20: Structure of d-Tubocurarine (Isoquinoline derivative)

Mechanism of action

d-TC and other non-depolarising blockers are quaternary compounds with two positively charged nitrogen in their structure. (see Fig. 3.19). These drugs have an affinity for N_M cholinergic receptors at the motor end plate but have no intrinsic activity over them. They block the N_M receptor and prevent binding of ACh to the site. As a result, necessary conformational change in the N_M receptor, needed for opening of sodium channel is prevented. In absence of end plate potential, the motor nerve impulses cannot induce contractions in the skeletal muscle. The net result is relaxation of skeletal muscles. They do not cause depolarisation by themselves but prevent depolarisation by ACh. The antagonism is competitive in nature. Anticholinesterase drugs like Physostigmin/Neostigmincan reverse the NMJ block due to increase in concentration of ACh. At higher concentrations, these drugs block sodium channels directly, which adds to the strength of blockade. This leads to further weakening of NMJ transmission and reduce ability of drug like Physostigmin/ Neostigmin to reverse the actions of non-depolarising muscle relaxants.

Pharmacokinetics

- These drugs are not absorbed when given orally. They are given intravenously but they differ in potency, rate of onset and duration of action. See table 3.5 and 3.6.
- They have relatively small volume of distribution (V_d). None of them cross blood-brain barrier. Hence, they do not produce CNS toxicity.
- These drugs do not cross placental barrier and hence do not affect the newborn if used during caesarean section.
- The route of elimination controls duration of action. Drugs excreted by kidney have longer duration of action. Drugs eliminated by liver have intermediate duration of action and drugs inactivated by plasma cholinesterase have shorter duration of action. See table 3.5 and 3.6.
- Steroidal NMJ blockers (Vecuronium, Rocoronium and Rapacuronium) may show accumulation and cause prolonged paralysis.
- Artracurium is chemically unstable at alkaline pH and has shorter duration of action during respiratory alkalosis caused by hyperventilation.
- There is no pharmacogenetic variation in metabolism in case of these drugs.

Table 3.5: Pharmacokinetics of long acting non-depolarising NMJ blockers; (Duration of action 35-100 minutes or more

Sr. No.	Drug	Onset (min)	Relative potency to d-TC	Elimination mechanism
1.	d-TC	4-5	1	Kidney 50%; Bile 50%
2.	Metocurine	4-5	4	Kidney 80%; Bile 20%
3.	Doxacurium	4-8	6	Mainly kidney 90%
4.	Pancuronium	4-6	6	Kidney 80%; Liver 20%
5.	Pipecuronium	2-4	6	Kidney 80%; Liver 20%

Table 3.6: Pharmacokinetics of short acting non-depolarising NMJ blockers (Duration of action 25-50 min)

Sr. No.	Drug	Onset (min)	Relative potency to d-TC	Mechanism of elimination
1.	Atracurium	2-4	1.5	Spontaneous non-enzymatic, plasma ChE
2.	Cis-atracurium	3-6	1.5-2	Spontaneous non-enzymatic 100%
3.	Mivacurium	2-3	4	Plasma ChE
4.	Vecuronium	2-4	6	Liver 80%; Kidney 20%
5.	Rocuronium	1-2	0.8-1	Liver 80%; Kidney 20%
6.	Rapacuronium*	1-2	0.5	Mainly liver 90%

*the drug has been withdrawn due to severe adverse reaction.

Pharmacodynamics

After intravenous injections of d-TC like drugs, motor weakness gives way to progressive flaccid paralysis. The fast moving smaller muscles like those of eyes, jaw, toes and larynx are affected initially. Larger muscles like that of limbs and trunk are affected next. Finally, the inter-costal muscles and then diaphragm are paralysed. Recovery of muscles usually occurs in the reverse order.

Some derivatives of d-TC have a tendency to liberate histamine from mast cells. Steroidal derivatives of d-TC like Pancuronium, Vecuronium, Pipecuronium, Rocuronium and Rapacuronium cause least histamine release.

At common clinical doses, d-TC and Metocurine exhibit partial blockade of autonomic ganglia. Other derivatives like Doxacurium, Mivacurium, Atracurium and cis-atracurium exhibit least blockade. Steroidal derivatives do not block autonomic ganglia.

Only Pancuronium has vagolytic action due to blockade of M_2 receptors leading to tachycardia. Other drugs are devoid of vagolytic action.

d-TC and drugs like Metocurine, Mevacurium and Atracurium produce hypotension partly due to histamine release and partly due to ganglionic blockade. Only Pancuronium causes tachycardia; other drugs do not.

Only d-TC can cause broncho-spasm due to release of histamine from mast cells.

d-TC like drugs decrease the tone and motility of GIT. Recovery is followed by constipation.

Reversal of blockade

Neostigmine and Pyridostigmine antagonise or reverse the non-depolarising neuromuscular blockade caused by d-TC like drugs. The effect is due to increase in concentration of ACh at motor end plate. Reversal of the blockade becomes necessary if long-acting or intermediate-acting d-TC like drugs are used. Short-acting drugs do not need such reversal.

Adverse effects

These are either related to skeletal muscle paralysis, histamine release, ganglionic blockade or vagolytic actions.

- Hypoxia and respiratory paralysis may be caused by d-TC like drugs. It may be accompanied with bronchospasm, hypotension and bradycardia.
- Pancuronium may cause tachycardia.

Synergists and antagonists

- Anticholinesterases like Neostigmine are antagonists to non-depolarising neuromuscular blockade caused by d-TC like drugs.
- Hypothermia enhances the depolarising action of ACh. Hence, it antagonises the action of non-depolarising blockers.
- Inhalational general anaesthetics like halothane decrease the sensitivity of post-junctional membrane to depolarisation and therefore act synergistically with d-TC like drugs. Hence, their doses should be reduced, when used along with inhalational anaesthetics.
- Aminoglycoside antibiotics like Gentamycin cause neuromuscular blockde by decreasing ACh release. Other antibiotics like Polymyxin-B, Clindamycin, Lincomycin and Tetracycline group of antibiotics may also cause neuromuscular blockade. All these drugs can act synergistically when used with d-TC like drugs.
- In large doses, most local anaesthetics block neuromuscular transmission and can act synergistically with d-TC like drugs. Other drugs like Quinidine, Propranolol, Diltiazem, Digitalis, Diuretics and Chloroquinine can also show synergism with d-TC like drugs.
- Myasthenia gravis markedly adds to neuromuscular blockde caused by d-TC like drugs. Conversely, patients with burns and those with upper motor neuron disease require larger doses of d-TC like drugs.

Atracurium: **ATRELAX TRACRIUIM** *is available as injection of 10 mg/ml. Pancuronium:* **PANCURONIUM BROMIDE, PANCONIUM** *is available as 2 mg/ml injection. Pipecuronium:* **ARDUAN** *is available as 4 mg/2 ml injection. Recuronium:* **CUROMID** *is available as 50 mg/ml injection and Vecuronium:* **VERUNIUM, VECURON** *is available 10 mg/2 ml or 4 mg/2 ml injection.*

(ii) Depolarising Blockers (persistent depolarisers): Succinyl Choline (SCh)

Only one depolarising neuromuscular blocker is available in clinical practice. It is Succinyl choline (SCh). Actions of SCh are detailed below;

Mechanism of action

SCh is an analog of ACh. SCh is hydrolysed by pseudocholinesterase but not by true AChE. As a result, only a small intravenous dose of SCh reaches NMJ after being hydrolysed by pseudocholinesterase. At NMJ, it acts like an excess of ACh and its actions persist for longer duration because it is not degraded by true AChE. SCh reacts with N_M receptors of motor end plate, open up sodium channel causing depolarisation which then spreads and causes repetitive excitation of muscle motor unirts leading to transient muscle fasciculations. Effectively, SCh continues to keep muscles next to NMJ in a polarized state. The action results in flaccid paralysis, which cannot be reversed by AChE inhibitors like Neostigmine. This is called as phase I block.

With higher doses of SCh or its prolonged infusion, phase I block can get converted in to a non-depolarising type phase II block. The phase II block resembles to that of d-TC and can be reversed by Neostigmine. Conversion from phase I to phase II is slow. During long surgeries, d-TC like drugs are preferred over SCh because of uncertainty of phase I/phase II in case of SCh. Only during short operative procedures, SCh is preferred because of muscle relaxation in phase I.

Pharmacokinetics

SCh possesses two quaternary groups in its structure (Fig. 3.21). It is not absorbed if given orally and does not cross bold-brain barrier or placental barrier. It is administered intravenously in a dose of 0.75-1.5 mg/kg. The duration of action is very short (5-10 minutes). It is primarily due to hydrolysois by pseudocholinesterase present in plasma. Its action is terminated by its diffusion from motor end plate to extra-cellular fluid. NMJ blockade by SCh may be prolonged in patients with genetic variation having atypical pseudocholinesterase. Ability of the enzyme pseudocholinesterase to metabolise SCh is expressed as "dibucaine number". For a normal person, dibucaine number is 80 and a number less than 80 indicates proportionate concentration of atypical enzyme.

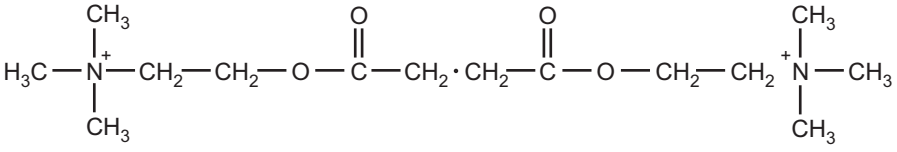


Fig. 3.21: Structure of Succinylcholine

Pharmacodynamics

After a single intravenous dose of SCh fasciculations over chest and abdomen occur briefly. Complete relaxation occurs within 1-2 minute and disappears within 5-10 minutes. Twitches on cheek and abdomen appear first. Paralysis then spreads to neck, limbs, face, trunk and then to respiratory muscles. The onset and recovery being rapid, the sequence of paralysis is not distinguishable.

SCh stimulates ganglia due to agonistic action on N_N receptor. Histamine release is less than that of d-TC. Initial bradycardia due to stimulation of vagal ganglia is followed by tachycardia and hypertension due to stimulation of sympathetic ganglia. However, blood pressure is not affected much due to vasodilatation caused by muscarinic actions.

Adverse effects

- **Hyperkalaemia**

  Efflux of potassium leads to hyperkalaemia. In susceptible patients like cases of burns, spinal injury and uraemia, hyperkalaemia can precipitate arrhythmia or cardiac arrest.

- **Malignant hyperthermia**

  It is a genetically inherited condition caused by mutation of calcium releasing channels of sarcoplasmic reticulum. In susceptible individuals, persistent release of calcium leads to persistent muscle contraction and increased heat production due to skeletal muscle contraction. The condition may be aggrevated if general anaesthetics like Halothane are used along with SCh.

- **Muscle rigidity**

  It is yet another genetic abnormality caused by mutation of voltage sensitive sodium channel. In such individuals SCh may complicate endotracheal tube insertion.

- **Prolonged apnoea**

  Persons with atypical pseudocholinesterase show prolonged apnoea.

- **Increased intra-gastric pressure**

  Nausea and vomiting with SCh occur due to increase in intra-gastric pressure as a consequence of fasciculations.

- **Rise in intra-occular pressure**

  The rise in intra-occular pressure is only for a short while (5-10 minutes). It occurs due to contractions of myofibrils and partly due to transient dilatation of related blood vessels.

- **Muscle soreness**

  Some patients show myoglobinuria following use of SCh. Hence, muscle soreness after recovery is a common observation in such patients.

Synergists and antagonists

- Neostigmine potentiates phase I block caused by SCh.
- Hypothermia potentiates the action of SCh.
- Calcium channel blockers like Verapamil or Diltiazem enhance NMJ blockade caused by SCh.
- Duration of action as well as toxicity of SCh increases in infants below 1 year, patients with collagen disease, thyrotoxicosis and in patients with atypical pseudo-cholinesterase.

SCh is available as injections of 50 mg/ml: **SCOLINE, ENTUBATE, MIDARINE.**

Therapeutic uses of NMJ blockers

- **Adjuvant to general anaesthesia**
  All NMJ blockers (d-TC like drugs and SCh) are used to provide skeletal muscle relaxation during abdominal or thoracic surgery and for endotracheal intubation. They are also used to counteract laryngospasm during barbiturate anaesthesia. They are also used to prevent muscle contractions during surgery. SCh is preferred for brief procedures. For relatively long term use, d-TC like drugs are preferred based on their pharmacokinetics.
- **To prevent trauma during electro-convulsive therapy (ECT)**
  SCh with Diazepam is used to prevent injuries or fractures due to excessive convulsions caused by ECT. The combination can also be used for reduction of fractures and other orthopaedic surgeries.
- **In different spastic conditions**
  In spastic conditions like tetanus or status epilepticus, NMJ blockers are used when Diazepam alone is not sufficient.
- **To control ventilation**
  In patients with obstructive airway disease, NMJ blockers eliminate chest wall resistance and eliminate ineffective spontaneous ventilation.

3.6.2 Peripheral Skeletal Muscle Relaxants

There are some drugs which relax skeletal muscles because of their direct action. These are called as peripheral muscle relaxants, directly acting muscle relaxants or spasmolytics. Dantrolene is the only drug in this category.

Mechanism of action

Dantrolene acts directly at the contractile mechanisms of voluntary muscles by reducing depolarisation-induced calcium release from sarcoplasmic reticulum. The contractile responses are not absolutely abolished by Dantrolene. The drug facilitates action of GABA resulting in depression of functions of brain stem and efferent motor neuron activity. Cardiac muscles are not affected.

Pharmacokinetics

When given orally, it is poorly absorbed but absorption is consistent with rise in proportionate plasma levels. Plasma half-life is 9-12 hours. It is given intravenously with a dose of 1 mg/kg and repeated if necessary to a maximum of 10 mg/kg.

Pharmacodynamics

It is useful to treat spasticity resulting from upper motor neuron lesions caused by spinal cord injury, multiple sclerosis and cerebral palsy. It is not useful in spasticity resulting from musculo-skeletal injury or rheumatoid disorders.

Therapeutic uses

It is a drug of choice for the treatment of malignant hyperthermia which is a genetic abnormality. Dantrolene is also used to treat neurolept-malignant syndrome.

Adverse effects

Generalised muscle weakness, sedation, diarrhoea and occasional hepatitis after prolonged use have been reported.

3.7 LOCAL ANAESTHETIC AGENTS

Local anaesthetics (LA) reversibly block the impulse conduction and produce a transient loss of sensation in a restricted region of the body. These drugs are preferred for performing minor surgery. Unlike general anaesthetics, they neither cause a loss of consciousness nor need a proper maintenance of vital functions during surgery.

Classification

LAs are classified as follows: (few examples are indicated in every category)

- Amide type
  - Longer acting: Bupivacaine, Dibucaine
  - Intermediate acting: Lidocaine, Mepivacaine
- Ester type
  - Longer acting: Tetracaine
  - Intermediate acting: Cocaine
  - Short acting: Procaine, Benzocaine
- Miscellaneous: Pramoxine, Oxethazaine

Chemistry

Esters have part of carboxyl group (–COO) in its structure. Amides have amide group (– NHCO) in its structure. Fig. 3.22 depicts structures of a representative ester and amide. LAs are weak bases and exist in the form of acid salts. They have aromatic part in their structure which are lipophilic in nature. They also have basic amine side chain, which is hydrophilic in nature. Lipophilic component is necessary for penetration through nerve membrane. Once inside the axon, it is the ionized form of LA which is active at the receptor site. At physiological pH, Las remain partly ionized.

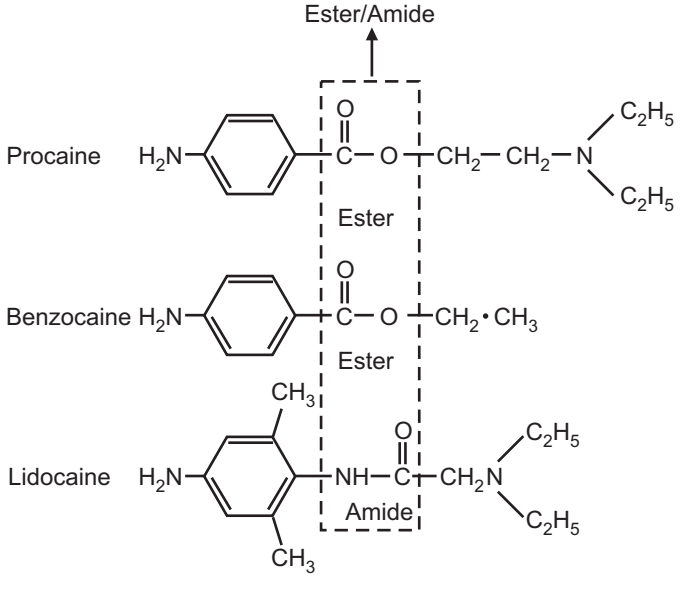


Fig. 3.22: Chemical structures of few local anaesthetics

Mechanism of action

LAs block the voltage-gated sodium channels and consequently block the nerve conduction by reducing permeability of sodium ions during depolarisation.

The blocking action of LA is favoured by depolarisation. A resting membrane is much less sensitive to LA than one that is repetitively stimulated. The phenomenon is voltage-dependent. The voltage-dependence of sodium channel opening reflects conformational changes which results from voltage sensors due to difference in trans-membrane potential. These voltage sensors are called as gates. Hence, these channels are referred as "voltage-gated sodium channels".

The sodium channels have an activation gate (AG) on its extracellular site and an inactivation gate (IG) on its intracellular site. The voltage-gated sodium channels can exist in three functional states as mentioned below:

- The resting or the closed state which prevails at the normal resting potential. In this state the activation gate is closed.
- The activated or the open state which is favoured by brief depolarisation, which opens the activation gate to allow sodium ions to flow inside along concentration gradient.
- The inactivated or blocked state resulting from a trap-door like occlusion of the channel by a floppy part of the intracellular region of the channel protein.

The flow of sodium ions ceases as soon as inactivation gate closes. After the action potential, many sodium channels are in the inactivated state. They revert to their resting state in a time-dependent manner and become available for activation once more. Fig. 3.23 depicts all these three states.

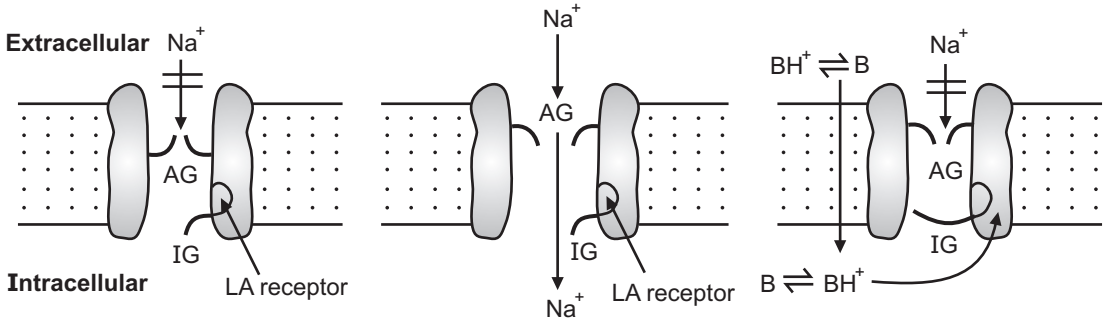


Fig. 3.23: A model of voltage-gated sodium channel

The LA-receptor is located in the trans-membrane pore of sodium channel in its intracellular half. The LA diffuses through the membrane in its unionised lipophilic form (B). It then re-ionises as BH^+ and binds to the LA receptor. The binding of LA to its receptor stabilises the channel in its inactivated state. Then IG gets closed and sodium ion flow ceases. (See Fig. 3.21). Thus, LAs prevent the initiation and propagation of the nerve impulse by reducing the passage of sodium ions through voltage-gated sodium channels.

Effect of pH on LA action

Action of LAs is strongly pH-dependent. LA action is more in alkaline pH and less in acidic pH. These drugs are weak bases and remain partly ionised and partly unionised at physiological pH. The unionised form is needed for its diffusion through axonal membrane. Once inside the axon, it is re-ionised and is in the cationic form (see Fig. 3.21) which binds to LA receptor inside the channel. LAs are less effective in infected tissue, because in infected area, the extracellular pH is acidic in nature. As a result, LA remains predominantly ionised resulting in its poor diffusion through the nerve.

Prolongation of action by vasoconstrictors

Anything which delays absorption of LA in to the circulation will prolong its action and reduce its systemic toxicity. Adrenaline, because of its vasoconstrictor action, prolongs the duration of action of LAs. It is used in the concentration of 1 : 100,000 to 1 : 200,000 for general purpose. In dentistry, the concentration range is 1 : 50,000 to 1 : 100,000. These concentrations double the duration of LA action. Nor-epinephrine is usually not preferred for the purpose.

Sometimes adrenaline may cause cardiac complications. In such cases an alternative vasoconstrictor named Felypressin (a synthetic vasopressin) may be used as an alternative.

Pharmacokinetics

The presence of ester or amide bond in a LA molecule governs its biotransformation and the possibility of causing hypersensitivity reactions.

- The ester-type LAs (e.g. Tetracaine, Chloroprocaine) are usually hydrolysed by pseudocholinesterase or by liver esterases. Hence, they have a shorter duration of action, in case of patients having genetic deficiency of the enzyme, the duration of action of LAs may be prolonged.
- The amide type of LAs (Lidocaine, Bupivacaine) are degraded by hepatic microsomes. As a result they have a longer duration of action.
- Hypersensitivity reactions are common with ester type of LAs; because they are hydrolysed to para-amino-benzoic acid (PABA). PABA or its derivatives are known to be potential allergens.
- Since PABA antagonises actions of sulphonamides, LAs can antagonise anti-bacterial action of sulphonamides.
- After oral ingestion, both Procaine and Lidocaine undergo significant first-pass metabolism. Hence, they are not used to correct cardiac arrhythmia.

Therapeutic uses

The local anaesthesia induced by LA is designated according to the technique or anatomical site where it is injected or applied. Thus, it is sub-classified in to following five types:

(i) Topical anaesthesia

It is also termed as surface anaesthesia. It is restricted to mucus membranes, damaged skin surface, wounds or burns. Surface anaesthetics do not work well on intact skin. The

corneal surface, mucosa of mouth, nose, pharynx, trachea and urethra are easily anaesthetised. Surface anaesthetics can also be used to facilitate endoscopic procedures and to reduce pain of haemorrhoids or anal fissures. Solutions, ointments or creams of LAscan be applied to produce surface anaesthesia. The names of anaesthetics and their respective concentrations used for topical/surface anaesthesia are:

Tetracaine: **AMETHOCAINE, ANETHANE** *(2%), Lidocaine (2-5%), Benzocaine:* **MUCOPAIN, ZOKEN** *(5%), Dycyclonine (0.5-1%), Proparacaine (0.5-1%) and Eutectic mixture of Lidocaine (2.5%) and Prilocaine (2.5%).*

(ii) Infiltration anaesthesia

In this case, the dilute solution of LA is injected under the skin to reach sensory nerve terminals. Infiltration is used for minor surgical procedures like incisions or excisions. Adrenaline or Felypressin may be added to retard absorption.

The available preparations are:

Lidocaine (1-2%): **LIGNOCAINE, GESICAINE, XYLOCAINE**, *Bupivacaine (0.25%):* **MARCAIN, BUPIVAN**, *Ropivacaine (0.5-1%), Mepivacaine (1-3%) and Prilocaine (1-4%):* **PRILOX, ASTHESIA**.

(iii) Conduction block anaesthesia

In this case, LA is injected around the nerve trunk so that the distal area around the site of injection gets anaesthetised. It is of two types: Field block or Nerve block.

In case of field block, the LA is injected sub-cutaneously in the surrounding area of the nerve so that all other nerves coming to a particular field are blocked. Field blocks are applied to the scalp and interior abdominal walls where the nerve travels superficially to supply the area.

In case of nerve block, the LA is injected around anatomically localised nerve trunks i.e. close to the mixed nerve. The block is usually described like radial nerve block, ulnar nerve block indicating name of the anaesthetised nerve. Nerve block lasts longer than field block or infiltration anaesthesia.

In both the types, the LA is injected around the nerve and not in to the nerve. Any injection in nerve is painful and can cause nerve damage. In both, field block and nerve block same anaesthetics are used. Choice of anaesthetic depends on duration of action.

For duration of action of 2-4 hours, intermediate acting LAs like Lidocaine (1.5%) or Mepivacaine (1.5%) are used. For longer duration, Bupivacaine (0.25-0.35%) is used.

Addition of epinephrine prolongs duration and reduces the plasma concentration of intermediate acting LAs.

(iv) Central nerve block anaesthesia

It is further divided in to epidural and spinal block anaesthesia.

(a) Epidural block anaesthesia

It is also named as peri-dural block. It is widely used to provide analgesia or anaesthesia in surgical or obstetric practice. It involves injecting a LA like Lidocaine, Bupivacaine or

Ropivacaine either alone or in combination with a small dose of opioid analgesic in to the epidural space in the lumbar, thoracic or cervical regions to provide segmental analgesia. One of these types is called as Caudal block which is administered in the caudal (sacral) region.

(b) Spinal block anaesthesia

It is also named as sub-arachnoid or intra-thecal block anaesthesia. It can also be used as spinal analgesia. It is produced by injecting a suitable LA in the spinal sub-arachnoid space between L2 and L3 or L3 and L4. It is used to anaesthetise lower abdomen and hand limbs. In this case, addition of vasoconstrictors like adrenaline is not preferred due to risk of restricting blood supply. During late pregnancy, lesser amounts of LA are required.

Fig. 3.24 depicts various sites of application for local anaesthetics.

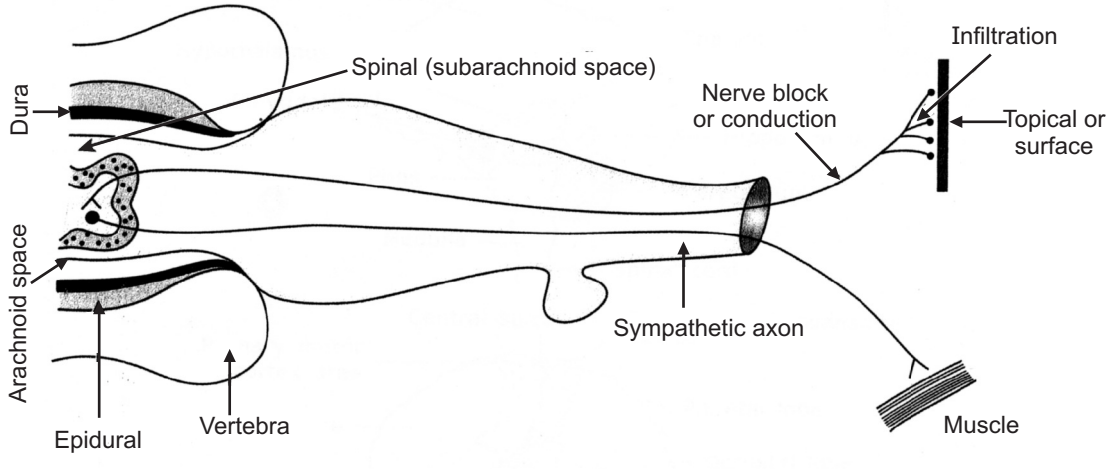


Fig. 3.24: Sites of application of local anaesthetics

Available preparations are Lidocaine (3-5%), Tetracaine (0.3-0.5%) or Bupivacaine (0.5-0.7%).

(v) Intravenous regional anaesthesia

It is also named as Bier's block. It is mainly used for the upper limb and for orthopaedic procedures. In this case, the limb is first elevated to ensure venous drainage and then tightly wrapped by an elastic bandage. Tourniquet is then applied proximally. Later, the elastic bandage is removed and Lidocaine (0.5%) is injected intravenously, distal to the tourniquet. Bupivacaine is avoided due to higher cardiac toxicity.

Available preparations are Lidocaine (0.5%) and Prilocaine (0.5%).

Following preparations are available for the purpose of different types of LAs:

Lidocaine: 2% jelly, 2% viscous preparation, 2% or 4% solution, 1% or 2% injection, 10% or 15% spray and combination product as (Lidocaine 53.3 mg/ml + dextrose 75 mg/ml) or with adrenaline (Lidocaine 21.3 mg/ml + adrenaline 0.005 mg/ml): **GESICAINE WITH ADRENALIN, XYLOCAINE WITH ADRENALIN,** *injection or with Prilocaine as eutectic mixture of (Lidocaine 2.5% + Prilocaine 2.5%).*

Other available preparations are Bupivacaine (0.5%, 1%) injection, Tetracaine (1%) cream.

Adverse effects

In general, adverse effects of all types of LAs are similar. They are mentioned below:

- **CNS**

  At low doses, LAs cause tongue numbness, sleepiness, mild headache, visual and auditory disturbances. At high concentrations they cause nystagmus and muscular twitching. Profound CNS stimulation can cause convulsions. Cocaine may produce long lasting CNS stimulation and euphoria. Cocaine is a drug of abuse and it is rarely used as LA.

- **CVS**

  LAs block sodium channels and depress abnormal cardiac pace-maker activity, excitability and conduction. Most LAs produce hypotension. Bupivacaine is cardiotoxic and can cause ventricular tachycardia and fibrillation. Lignocaine has a quinidine-like action on heart and is used in the treatment of cardiac arrhythmia.

- **Blood**

  Large doses of Prilocaine can cause accumulation of its metabolite called ortho-toluidine, which oxidises haemoglobin to methaemoglobin. Higher levels of methaemoglobin can cause cyanosis. Methylene blue or ascorbic acid can be a remedy to restore haemoglobin.

- **Allergic reactions**

  The ester type of LAs are metabolised to PABA or its derivatives, which are responsible for allergic reactions in some individuals. The result is contact dermatitis, rashes and asthma. Amide group of LAs do not cause allergic reactions.

Drug interactions

- Hypertensive patients receiving therapy of propranolol are sensitive to hypertensive responses of adrenaline, present in few formulations of LA. Simultaneous blockade of β_1- and β_2-receptors leads to an unopposed vasoconstriction by adrenaline because of action on α_1-receptors. Drugs like Haloperidol having α_1-receptor blocking activity may cause hypotension, if administered along with Xylocaine and adrenaline.
- Persons with acute alcohol intoxication need a higher dose of Xylocaine and adrenaline combination for getting proper LA effects. As a result, availability of Xylocaine at the desired site of action is reduced.
- Special care should be taken while giving injection of Xylocaine and adrenaline to a patient of cardiac failure taking Digoxin because of possibility of developing cardiac arrhythmias.
- In coronary care units, where Xylocaine is infused in large doses to treat ventricular arrhythmias, co-administration of Propranolol can cause Xylocaine toxicity. This is because Propranolol inhibits metabolic oxidation of Xylocaine. Propranolol also decreases hepatic blood flow and thus diminishes its delivery to liver for metabolic degradation.

3.8 DRUGS USED IN MYASTHENIA GRAVIS AND GLAUCOMA

Diseases like myasthenia gravis and glaucoma have different Pathophysiology as mentioned below. Anti-cholinesterases are useful for treating myasthenia gravis. Glaucoma is treated by different kinds of drugs. Drugs belonging to both these categories are discussed below:

3.8.1 Drugs for Myasthenia Gravis

Etiology and Symptoms

Myasthenia gravis is an acquired auto-immune disorder causing fatigue and weakness of skeletal muscles. The disease is associated with production of IgG type of antibodies to ACh receptors (N_M) at the post-junctional motor end plate. In 90% of patients having this disease, anti-ACh antibody titre is raised. Reduction in number of N_M receptors results in reduction in amplitude of the end plate potential which in turn fails to trigger an action potential.

The symptoms include weakness of muscle and fatigue which worsens after excersice but goes off after rest. The weakness in muscles is not associated with pain. In early stages of disease, the fast moving muscles are affected first. Hence, symptoms start with ptosis, diplopia, slurring of speech, difficulty in swallowing and weakness of extremities. Subsequently, all muscles are progressively affected including respiratory muscles. The thymus shows abnormality in about 75% cases of myasthenia gravis.

Treatment of Myasthenia Gravis

Any reversible anti-AChE drug of intermediate duration of action is useful for treatment of myasthenia gravis. Initially, the doses are given on an empirical basis but later titrated for prolonged therapy.

Initially Neostigmine is given in a oral dose of 15-30 mg/day in divided doses or 0.5-2.5 mg as intramuscular or sub-cutaneous injection with gradual increment till therapeutic goals are achieved. Alternatively oral Pyridostigmine 60 mg three times a day is followed by gradual increase till satisfactory response. Another alternative is oral Ambenonium 2.5-5 mg, every 6 hours.

Sustained release preparations of Pyridostigmine are also available, which can be given at bed time. Longer acting AChE inihibitors like organophosphates are not used.

During prolonged therapy, titration of the dose is done. The patient's condition may swing between myasthenia gravis (due to lower doses of drugs) or cholinergic crisis (due to toxicity of drugs). Both the conditions can end up in to muscular weakness. In such cases, doses of anti-AChE drug need to be adjusted. Prior to such dose adjustments, Edrophonium is given intravenously in a dose of 2 mg. If the condition worsens due to Edrophonium, the muscular weakness is due to overdosing of AChE dose like Neostigmine. On the contrary, if the condition of the patient improves after Edrophonium dose, the muscle weakness is due to myasthenia gravis. Based on the response to Edrophonium, the dose of anti-AChE drug is adjusted.

Drugs Causing Myasthenia Gravis

Following drugs are known to aggravate myasthenia gravis. See table 3.7. Doses of these drugs should be reduced or these drugs may be withdrawn during treatment of myasthenia gravis.

Table 3.7: Drugs which aggravate myasthenia gravis

Sr. No.	Category of drug	Examples
1.	Antibiotics	Aminoglycosides (Streptomycin, Gentamycin), Polymixins, Colistin
2.	Anti-arrhythmics	Procainamide, Quinidine and Propranolol
3.	CNS depressants	Morphine (respiratory depression)
4.	Miscellaneous	d-TC, Quinine, Methoxyflurane and Lithium

Since etiology of myasthenia gravis originates in auto-immunity, drugs like glucocorticoids (Prednisolone), immune-supperssants (Azathioprine, Cyclosporine) are used to treat myasthenia gravis. In addition, techniques like thymectomy or plasmapheresis are also used to treat myasthenia gravis.

3.8.2 Drugs for Glaucoma

Glaucoma is characterised by an increase in intra-occular pressure (IOP) which, if persistent, can lead to damage to optic disc resulting in blindness. Usually glaucoma is caused by impaired drainage of aqueous humour, produced by the ciliary epithelium in the posterior chamber of the eye. Refer to Fig. 3.8. Normally, aqueous humour flows in to the anterior chamber by passing between the lens and the iris and then out through the pupil. Finally, it leaves the anterior chamber by flowing through the trabecular mesh work and in to the canal of Schlemm (Fig. 3.8) which lies at the base of an angle formed at the intersection of cornea and the iris. This region is called the ocular angle.

There are three types of glaucoma: primary, secondary and congenital. Treatment is available for primary glaucoma and certain types of secondary glaucoma (after trauma or after cataract operation). There is no treatment for congenital glaucoma.

The primary glaucoma is associated with a direct disturbance in outflow of aqueous humour. It is divided in to two sub-types: narrow angle glaucoma and wide angle glaucoma.

(i) Narrow angle glaucoma (closed angle, acute congestive or angle closure glaucoma)

In this case, the pressure from the posterior chamber pushes the iris forward, closing the ocular angle and preventing the drainage of aqueous humour. The iris may also physically block the passage of aqueous humour through tne canal of Schlemm. This is medical emergency. Patients present with a painful red eye, sweating, headache with nausea and vomiting as a result of rise in IOP. The drugs may control the acute attack but the long range treatment involves surgery.

(ii) Wide angle glaucoma (open angle, chronic simple glaucoma)

In this case, the ocular angle remains wide but the trabecular mesh work starts losing patency due to progressive degeneration. As a result, the outflow of aqueous humour gets impeded. In this type, the surgical intervention is not much helpful. Control of IOP is usually dependent on long range drug therapy.

The cholinomimetic (parasympathomimetic) drugs decrease the IOP in both types of glaucoma; however the mechanisms are different. In closed angle glaucoma, the papillary constriction lowers the IOP by pulling the iris away from the trabecular mesh work with consequent opening of the ocular angle. In wide angle glaucoma, it is the contraction of the longitudinary ciliary muscle which stretches the trabecular mesh work and opens the tubules to facilitate the drainage of aqueous humour leading to decrease in IOP.

The treatment is started with 0.5% Pilocarpine, three times a day as eye drops. If it is not effective, Physostigmine may be added. The drugs used to treat glaucoma, along with their mechanism and dosage is listed in table 3.8.

Table 3.8: Drugs used in treatment of glaucoma

Sr. No.	Group	Mechanism	Drugs	Dosage regimen
1.	Directly acting cholinomimetics	Contraction of ciliary muscle, papillary constriction, pulling of iris, drainage of aqueous humour, decrease in IOP	Pilocarpine	0.5-4% topically thrice a day; or as sustained release ocular inserts
2.	Reversible anti-AChE	-do-	Physostigmine	0.25-5% topically thrice a day
3.	Reversible anti-AChE	-do-	Demecarium	0.25-5% topically twice a week
4.	Irreversible anti-AChE	-do-	Ecothiophate	0.05-0.25% topically once in two weeks
5.	Irreversible anti-AChE	-do-	Isoflurophate	0.03% topically
6.	β-blockers	Reduce formation of aqueous humour	Timolol	0.25-0.5% twice a day
7.	β-blockers	-do-	Betaxolol	0.25-0.5% twice a day
8.	β-blockers	-do-	Levobunolol	0.25-0.5% once a day
9.	β-blockers	-do-	Carteolol	1% solution topically
10.	Non-selective α-agonists	Facilitate outflow of aqueous humour	Epinephrine	0.5-2% topically

contd. …

11.	Non-selective α-agonists	-do-	Dpipvefrine	0.1% twice or thrice a day
12.	Selective α_{2}-agonists	Reduce formation of aqueous humour	Apraclonidine	0.5-1% topically
13.	Selective α_{2}-agonists	-do-	Brimonidine	0.2% topically
14.	Carbonic anhydrase inhibitors	Reduce formation of aqueous humour	Acetazolamide	250-500 mg three times a day orally
15.	Carbonic anhydrase inhibitors	-do-	Dorzolamide	2% solution twice a day topically
16.	Carbonic anhydrase inhibitors	-do-	Brinzolamide	1% solution twice a day topically
17.	Hypertonic solutions	Reduce IOP by osmotic action	Mannitol 20%	Infused intravenously
18.	Hypertonic solutions	-do-	Glycerol	Given orally
19.	Prostaglandins	Reduce IOP by increasing outflow of aqueous humour	Latanoprost	0.005% solution once daily
20.	Prostaglandins	-do-	Bimatoprost	0.03% solution once daily

QUESTIONS

Long Answer Questions:

1. Comment on organisation of nervous system.
2. Describe the role of autonomic nervous system.
3. Give a summary of effects of stimulation of sympathetic nervous system.
4. Give a summary of parasympathetic nervous system.
5. Compare and contrast parasympathetic nervous system with sympathetic nervous system.
6. Discuss distribution and functions of adrenergic receptors.
7. Classify neurotransmitters with suitable examples.
8. Discuss the process of biosynthesis, storage and release of Ach.
9. Discuss the process of biosynthesis, storage and release of adrenaline/nor-adrenaline.
10. Comment on metabolism of caecholamines.

11. Classify muscarinic receptors.
12. Classify α-receptors.
13. Classify β-receptors.
14. Give a summary of therapeutic uses of anti-muscarinic drugs.
15. Comment on clinical uses of blockers of α-receptors.
16. Comment on clinical uses of β-receptors.
17. Comment on non-catecholamine sympathomimetics.
18. Write pharmacological actions, mechanism of action, clinical uses and adverse reactions to Clonidine.
19. Write pharmacological effects of Amphetamine.
20. Write pharmacological actions, clinical uses and adverse effects of Prazosine.
21. Describe pharmacological actions of Propranolol.
22. Classify β-blockers with suitable examples.
23. Comment on mechanism of action of neuromuscular blocking agents.
24. Discuss pharmacodynamic effects of dTC.
25. Comment on pharmacokinetics and pharmacodynamics of succinyl choline.
26. Classify local anaesthetics and elaborate their mechanism of action.
27. Comment on etiology, symptoms and treatment of myasthenia gravis.
28. With suitable examples comment on drugs aggravating myasthenia gravis.
29. What is pathophysiology and treatment for glaucoma.

Small Answer Questions:

1. Define following terms:
    - Neurotransmission
    - Neuromodulation
    - Neuromediation
2. Write short nots on:
    - Effects of ACh on eye.
    - Muscarinic receptors
    - Nicotinic receptors
    - α-receptors
    - β-receptors
    - Physostigmin
    - Neostigmine
    - Beladona poisoning
    - Pilocarpine
    - Glaucoma
    - Atropine
    - Dicyclomine
    - Endogenous catecholamines.
    - Dale's vasomotor reversal
    - Isoprenaline

- Clonidine
- Ergot alkaloids
- dTC
- Succinyl choline
- Dantroline
- Pharmacokinetics of local anaesthetics
- Drug interactions of local anaesthetics
- Adverse effects of local anaesthetics

■■■

Unit ... 4

PHARMACOLOGY OF CENTRAL NERVOUS SYSTEM - I

♦ LEARNING OBJECTIVES ♦

After completing this chapter, student should be able to understand:

- *Neurohumoral transmission in CNS with special emphasis on GABA, Glutamate, Glycine, 5-HT, Dopamine*
- *Pharmacology of general anaesthetics/pre-anaesthetics*
- *Pharmacology of sedatives, hypnotics and centrally acting muscle relaxants*
- *Pharmacology of antiepileptics*
- *Pharmacology of alcohol*

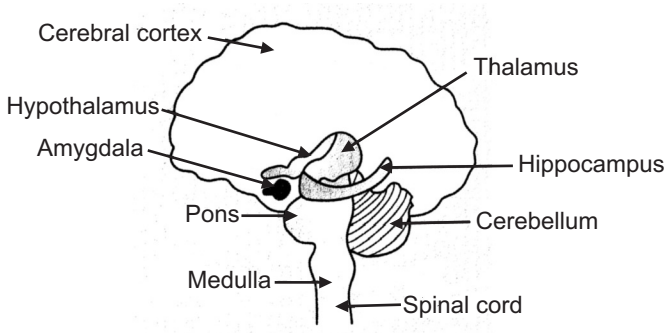
4.1 ORGANISATION OF CNS

The brain works through chemical neurotransmission. It is concerned with all processes in the body like circulation, digestion, respiration, movements, psychic processes like emotional feelings, attitude, thoughts, memory including balanced co-ordination. It also secretes certain hormones which control various functions in the body. The brain is protected by a specialized system of capillary endothelial cells known as blood-brain-barrier (BBB). The role of BBB is as follows:

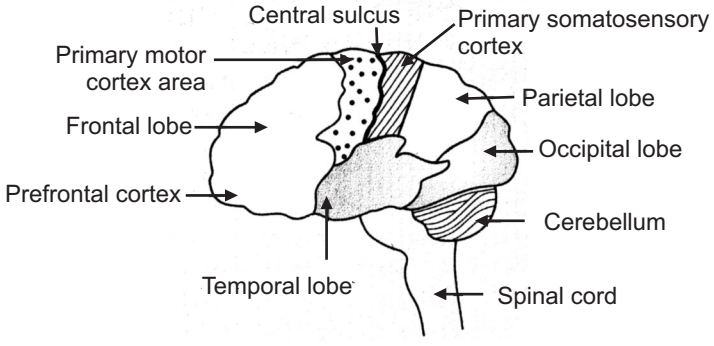
- To preserve the internal environment of the brain.
- To maintain the desired concentration of nutrients and to regulate the levels of circulating neurotransmitters such as E, NE ACh, 5-HT, and DA.
- To protect the brain tissue, both from toxic substances which may circulate in blood and also from neurotransmitters like E, NE, ACh and DA, which are released peripherally but can also bind to CNS receptors to cause adverse effects.

The BBB does not cover all parts of the brain. The organs of CNS not covered by BBB include the following:

- Area posterma (beneath the floor of fourth ventricle i.e. CTZ) and vomiting centre.
- Pineal gland
- Pituitary gland
- Median eminence
- Choroid plexus capillaries



(a) Anatomical structures in the brain



(b) Regions of cerebral cortex

Fig. 4.1

The major anatomical divisions of the brain (Fig. 4.1) are as follows:

- Cerebrum (cerebral cortex of cerebral hemispheres)
- Sub-cortical region including thalamus and hypothalamus (diencephalon)
- The mid-brain (the upper segment of brain stem)
- The hind-brain composed of pons, medulla and cerebellum.
- The spinal cord

The cerebrum (cerebral cortex) is the largest part of the human brain and is divided in to left and right hemispheres. Left hemisphere is associated with logic and reasoning while the right hemisphere is related to creativity. The cerebral cortex consists of four regions as mentioned below (Fig. 4.1):

- The frontal cortex, which is associated with higher cognitive functions and long-term memory storage. The posterior part of the frontal cortex, called as primary motor cortex controls fine movements.
- The parietal lobe integrates and processes sensory information from touch, muscle stretch receptors and joint receptors. Hence, it is called as somato-sensory cortex.
- The temporal lobe is involved in auditory functions and language and also processes sensory information originating from ears and vestibular organs.
- The occipital lobe is involved in visual processing and receives information from visual pathways. It is also referred as visual cortex.

Major cholinergic and dopaminergic pathways pass through cerebral cortex region.

The thalamus has both sensory and motor functions. It is a relay centre for sensory pathways to the cortex. It is related to appreciation of pain, temperature and crude touch sensation. The hypothalamus located below thalamus is involved in homeostasis, emotion, thirst, hunger, circadian rhythm and control of autonomic functions. It also controls pituitary gland. The limbic system consists of hippocampus (involved in learning and memory), the amygdale (associated with emotions, fear and memory) and the ventral tegmental area or nucleus accumbens (involved in addiction). Thus, the limbic system consists of structures below the cerebral cortex which control emotions and instincts along with motor and visceral activities. The basal ganglia is a part of extra-pyramidal system consisting of corpus striatum (caudate nucleus + putamin + globus pallidus) and substantia nigra. It provides extra-pyrimidal control of skeletal muscle tone and its co-ordination with posture. Its degeneration produces tremors and rigidity. It contains the major dopaminergic pathway of the CNS.

The reticular formation is a heterogenous mass of cell bodies embedded in a network of dendrites and axons located in the central core of medulla, pons and mid-brain. It is a diffused multi-synaptic system. A complex interrelated group of pathways passing through the reticular formation is called as reticular activating system (RAS). It is intimately related to sleep-wakefulness cycle and co-ordination of gaze and eye movements. All sensory information is rooted through the RAS. It also controls the muscle tone, posture and vital functions like respiration and circulation. It has major monoamine containing neurons of the brain.

The medulla and pons (including mid-brain) are called as brain stem and are involved in vision, hearing and in body movements. The medulla regulates vital functions like breathing and heart rate. The pons control motor and sensory functions and plays a vital role in consciousness and sleep. The cerebellum is associated with the control of vestibular functions, body posture and balance. Cerebellum and brain stem relay information from the cerebral cortex and the limbic system to the spinal cord. The spinal cord integrates the sensory and motor reflexes and also controls the muscle tone.

4.2 NEURO-HUMORAL TRANSMISSION IN THE CNS, SPECIAL EMPHASIS ON IMPORTANCE OF VARIOUS NEUROTRANSMITTERS LIKE GABA, GLUTAMATE, GLYCINE, SEROTONIN, DOPAMINE

4.2.1 Neurohumoral Transmission in the CNS

Four processes occur in relation to nerve transmission within the CNS. These processes are mediated through different transmitters. They are as follows:

- Neurotransmission occurs through neurotransmitters, which are released in to synaptic cleft to rapidly stimulate or inhibit the post-synaptic neurons.
- Neuro-modulation occurs through neuromodulators, which are releasd by neurons and by astrocytes and act either to slow or enhance the pre- or post-synaptic responses.
- Neuromediation occurs through neuromediators, which are second messengers like cAMP, cGMP and IP_3.

- Neurotropic effects occur through neurotropic factors, which are secreted by neurons, astrocytes, microglia and act over a longer time to regulate the growth and morphology of neurons.

Some of the major neurotransmitters are discussed beolow:

4.2.2 GABA

GABA (Gamma-Aminobutyric Acid) is a major inhibitory neurotransmitter in mammalian CNS. It is present fairly uniformly in the brain. Very little amount exists in the periphery. GABA is synthesised from glutamate by the action of enzyme L-glutamic acid-1-decarboxylase (GAD). (Fig. 4.2). It is further metabolised by GABA transaminase (GABA-T) to succinic semi-aldehyde and succinic acid. Glutamate needed for synthesis of GABA is formed mainly from the TCA cycle product (α-oxaglutarate) by the action of enzyme GABA-T. Two types of GABA receptors have been identified: $GABA_A$ and $GABA_B$.

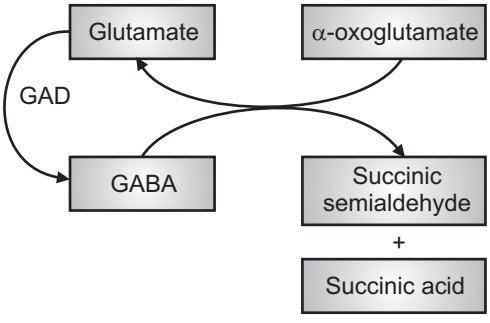
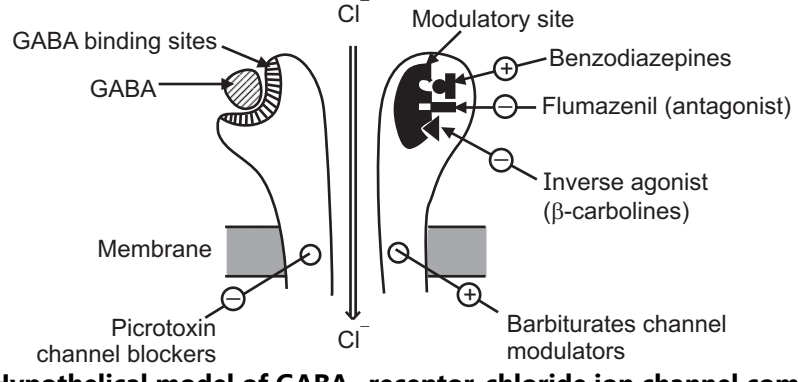


Fig. 4.2: Synthesis and Metabolism of GABA

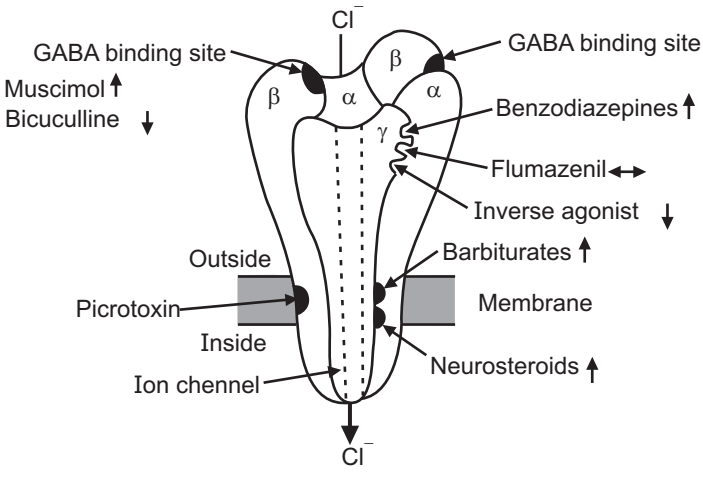
4.2.2.1 $GABA_A$ Receptors

These are ionotropic receptors. They are most prevalent receptors. They are located post-synaptically and are directly linked with chloride ion channel opening which causes hyper-polarisation and reduction in the membrane excitability. Muscimom is an agonist of $GABA_A$ receptors, while Bicuculline is its antagonist. The receptor has several different accessory binding sites as shown in Fig. 4.3. The sites are as follows:

- GABA binding site.
- The modulatory sites to bind Benzodiazepines (BZDs); their antagonists like Flumazenil and inverse agonist like carbolins also bind to the same site.
- The modulatory as well as blocking site at chloride ion channel as for barbiturates and picrotoxin.



(a) Hypothelical model of $GABA_A$ receptor-chloride ion channel complex



(b) Sites of various drugs action

Fig. 4.3

These receptors have a pentameric structure assembled from five sub-units selected from seven polypeptide classes, named as α, β, γ, δ, ε, θ, ρ (alpha, beta, gamma, delta, epsilon, theta and rho respectively). The major isoform of $GABA_A$ receptor in the brain consists of five sub-units, namely two α_1, two β_2 and one γ_2 sub-units. It is known that binding of GABA with its site, located between α_1 and β_2 sub-units, triggers chloride channel opening with resultant membrane hyper-polarisation. Binding sites for BZDs lies between α_1 and γ_2 sub-units which facilitates GABA binding to its receptor sites and increases the frequency of chloride channel opening.

The adjacent site between α and β sub-units of $GABA_A$ receptors are the functional receptional receptors which respond to barbiturates but not to BZDs. Convulsants like Picrotoxin block the chloride ion channel directly. Sites of action for few other drugs have been indicated in Fig. 4.3.

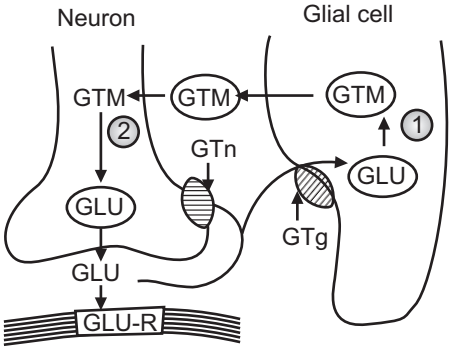
4.2.2.2 $GABA_B$ Receptors

Unlike $GABA_A$ receptor, $GABA_B$ receptor is not modulated by BZDs or barbiturates. It is not linked to chloride channel. It is a G-protein coupled receptor. Its activation decreases formation of cAMP. These receptors cause pre- and post-synaptic inhibition (hyper-polarisation) by inhibiting calcium channel opening and increasing K^+ conductance. The peripherally acting skeletal muscle relaxant, Baclofen, is a $GABA_B$ receptor agonist and is used to treat spastic disorders. The competitive antagonist for $GABA_B$ receptor is Saclofen, which has no clinical use.

4.2.3 Glutamate

In brain, glutamate (GLU) is synthesised in the nerve terminals from two sources: from glucose via Krebs cycle and transamination of oxaglutarate (Fig. 4.2) and from glutamine which is synthesised in the glial cells (Fig. 4.4). GLU is stored in synaptic vesicles and released by calcium dependent exocytosis. After release and action, GLU is recaptured by neuronal GLU-transporters (GTn) in to the neuron and by glial type transporters (GTg) in to the glial

cells. Glial glutamate is then converted to glutamine by the enzyme glutamine synthetase. Later, glutamine enters the adjacent neuron to replenish the glutamine after hydrolysis by mitochondrial glutamase. (Fig. 4.4). Thus, glutamine serves as a pool of inactive transmitter within glial cells.



Key: GLU-R – glutamate receptor; GTM – glutamine; GTn – glutamate transporter neuronal type; GTg – glutamate transporter glial type; (1) glutamine synthetase; (2) glutaminase

Fig. 4.4: Synthesis, Storage, Release and Metabolism of GLU

GLU and aspartate (ASP) are the excitatory neurotransmitters widely concentrated in cortex, basal ganglia and sensory pathway. Five different types of glutamate receptors have been identified. Out of these five types, three (NMDA, AMPA and Kainate)are ionotropic receptors. The other two are metabotropic receptos. Role of metabotropic receptors is being unfolded by new research. Ionotropic receptors are discussed below.

4.2.3.1 NMDA Receptors

NMDA refers to **N-m**ethyl-**D-a**spartate. The receptors are involved in a wide range of diverse functions like memory acquisition, development of synaptic plasticity, epilepsy and the neuronal excitotoxicity due to cerebral ischaemia. NMD receptor is a pentamer, composed of two different sub-units called as NR1 and NR2. It is ligand-gated ion channel receptor with high permeability to calcium and sodium ions. It has a wider distribution in brain (hippocampus, cerebral cortex, glial cells) and spinal cord. The receptor has atleast six binding and modulatory sites. The model of receptor is shown in Fig. 4.5.

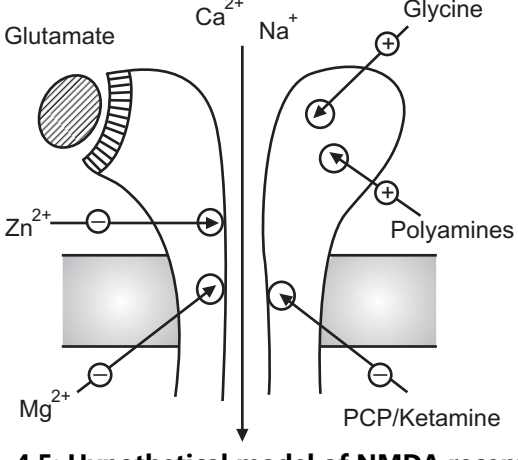


Fig. 4.5: Hypothetical model of NMDA receptor

4.2.3.2 AMPA and Kainate Receptors

AMPA refers to α-**a**mino-3-hydroxy-5-**m**ethylisoxazole-4-**p**ropionic **a**cid. Both AMPA and Kainate receptors mediate fast excitatory synaptic transmission associated with influx of sodium ions through sodium channels. Both are different than NMDA receptor.

AMPA receptors are pentamers consisting of $GLUR_{1-4}$ sub-units. Kainite receptors are also pentamers but consist of $GLUR_{5-7}$ and KA_{1-2} sub-units. Domoate and Kainate are the preferred agonists to kainite receptors.

Both NMDA and metabotropic receptors play an important role in long-term adaptive changes (synaptic plasticity) as well as pathological changes (excitotoxicity) in the brain. Normal stimulation of glutamate receptor plays a central role in learning and memory but over-stimulation of glutamate receptor, particularly NMDA type results in excitotoxicity in brain leading to neuro-degeneration and apoptosis.

4.2.4 Glycine

It is an inhibitory neuro-transmitter, enriched in medulla, spinal cord, the lower brain stem and retina. It is structurally and functionally similar to $GABA_A$ receptor and is directly linked to chloride ion channel. Strychnine-sensitive glycine receptor is a pentameric structure, α sub-unit of which binds both to glycine and strychnine. Strychnine is a competitive antagonist at glycine receptor.

Activation of NMD receptors requires low concentration of glycine along with glutamine. Binding sites of glutamate and glycine are different but both have to be occupied; only then the receptor channel opens.

4.2.5 Serotonin (5-Hydroxytryptamine, 5-HT)

5-HT has diverse pharmacological and physiological roles which include as a neurotransmitter in CNS, as a regulator of smooth muscle function in CVS and GIT and as regulator of platelet function, besides other subsidiary roles in several functions.

(a) Distribution, Biosynthesis, Release and Metabolic Degradation

5-HT is formed by dietary tryptophan which is converted to 5-hydroxy tryptophan by the enzyme Tryptophan hydroxylase. 5-hydroxy tryptophan is further converted to 5-HT by a non-specific aromatic L-amino acid decarboxylase (dopa decarboxylase). (Fig. 4.6). 5-HT is stored in specialised cells like enterochromaffin cells and neurons as co-transmitter together with various peptide hormones like somatostatin, vasoactive intestinal peptide (VIP) and substance P.

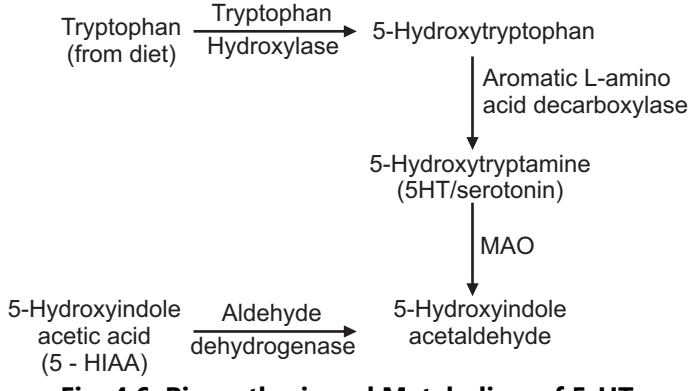


Fig. 4.6: Biosynthesis and Metabolism of 5-HT

Degradation of 5-HT occurs through oxidative deamination by MAO, to 5-hydroxy indole acetaldehyde followed by its oxidation to 5-hydroxy indole acetic acid (5-HIAA), which is excreted in urine.

(b) Pharmacological Actions of 5-HT

Various actions of 5-HT, evident on different systems are indicated below:

(i) CNS

5-HT is involved in the regulation of mood, behaviour, sleep, depression, pain perception, sexual activity, thermo-regulation and in the hypothalamic control of the release of pituitary hormones. 5-HT is also synthesised in pineal gland where it is precursor for the synthesis of melatonin, a melanocyte stimulating hormone, which influences sleep. Externally injected 5-HT does not cross BBB.

(ii) CVS

5-HT directly causes contraction of vascular smooth muscle (including intra-cranial vessels), except in skeletal muscles and heart where it causes vasodilatation and bradycardia. When injected intravenously, it produces a typical triphasic response. There is an early sharp fall in heart rate and blood pressure. The bradycardia is mediated by vagal outflow to the heart and can be blocked by atropine. The hypotension is a consequence of decrease in cardiac output caused by bradycardia. Thereafter there is a rise in blood pressure due to peripheral vasoconstriction and increase in cardiac output. Finally, there is a sustained hypotension due to dilatation of blood vessels of skeletal muscles. Still, 5-HT is not involved in physiological regulation of blood pressure.

5-HT causes blood platelets to aggregate by activating 5-HT_{2A} receptors and the aggregation is followed by further release of 5-HT. If the endothelium is damaged, the release from adherent platelet causes vasoconstriction which impairs blood flow. Platelet-derived 5-HT plays an important role in vascular diseases.

(iii) GIT

5-HT stimulates peristalisis and gastric secretions via 5-HT_4 receptors. Activation of 5-HT_4 receptors in CNS causes increased release of ACh, which mediates a pro-kinetic (motility enhancing) effect of 5-HT. Some of the 5-HT_4 receptor agonists like Cisapride and Mozapride are also pro-kinetic. Overproduction of 5-HT, as in carcinoid tumour (a tumour of enterochromaffin cells) is associated with severe diarrhoea.

(iv) Miscellaneous Effects

- 5-HT, like Histamine, stimulates perception of pain and itch by activating 5-HT_3 receptors on afferent nerve endings.
- 5-HT constricts bronchial smooth muscles by facilitating ACh release from bronchial nerve endings. It may result in hyperventilation due to stimulation of bronchial sensory nerve endings by 5-HT.
- 5-HT reduces food intake and also has an anorexigenic effect.

(c) Location and Importance of 5-HT

Serotonergic neurons are found near the middle raphe nuclei of the brain stem and project to the cortex, cerebellum and the spinal cord. About 90% of the serotonin in the body is found in enterochromaffin cells in the GIT and remaining 10% is shared by platelets and the brain. Serotonergic system plays an important role in schizophrenia, depression, temperature regulation and eating disorders. In addition, serotonin is synthesised in the pineal gland where it serves as a precursor for the synthesis of melatonin.

(d) 5-HT Receptors

5-HT acts on more than a dozen receptor sub-types. Mainly there are seven main types of receptors (5-HT_1, 5-HT_2,...5-HT_7). Of these, 5-HT_1 and 5-HT_2 are sub-divided further. Except for 5-HT_3 sub-type which is ionotropic, all others are metabotropic (G-protein coupled) receptors. 5-HT_{1A} agonists (Buspirone) are used to treat anxiety disorders; 5-HT_{1D} receptor agonists (Sumatriptan) are used to treat migraine and cluster headaches; 5-$HT_{2A/2C}$ antagonists (Clozapine) are used to treat schizophrenia, while 5-HT reuptake inhibitors (SSRIs Fluoxetine) are used to treat depression and obsessive-compulsive disorders.

(i) 5-HT Receptor Agonists

5-HT has no clinical application as drug. However, following selective agonists have therapeutic value:

- **Bispirone** group of anti-anxiety drugs are partial agonists of 5-HT_{1A} receptors in CNS.
- **Sumatriptan** and its conginers are selective agonists of 5-HT_{1D} receptors, which being cerebral vasoconstrictors are useful to treat acute migraine attacks.
  Dosage of Sumatriptan is 25-100 mg as a single oral dose. It is less effective orally. Sub-cutaneous injection is repeated once in 24 hours. It is also given as 5-20 mg nasal spray to a maximum of 40 mg in 24 hours.
  Other drugs in this category are Almotriptan, Eletriptan, Naratriptan, Zolmitriptan and Rizatriptan.
- **Cisapride and Renzapride** are selective 5-HT_4 receptor agonists which increase GIT motility and are used to treat gastro-esophageal reflux disease (GERD). **Tegaserod** is a new addition in this category.
- **Dexfenfluramine** is a non-selective 5-HT receptor agonist. It blocks 5-HT transporter and inhibits 5-HT uptake. It was earlier used as appetite suppressant. It is withdrawn due to cardio- and neurotoxicity. **Sibutramine** also acts similar to Dexfenfluramine, and is used to treat obesity.
- **d-Lysergic acid diethyl amide (LSD)** is another non-selective 5-HT receptor agonist. It is a potent hallucinogen and a drug of abuse.

Sumatriptan is available as tablets of 25 mg, 50 mg and 100 mg. It is also available as 6 mg/ml injection.

(ii) 5-HT Receptor Antagonists

Clinically useful 5-HT antagonists are discussed below:

Ketanserin and Ritanserin are antagonists of 5-HT_{2A} receptors. **Ketaneserin** is an anti-hypertensive drug due to its α_1- adrenoceptor blocking action. In addition, due to blockade of 5-HT_{2A} receptors, they antagonise platelet aggregation caused by 5-HT. This action provides symptomatic relief in conditions like Raynaud's disease. **Ritanserin** is a conginer of Ketanserin. It is more selective 5-HT_{2A} antagonist and has insignificant α_1 blocking action. It reduces thromboxane formation and increases bleeding time by inhibiting platelet aggregation time.

Ondansetron, Dolasetron and Granisetron are 5-HT_3 receptor antagonists and are used for treating chemotherapy-induced emesis.

Clozapine, Olanzapine, Quetiapine and Risperidone are 5-HT_{2A} and 5-HT_{2C} receptor antagonists. In addition, they are also dopamine receptor antagonists and are used as a typical anti-psychotic agents.

Methysergide is one of the ergot alkaloids. It is a potent 5-$HT_{2A\text{-}2C}$ antagonist with some non-selective action on 5-HT_1 receptors. Earlier it was used for prophylaxis of migraine. Its use is declining.

Cyproheptadine has 5-HT_{2A} receptor antagonist action along with histamine H_1 blocking effect. It has a mild anti-cholinergic activity and CNS depressant effect. It is useful in controlling skin allergies and in cold urticaria.

(iii) 5-HT Receptor Partial Agonists/Antagonists

Ergot alkaloids possess partial agonist-antagonist actions on 5-HT receptors. The most important alkaloids in this group are Ergotamine and Dihydroergotamine. Both are partial agonists/antagonists on 5-HT_1 receptors. Ergometrine is a uterine stimulant and 5-HT_2 receptor agonist. It is used in obstetric practice to prevent post-partum haemorrhage. Ergot alkaloids are contraindicated in pregnancy, peripheral vascular disease, coronary artery disease and hypertension.

4.2.6 Dopamine (DA)

It is the most important of the biogenic neurotransmitters in CNS. Parkinson's disease is characterised by a marked reduction in the concentration of DA in basal ganglia, while in schizophrenia there is dopaminergic overactivity in the pathway of brain which controls behaviour. DA is primarily an inhibitory neurotransmitter. Its deficiency causes extra-pyramidal disturbances.

Five types of DA receptors (D_1 ro D_5) have been identified. Among them D_1 and D_5 belong to one group, while D_2, D_3 and D_4 belong to another group. D_1 and D_5 stimulate release of cAMP by activation of adenylyl cyclase and also stimulate phosphatidyl inositol (PIP_2) hydrolysis. These receptors are coupled to G_S protein (metabotropic rececptors). Its inhibition causes extra-pyramidal disorders. Unlike this, D_2, D_3 and D_4 receptors inhibit cAMP release, block calcium ion channels and open potassium ion channels. These are coupled to G_1 proteins and are involved in control of behaviour, voluntary movements, prolactin release and in other endocrine consequences. Some of the atypical neuroleptics possess antagonistic properties D_3 and D_4 receptors.

4.3 GENERAL ANAESTHETICS AND PRE-ANAESTHETICS

The distinguishing features of general anaesthesia include varying degree of analgesia, amnesia, loss of all sensations, reflexes and consciousness. In addition, it also involves relaxation of muscles with partial loss of homeostatic control over respiratory and cardiovascular functions. General anaesthesia develops in to four different stages after administration of general anaesthetics. The stages are as follows:

4.3.1 Stages of Anaesthesia

Stage I

It is the state of analgesia, because sensory transmission in spino-thalamic tract is inhibited. There is no amnesia. Consciousness and sense of touch are present, while sense of hearing is enhanced.

Stage II

It is the state of excitement and delirium. The patient shows violent behaviour and is amnesic. There is irregular rise in blood pressure and respiratory rate. To avoid these symptoms, a short acting barbiturate like thiopental sodium is given intravenously before administration of inhalation anaesthetic.

Stage III

It is the stage of surgical anaesthesia. Regular respiration and relaxation of skeletal muscle occurs during this stage. It is divided in to following four planes:

- **Plane 1:** During this plane, there are revolving movements of eye balls which while attaining plane 3 get fixed. Respiration and skeletal muscle tone are normal.
- **Plane 2:** Most surgical procedures are performed during this plane. There is progressive loss of corneal, light and laryngeal reflexes. Respiration is slow but regular.
- **Plane 3:** It is a plane of marked muscle relaxation. Respiration is abdominal. Eye ball movement is absent. Pupils are dilated. Light, corneal and laryngeal reflexes are absent.
- **Plane 4:** It is a plane of complete muscle relaxation. Pupils are dilated. There is complete loss of light, corneal and laryngeal reflexes. Respiration is abdominal.

Stage IV

It is a stage of medullary paralysis. It appears due to overdose of the general anaesthetic. During this stage, there is severe depression of respiratory centre and vasomotor centre in medulla. The stage is fatal causing death of the patient.

The most reliable index for attainment of stage III is loss of corneal reflex and establishment of regular respiratory pattern. A fall in BP, cardiac and respiratory depression are the signs of deep anaesthesia. As against this, resistance to insertion of endotracheal tube is the sign of light anaesthesia. Monitoring of vital signs reduces the dose requirement of general anaesthetic which contributes to rapid recovery from general anaesthesia.

4.3.2 General Anaesthetics

They are classified as inhalation anaesthetics and intravenous anaesthetics. Their names are given below:

- **Inhalation Anaesthetics**
  They exist in two forms: gas or liquid. The only gas used for the purpose is nitrous oxide. The halogenated liquids are Halothane, Methoxyflurane, Enflurane, Isoflurane, Sevoflurane and Desflurane.
- **Intravenous Anaesthetics**
  They are sub-classified as fast inducers, slow inducers and dissociative anaesthetics.
  - Fast inducers are either barbiturates or non-barbiturates. Examples of barbiturates are Thiopental and Methohexital. Examples of non-barbiturates are Propofol and Etomidate.
  - Examples of slow inducers are Benzodiapines like Diazepam, Lorazepam and Midazolam.
  - Ketamine is the only dissociative anaesthetic.

Pharmacokinetic Principles

There are three factors which need attention. They are induction, maintainence and recovery. The principles of pharmacokinetics should be understood in the context of these factors.

- **Induction**
  It means the time interval between the administraton of anaesthetic drug and the development of stage of surgical anaesthesia. Lipophilicity is the key factor governing pharmacokinetics of inducing drugs. Being highly lipophilic, after a single intravenous bolus injection, these drugs preferentially enter in the brain. Redistribution out of CNS in to muscle, viscera and lipophilic adipose tissue are the main causes for termination of action.
- **Maintainence**
  It is the period during which the patient remains in a sustained stage of surgical anaesthesia (stage III, plane-2). During this stage, the anaesthesiologist monitors the patient's vital signs and response to various stimuli by controlling concentration of anaesthetic to be inhaled or infused based on depth of anaesthesia. The factors which influence uptake and distribution of the anaesthetic, govern the rate at which an effective concentration of the anaesthetic reaches the brain. This requires transfer of anaesthetic from alveolar air to the blood and then to the brain. The rate of transfer depends on following factors:
  - Alveolar wash-in
  - Solubility characteristic of anaesthetic drug
  - Concentration of the drug in the inspired air
  - The pulmonary ventilation rate
  - Cardiac output
  - The partial pressure gradient of the drug between arterial and venous blood before its redistribution

- **Recovery**

  The recovery phase starts when the anaesthetic drug is discontinued. During this phase, the anaesthesiologist has to ensure that there are no delayed toxic reactions. Frequently, oxygen is given during last few minutes of anaesthesia and in early post-anaesthetic period. Metabolism of anaesthetic is an important factor during recovery. The gradation of metabolism of anaesthetics by liver is as follows: methoxyflurane > halothane > enflurane > sevoflurane > isoflurane > desflurane > nitrous oxide. Nitrous oxide is almost totally washed out by exhalation.

Potency of Inhaled Anaesthetics

The potency of inhaled anaesthetics is quantified by the term Minimum Alveolar Concentration (MAC). MAC is the minimum concentration of the anaesthetic which is required to prevent movement in 50% of patients in response to a standard surgical skin incision. MAC values are expressed as percentage of anaesthetic gas in the inspired mixure. Smaller MAC values indicate greater potency of anaesthetic. Higher the lipid solubility of the anaesthetic, lower is its MAC value.

MAC value of an anaesthetic decreases with age, hypothermia and by concurrent use of CNS depressant drugs like sedative-hypnotics, anxieolytics and narcotic analgesics. Sex, species, acid-base balance and changes in arterial blood pressure do not influence MAC. The rank order of MAC values (%) of different inhalation anaesthetics is: methoxyflurane (0.16%) < halothane (0.75%)< isoflurane (1.2%) < enflurane (1.7%) < sevoflurane (1.9%) < desflurane (6%) < nitrous oxide (> 100%). The MAC value of nitrous oxide indicates that it is least potent. It indicates that even if 100% of nitrous oxide gas is inspired, its potency is still not equal to 1 MAC.

Mechanism of Action

Inhalation anaesthetics are non-selective in their action. At molecular level, anaesthetics interact with hydrophobic regions of neuronal membrane proteins which are on interface with membrane lipids. Inhaled anaesthetics like barbiturates, benzodiazepines, etomidate and propofol facilitate GABA-mediated inhibition and there by increase chloride ion flux through its channel. Ketamine blocks the action of glutamate on NMDA receptor. Inhalation anaesthetics like enflurane and isoflurane decrease the duration of opening of nicotine receptor activated sodium ion channels leading to decrease in excitatory effects of ACh at cholinergic synapses. By influencing neuronal membrane proteins, general anaesthetics disrupt neuronal firing and sensory processing in the thalamus, causing loss of consciousness and analgesic effects. In addition, motor activity reduce because they decrease neuronal output from the internal pyramidal layer of cerebral cortex.

4.3.2.1 Specific Inhalation Anaesthetics

(i) Nitrous Oxide

It has a mild sweetish smell. It is neither inflammable nor explosive. It is used to maintain surgical anaesthesia with 30% oxygen and other volatile anaesthetics like halothane, isoflurane or propofol and a muscle relaxant if required.

It has a strong analgesic action. Inhalation of 50% nitrous oxide and 50% oxygen has effects comparable to standard dose of morphine. Induction is rapid and recovery takes only 4 minutes. It has no adverse effects on CVS, respiratory system, kidney and liver.

It is less potent; does not cause bronchodilation and has no muscle relaxant effects. The incidence of post anaesthetic nausea and vomiting increases with the duration of anaesthesia. Exposure for more than 4 hours can cause megaloblastic changes in bone marrow.

(ii) Halothane

It is a halogenated volatile anaesthetic. It is relatively inexpensive. It has a mild sweetish odour, non-irritant and non-inflammable. It is a poor analgesic and poor muscle relaxant. It may be used along with nitrous oxide/opioids and skeletal muscle relaxants.

It is pleasant to breathe and not hepato-toxic to children. It is preferred for paediatric use. It is a potent anaesthetic. It abolishes pharyngeal and laryngeal reflexes. It is a bronchodilator and is preferred for asthmatic patients. It inhibits intestinal and uterine contractions and can be used for assisting external or internal version of foetus during late pregnancy. Recovery from halothane is smooth except for shivering, nausea and vomiting.

Its induction and recovery is relatively slow. It is poor analgesic and muscle relaxant. It causes bradycardia and transient fall in BP. It reduces cardiac output and sensitizes myocardium to arrhythmic effects of catecholamines. It is metabolised to trifluroethanol and bromide ion. This may induce delayed fever, anorexia, nausea, vomiting and occasional hepatitis. Repeated administration can cause severe hepatic necrosis; hence it is not repeated within 2-3 weeks. Its use during labour can prolong delivery and can cause post-partum haemorrhage. Normalisation of mental function takes several hours after recovery. It can cause malignant hyperthermia in genetically predisposed cases. Succinyl choline, if used as a muscle relaxant, can worsen the condition. Dantrolene in a dose of 1 mg/kg is given intravenously to treat the condition.

Halothane is available as liquid in a pack of 30 ml, 50 ml, 200 ml: **FLUOTHANE HYPNOTHANE.**

(iii) Methoxyflurane

Because of slow induction, slow recovery, hepatotoxicity and nephrotoxicity, it is not used in clinical practice now.

(iv) Enflurane

It is non-irritating, non-inflammable liquid with mild odour. It decreases heart rate, cardiac output and blood pressure. It also causes uterine relaxation. Unlike halothane, it does not sensitize the heart to catecholamines; hence arrthmia is rare. It causes bronchodilation and is a better skeletal muscle relaxant in comparison to halothane. It has a rapid induction and rapid recovery.

It is contraindicated in epileptic patients due to CNS excitation. It has a greater respiratory depressant action. About 5-8% of the drug is metabolised to fluoride ions with a possibility of polyuric renal failure. Hence it is contraindicated in renal failure. Incidence of hepatotoxicity is relatively low.

(v) Isoflurane

It is a structural derivative of enflurane. It is more potent than enflurane. It is non-inflammable liquid with pungent odour. It exhibits rapid induction and recovery. It is relatively expensive.

It does not cause dilation of pupils and light reflex is not lost. It undergoes minimal metabolism and less fluoride is produced. Hence, hepatotoxicity and nephrotoxicity is less. It does not induce cardiac arrhythmia. Low concentrations of isoflurane do not increase cerebral blood flow or intracranial pressure. It depresses cortical EEG activity and is preferred for neurosurgery. It is also a muscle relaxant. It is a potent coronary vasodilator. It irritates upper airway, but it is a bronchodilator.

It has a pungent odour and causes bronchial irritation. Hence, induction is unpleasant. In patients of coronary artery disease, it may cause redistribution of blood from the area of inadequate perfusion to one of normal perfusion. Being a vasodilator, it causes hypotension and reflex tachycardia.

Isoflurane is available as inhalant liquid in a pack of 30 ml, 100 ml or 250 ml: **FORANE, ISORANE, SOFANE**.

(vi) Desflurane

It is structurally similar to isoflurane. It is non-inflammable, non-explosive but irritant anaesthetic. It has a rapid induction and recovery. It is preferred for out-patient surgery.

Recovery from anaesthesia, psychomotor and cognitive skills is rapid. It undergoes negligible metabolism; hence there is less generation of fluoride ions. Thus, it is relatively safer. It is preferred for prolonged anaesthesia. It rarely precipitates malignant hyperthermia and does not sensitize myocardium to catecholamines. Muscle relaxation is equal to isoflurane and seizure provoking potential is negligible.

It is irritant to airways and may provoke breath holding apnea, laryngospasm, coughing and increased salivation. It is not suitable for children. Depth of anaesthesia fluctuates rapidly with change in inhaled concentration. Incidence of post-operative nausea and vomiting is relatively larger.

(vii) Sevoflurane

It is a non-pungent, non-inflammable anaesthetic. Induction is rapid and smooth. Recovery is also faster than halothane. Being non-pungent, it does not cause respiratory irritation. It is better accepted by children. Induction and recovery are fast. It is a good muscle relaxant. Sensitization of myocardium is relatively less. It is a good choice for inhalation, particularly in children.

It is not a bronchodilator. It may trigger malignant hyperthermia in susceptible patients. About 2% of the drug is metabolised; hence generation of fluoride is less. Thus, it is relatively safe. It is degraded by contact with CO_2 absorbants like soda lime. It is avoided in patients with renal failure. Reported adverse effects are shivering, nausea and vomiting. It is a relatively safe anaesthetic.

4.3.2.2 Specific Intravenous Anaesthetics

Unlike inhaled anaesthetics, intravenous agents do not need specialised vapouriser equipment for their delivery. Intravenous anaesthetics are classified based on their induction time: fast or slow.

(i) Fast Inducers

Drugs like thiopental, methohexital, etomidate and propofol are used because of their fast onset. Recovery also is sufficiently rapid. For short surgical procedures, these agents are used alone. In case of surgery with longer duration, intravenous anaesthetics may be followed by inhalation anaesthetics.

(a) Thiopental

It is a ultra-short acting thiobarbiturate. It induces anaesthesia smoothly within less than a minute. Following an intravenous bolus injection, it crosses BBB rapidly. Due to high lipid solubility, brain equilibrium is attained swiftly. Subsequently, it diffuses rapidly from brain to body fats, muscles and other tissues. Because of rapid removal from brain, it is short acting. Induction dose is 3-5 mg/kg. It is metabolised in liver at a rate of 12-15% per hour. It reduces cerebral blood flow and intracranial pressure. Hence, it is a drug of choice for patients with cerebral edema and brain tumours.

Laryngospasm may be caused if anaesthesia is light. It has no muscle relaxant action. It has no analgesic activity. Shivering and delirium may occur during recovery. Barbiturates precipitate acute intermittent porphyria by inducing the enzyme ALA synthetase. Since pH of intravenous thiopental is 11, it may cause local tissue damage. It also reduces respiratory rate and tidal volume.

Thiopental: **INTRAVAL, PENTOTHAL** *sodium is available as 500 mg, 1 gm powder in a vial for making fresh injection.*

(b) Methohexital

It is a thiobarbiturate similar to thiopental with a short terminal half-life (4-5 hours). Its use has declined due to restlessness, coughing and hiccups during recovery.

(c) Propofol

Induction of anaesthesia occurs with a dose of 1.5-2.5 mg/kg within 30 seconds. Induction is smooth and pleasant with low incidence of excitation. Recovery is rapid with low incidence of nausea and vomiting. On stopping the drug, plasma concentration falls rapidly due to redistribution and metabolism. It is non-irritant to respiratory airways. It has no analgesic or muscle relaxant effects.

It causes dose-dependent cortical depression and has anti-convulsant action. Risk of laryngospasm is low. It is preferred for out-patient surgery.

Apnoea and pain at the site of injection are common adverse effects. It produces marked decrease in systemic blood pressure during induction. It decreases peripheral resistance and can cause bradycardia.

Propofol: **CRITIFOL, PROPOFOL, PROPOVAN** *is available as injection of 1% in 10 ml, 20 ml, 50 ml; 10 mg/ml and 20 mg/ml.*

(d) Etomidate

It has a shorter duration of action (5-10 minutes) and produces much less cardiovascular and respiratory depression. It causes pain on injection; excitatory muscle movements are common on induction and incidence of nausea and vomiting are frequent after recovery. It is a poor analgesic and causes adrenocortical suppression. Hence, it is not preferred for prolonged use. It is occasionally used for emergency anaesthesia because it causes relatively lesser hypotension.

(ii) Slow Inducers

Benzodiazepines (BZDs) are preferred for endoscopies, cataract operations, cardiac catheterisation, angiographies, fracture settings and electro-convulsive therapy (ECT). In addition, they are used as pre-anaesthetics and also for inducing and maintaining anaesthesia. When injected intravenously, they produce sedation, muscle relaxation and amnesia.

Diazepam (0.2-0.5 mg/kg), Lorazepam (0.04 mg/kg) and Midazolam (0.07-0.08 mg/kg) are used intravenously for causing anaesthesia. BZDs are slow inducers but they produce amnesia which is clinically useful. Midazolam is frequently used because it produces higher (> 50%) amnesia. It has a rapid onset and shorter elimination half-life (2-4 hours). It is relatively more water soluble and produces lesser irritation. BZDs do not depress respiration or cardiac functions. They do not cause post-operative nausea or vomiting. They are poor analgesics. An opioid or nitrous oxide is added if analgesia is needed.

Lorazepam: **ATIVAN, LARPOSE, LORVAN, TRAPEX, LOPERZ** *is available as 1 mg, 2 mg tablet or 2 mg/ml injections. Midazolam:* **MIDAZ, MEZOLAM, FULSED** *is available as 1 mg/ml or 5 mg/ml injections. Diazepam:* **VALIUM, CALMPOSE** *is available as 5 mg, 10 mg tablet or 5 mg/ml injection.*

4.3.2.3 Dissociative Anaesthetic - Ketamine

Ketamine is characterised by a feeling of dissociation from surrounding, profound analgesia, immobility and amnesia with light sleep. Its primary site of action is cortex and limbic system. It acts by blocking the action of glutamate at NMDA receptor. It is a highly lipophilic drug. After its diffusion into brain, it is redistributed in different body compartments with simultaneous hepatic metabolism and both urinary as well as biliary metabolism. Its usual intravenous induction dose is 1-2 mg/kg.

It is the only intravenous anaesthetic with significant analgesic properties and CNS stimulation. It increases heart rate, blood pressure and cardiac output. It increases cerebral blood flow and intracranial pressure. It is contraindicated in patients of hypertension, ischaemic heart disease, schizophrenia and epilepsy. It is useful in patients of hypovolaemic shock. Recovery is associated with delirium characterised by frightening dreams and disorientation. Intravenous use of Diazepam or Midazolam, prior to ketamine minimises these adverse effects. It is also used with Propofol for outpatient anaesthesia and in children for burn dressing. It is also useful in asthmatic patients because of its bronchodilator effect.

4.3.3 Pre-Anaesthetics

The aim of pre-anaesthetic medication is to ensure comfort to the patient and minimise adverse effects of anaesthesia. The drugs given before anaesthesia and surgery reduce anxiety, apprehension, provide analgesia, reduce chances of emesis and autonomic effects during anaesthesia and induce amnesia.

Following drugs are used as preanaesthetics:

(a) Antianxiety Drugs

Benzodiazepines (BZDs) like diazepam (5-10 mg oral) or lorazepam (2 mg IM) are used. Midazolam (70-100 µg/kg IV) may also be given.

(b) Sedative Hypnotics

In addition to BZDs, promethazine (25 mg IM) is widely used. It is an antihistamine with sedative, antiemetic and anticholinergic actions. It causes neglible respiratory depression and is useful for children.

(c) Opioid Analgesics

Morphine (8-12 mg IM) or pethidine (50-100 mg IM) is used for the purpose. Fentanil (50-100 µg IM/IV) may also be used.

(d) Anticholinergics

Atropine (0.5 mg IM) or hyoscine (0.5 mg IM) or glycopyrrolate (0.1-0.3 mg IM) are used. They reduce salivary, bronchial secretions; produce bradycardia and hypotension. They also prevent laryngospasm.

(e) Antiemetics

Metoclopramide (10 mg IM), domperidone (10 mg oral) or ondansetron (4-8 mg IV) are used for gastric emptying prior to emergency surgery. These drugs may be combined with histamine H_2 receptor blockers.

(f) H_2 Receptor Blockers

Ranitidine (150-300 mg oral) or famotidine (20-40 mg oral) are given in night before and in the morning before surgery. Proton pump inhibitors like omeprazole (20 mg) may be given with H_2 blockers.

4.4 SEDATIVES, HYPNOTICS AND CENTRALLY ACTING MUSCLE RELAXANTS

4.4.1 Sedatives and Hypnotics

Sedation indicates decrease in alertness and a decreased responsiveness to any level of stimulation without inducing sleep. During hypnosis, a person becomes passive, highly suggestive and obeys the commands. Hypnosis resembles natural sleep but the person can be aroused by strong stimuli like pin prick or the sound of alarm clock.

The sequence of events during non-specific CNS depression starts from anxiety followed by disinhibition, sedation, hypnosis, anaesthesia, coma and ultimately death. The effects of drugs depend on their dose, route of administration and their physico-chemical characters.

Drugs under this category are classified as follows:

[I] Benzodiazepines (BZDs)

Although BZDs were introduced after barbiturates, they are preferred drugs for hypnotic and sedative activities. A comparison between BZDs and barbiturates is listed below:

- BZDs do not provide anaesthesia even in high doses and the patient can be aroused. Barbiturates can cause loss of consciousness and have lower margin of safety.
- BZDs are not enzyme inducers and do not cause metabolic tolerance. Drug interactions are less.
- BZDs have a very low abuse liability; barbiturates cause psychic and physical dependence.
- BZDs do not affect REM sleep and cause less disturbance of normal sleep while barbiturates cause marked suppression of REM sleep.
- BZDs show no hyperalgesia while barbiturates may increase sensitivity to pain.
- BZDs exhibit amnesia without automatism while barbiturates cause amnesia with automatism. Automatism can lead to accidental poisoning.
- BZDs can be used as day-time anxiolytic-sedative in sub-hypnotic doses while barbiturates cause drowsiness.
- BZDs, in hypnotic doses do not affect respiration or cardiovascular functions while barbiturates cause respiratory depression and hypotension.
- Flumazenil is a specific antagonist for BZDs; there is no specific antagonist to barbiturates.

Characteristics of BZDs are discussed below:

Site of Action

BZDs exhibit relatively greater depressant action on limbic system which regulates thoughts and mental functions. They have relatively lesser depressant action on mid-brain ascending RAS which maintains wakefulness. Hence, they exhibit anxieolytic action with less sedative effects. At higher doses they depress RAS and induce sedative-hypnotic action. This effect differs qualitatively with individual BZD. Muscle relaxation is produced due to action on medulla, by inhibiting polysynaptic reflexes in the spinal cord. They also cause ataxia due to action on cerebellum.

Mechanism of Action

BZDs facilitate action on $GABA_A$ receptors. $GABA_A$ receptor has different binding sites. (Fig. 4.7). The sites are as follows:

- GABA-binding site
- The modulatory sites to bind BZDs, their antagonists and inverse agonists
- The modulatory as well as blocking site at chloride ion channel

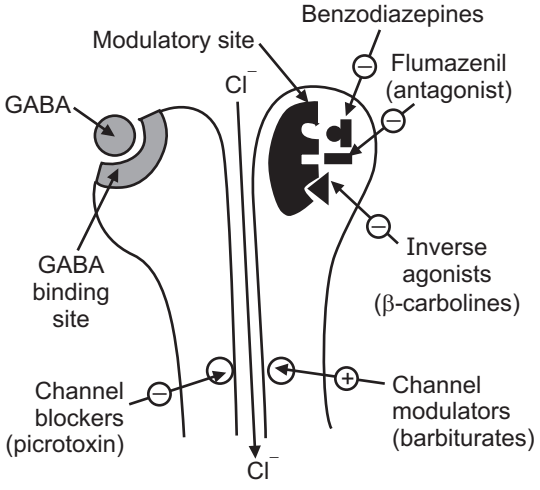


Fig. 4.7: Main sites of drug action at $GABA_A$ receptor

BZDs selectively bind with high affinity to the modulatory site on $GABA_A$ receptor in such a way that the binding of GABA to $GABA_A$ receptor is facilitated. This modulatory site is distinct from the GABA binding site and is specific for BZDs; hence it is also called as "benzodiazepine receptor". BZDs neither substitute for GABA, nor activate $GABA_A$ receptor but enhance binding of GABA to the binding site of $GABA_A$ receptor. BZDs appear to increase the frequency rather than duration of GABA-gated chloride channel opening.

BZD Inverse Agonists and Antagonists

Inverse agonist to BZDs is β-carbolene which exerts opposite signs to that of BZDs leading to anxiety and convulgence. β-carbolene has no therapeutic use. Antagonist to BZDs is flumazenil. It is clinically useful to treat overdose toxicity of BZDs. It undergoes significant first pass metabolism in liver. Hence, it is preferred by intravenous route in a dose of 0.5 mg. It is given at the rate of 0.2 mg/minute up to maximum dose of 5 mg. It is given till the patient recovers. Its half-life is 1-2 hours.

Pharmacokinetics

There are marked variations in pharmacokinetics of BZDs. Only Midazolam is given either by IM or IV route. All other BZDs are given orally. BZDs like diazepam, oxazepam and chlordiazepoxide are more than 90% bound on proteins. There is no significant displacement reaction. They have high volume of distribution, they cross placental barrier and are to be used cautiously in pregnancy. Many of the phase I metabolites of BZDs are pharmacologically active; hence their half-life is extended. Active metabolites of parent drugs are as follows:

- **Midazolam:** hydroxymethyl midazolam
- **Diazepam:** oxazepam, nordiazepam (clorazepate)
- **Flurazepam:** dismethylflurazepam and hydroxymethyl flurazepam
- **Alprazolam:** alpha-hydroxyalprazolam
- **Chlodiazepoxide:** dismethyldiazepam and oxazepam

Accumulation, with multiple dosing is not clinically significant with short acting BZDs but it is significant with intermediate acting and long acting BZDs. Withdrawal effects are milder with long acting BZDs.

Therapeutic Uses

- To treat anxiety neuroses: BZDs like alprazolam, lorazepam, oxazepam, diazepam and chlordiazepoxide are commonly used for this purpose.
- To treat insomnia: BZDs are the hypnotic drugs of choice. Rapidly acting and rapidly eliminated BZDs like triazolam (0.1-0.25 mg) or temazepam (15-20 mg) are preferred for transient insomnia caused by jet-lag, shift work, new place or overnight journey. For short term insomnia, drugs like temazepam (15-30 mg), flurazepam (15-30 mg) or estazolam (1-2 mg) are given at bed time. For long-term chronic insomnia, long acting BZDs like flurazepam (15-30 mg) or nitrazepam (5-10 mg) are preferred.
- For pre-anaesthetic medication and induction of anaesthesia: diazepam, lorazepam and midazolam are generally used. Intravenous midazolam is preferred due to high degree of amnesia, rapid onset and shorter duration of action.
- As skeletal muscle relaxants: diazepam is preferred for the purpose if the spasticity has origin in CNS.
- As anti-convulsants: slow intravenous diazepam or clonazepam is used to treat status epilepticus. Clonazepam is used for myoclonic/petit mal seizures. Tolerance develops to these drugs. Continuous, slow infusion of diazepam can be used to prevent titanic spasm.
- Treatment of alcohol withdrawal: diazepam, oxazepam and chlordiazopoxide are used to control withdralwal effects of alcohol.

Adverse Reactions

Following adverse effects are observed with BZDs:

- BZDs cause dose dependent drowsiness, fatigue, disorientation, lethargy and impairment of psychomotor skills. Fast IV injection can precipitate cardiac arrest.
- Tolerance develops slowly. There is no induction of hepatic microsomal enzymes.
- Dependence is mild. Withdrawal effects include anxiety, insomnia, impaired concentration, headache, irritability, tremors, palpitation and vivid dreams.
- Advancing age retards rate of phase I metabolism. Hence, effects of long-acting BZDs tends to increase in elderly people resulting in increased confusion and forgetfulness.
- Paradoxical stimulation may occur rarely, especially with flurazepam.
- Flunitrazepam is a tasteless BZD which is misused in sexual assaults. It has been misused to obliterate memory of events to escape judicial punishment for sexual assaults.

Drug Interactions

Following drug interactions are observed with BZDs:

- BZDs potentiate effects of other CNS depressants like alcohol, hypnotics and neuroleptics.
- Smoking decreases the activity of BZDs.
- Aminophylline antagonises sedative effects of BZDs.
- Enzyme inhibitors like cimetidine and ketoconazole enhance BZD action.

Alprazolam: **ALPRAX, ALZOLAM, RESTYL, TRIKA** *is available as 0.25 mg, 0.5 mg. 1 mg tablets or 0.5 mg, 1 mg, 1.5 mg SR tablets. Chlordiazepoxide:* **LIPRIUM, ODIP** *is available as 10 mg, 25 mg tablets. Diazepam is available as 5 mg, 10 mg tablets or 5 mg/ml injection. Midazolam:* **MEZOLAM, FULSED** *is available as 1 mg/ml, 5 mg/ml injection. Lorazepam:* **ATIVAN, LARPOSE, LORVAN, TRAPEX, LOPERZ** *is available as 1 mg, 2 mg tablets or 2 mg/ml injection. Oxazepam:* **SEREPAX** *is available as 15 mg, 30 mg tablet. Nitrazepam:* **HYPNORIL, NITROSUN** *is available as 5 mg, 10 mg tablet. Flurazepam:* ***NINDRAL, FLURAZ*** *is available as 15 mg capsule. Clonazepam:* **LONAZEP, RIVOTRIL, *EPITRIL*** *is available as 0.5 mg, 1 mg, 2 mg tablet.*

[II] Non-benzodiazepine Hypnotics

Two types of BZD receptors have been identified: BZ_1 and BZ_2. BZ_1 receptors are found throughout the brain and in large concentrations in the cerebellum. They are responsible for antianxiety, sedative and hypnotic effects. BZ_2 receptors are found mainly in the cerebral cortex, hippocampus and spinal cord and are associated with muscle relaxation, anticonvulsant action and amnesia. Non-benzodiazepines like Zolpidem, Zaleplon, Zopiclone and Eszopiclone act on BZ_1 receptors only. Benzodiazepines like Clobazam act preferably on BZ_2 receptors and exert muscle relaxant anticonvulsant actions.

As hypnotic, Zolpidem (half-life 2-3 hours) and Zaleplon (half-life 3-4 hours) have faster onset of action with shorter duration of action. Drugs like Zopiclone (half-life 6-8 hours) and Eszopiclone (half-life 6 hours) are slightly longer acting. In therapeutic doses they hardly alter REM sleep and have minimal day time sedation. The problem of rebound insomnia is minimal. Their effects can be blocked by Flumazenil.

These drugs have minimal muscle relaxant and anticonvulsant action. The risk of tolerance and dependence is less. Side effects and safety in overdoses are similar to that of BZDs. Dose reduction is needed in hepatic disease and in elderly patients. Adverse reactions like day time drowsiness and night mares occur only in high doses.

Zolpidem: **NITREST, ZOLPIGEM, ZOLPINITE** *is available as 10 mg tablet. Zaleplon:* **ZAPLON, ZASO** *is available as 5 mg or 10 mg tablet. Zopiclone:* **ZOLINOX, ZOPICON, ZOLIUM** *is available as 7.5 mg tablet and Eszopiclone:* **FLUNITE** *is available as 1 mg, 2 mg tablets.*

[III] Barbiturates

The general structural formula of barbiturates is shown in Fig. 4.8. If R_1 and R_2 are aliphatic alkali groups, then the resultant barbiturate or thiobarbiturate (if X is sulphur) possesses sedative hypnotic properties. If R_1/R_2 is phenyl group, then the resultant drug has anticonvulsant-sedative action (e.g. Phenobarbital). Thiobarbiturates are more lipid soluble and are ultra-short acting.

General structure of Barbiturates:

If X → O; it is barbiturate.

If X → S; it is thiobarbiturate.

R_1 and R_2 are substituents.

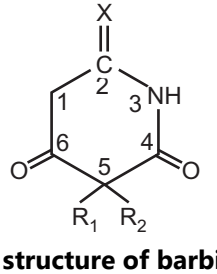


Fig. 4.8: General structure of barbiturates

Mechanism of Action

Barbiturates act on the channel modulatory site of $GABA_A$ receptor and potentiate the GABA mediated inhibitory effects by increasing the duration of chloride channel opening (Fig. 4.7). At higher doses, barbiturates directly increase chloride ion conductance and exhibit GABA-mimetic action and not a GABA-facilitatory action.

Classification

Barbiturates are classified based on their duration of action. Thiopental and Methohexital are ultra-short acting barbiturates with duration of action ranging from 15-20 minutes. Pentobarbital and Amobarbital are shorter acting barbiturates with 3-8 hours as duration of action. Phenobarbital and Mephobarbital are longer acting barbiturates with 12-24 hours as duration of action.

Pharmacokinetics

- The rate of absorption of barbiturates depends on their lipid solubility. The pH of solutions of sodium salts is usually alkaline. Hence, IM/SC injections can cause necrosis and pain at the site of injection. They remain unionised in acidic pH and fully ionised at alkaline pH.
- They are widely distributed depending on lipid solubility and regional blood flow. The action of ultra-short acting barbiturates is terminated due to redistribution from brain to other tissues, muscles and fat/adipose tissue.
- They are metabolised both by phase I and phase II processes. Phase I involves microsomal oxidation while phase II involves glucuronyl conjugation.
- On prolonged use, they cause induction of liver microsomal enzymes resulting in development of metabolic tolerance.
- They are excreted through urine; but are readily reabsorbed from renal tubules. Alkalinisation of urine promotes their excretion.

Pharmacological Effects

- The ultra-short acting barbiturates exhibit dose-dependent CNS depressant action. The long acting barbiturates possess sedative-anticonvulsant actions. These two actions are independent. They disrupt the balance between REM: Non-REM sleep by decreasing the duration of REM sleep. Hence, on withdrawal of barbiturates, there is a rebound increase in REM sleep which leads to a feeling of disturbed sleep.
- They may show hyperalgesic action i.e. they may increase reaction to painful stimuli.
- Sedative-hypnotic doses have no effect on cardiovascular system. High doses decrease blood pressure, heart rate and depress myocardium.
- Sedative hypnotic doses do not affect respiration. Higher doses depress respiration and cause shallow berathing, pulmonary edema and laryngeal edema.
- Prolonged use increases the size and weight of smooth endoplasmic reticulum leading to enzyme induction.
- Higher doses have relaxant effect on GIT, bladder and uterus and decreases urine flow from kidneys due to decrease in renal blood flow, increase in ADH release and relaxation of bladder.

Therapeutic Uses

- As sedative-hypnotics: These days BZDs have superseded barbiturates.
- In anaesthesia: Ultra-short-acting barbiturates like thiopental are used as intravenous fast inducing anaesthetics.
- As anticonvulsants: Long-acting barbiturates like Phenobarbital are used for the purpose.
- To treat hyperbilirubinaemia: They increase activity of enzyme glucuronyl transferase by induction. Hence, bilirubin gets conjugated faster and excreted through bile. They also increase the bile flow.

Adverse Effects

- Repeated use of barbiturates causes metabolic tolerance due to enzyme induction. This leads to accelerated metabolism of several concommittantly administered drugs.
- They can cause psychic as well as physical dependence on withdrawal after prolonged use. Withdrawal symptoms include tremors, insomnia, headache, restlessness and delirium.
- They cause hangover, impairment of judgement and drug automatism.
- They cause respiratory depression, laryngeal edema and hypersensitivity reactions causing skin rash, swelling of lips and eyelids.

Drug Interactions

Barbiturates reduce effectiveness of drugs like oral contraceptives, anticoagulants, tolbutamide and theophylline due to induction of enzymes.

Contraindications

- They are contraindicated in liver dysfunctions, kidney disease and severe pulmonary insufficiency.
- Patients with family history of porphyria or in case of acute intermettant porphyria. This is because barbiturates cause induction of the enzyme ALA-synthetase which is responsible for synthesis of porphyrins. The net effects are porphyria and neurotoxicity.

Acute Toxicity and Treatment

Barbiturate poisoning is mostly suicidal and rarely accidental. It leads to respiratory failure, cardiovascular collapse, coma and renal failure. The treatment includes gastric lavage, artificial respiration and forced alkaline dialysis.

[IV] Miscellaneous Drugs

(i) Melatonin and Ramelteon

Melatonin is a hormone produced in the pineal gland from the amino acid tryptophan. Normally, it is involved in skin colouration, but it is also secreted during hours of darkness and affects sleep pattern. The light stimulates the retina and transmits the signal to pineal

gland to inhibit release of melatonin. Darkness promotes melatonin secretion. It is primarily used to elevate symptoms of jet lag and other disorders resulting from delay of sleep. It has been found useful in elderly hypnotic-dependent insomniacs. Food increases its bioavailability. It undergoes first pass metabolism and is excreted by kidney. It decreases serum luteinizing hormone and increases prolactin levels. It is contraindicated in patients taking corticosteroids like dexamethasone.

Ramelteon is a selective agonist to receptors of melatonin. It has been approved for treatment of insomnia in which there is difficulty in falling asleep. Adverse effects include fatigue, dizziness and somnolence.

Melatonin: **MELOSET, ZYTONIN** *is available as 3 mg tablet.*

(ii) Triclofos

It is similar to chloral hydrate; both get converted in to trichloroethanol. Triclofos is more palatable, causes less GIT upset and is better tolerated. Its onset of action is less than 30 minutes and duration of action is 8-12 hours. It is used for short term management of insomnia in children for sedation during recurrent colic. Dose is 1 gm at bed time.

Triclofos: **PEDICLORYL, TRICLORYL** *is available as 500 mg tablet/5 ml syrup.*

(iii) Hydroxyzine

It is an antihistamine with antiemetic, sedative, anticholinergic and local anaesthetic action. It is used for short term management of anxiety, pre-anaesthetic sedation and pruritus. Its onset of action is 15-30 minutes and duration of action is 6 hours. Usual oral dose is 50-100 mg three times a day. Its active metabolite is cetrizine.

Hydroxyzine: **ATARAX** *is available as 10 mg, 20 mg tablet or 6 mg/ml syrup.*

(iv) Promethazine

It is a sedative antihistamine with antiemetic and anticholinergic properties. It is used for night time sedation in a dose of 25 mg at bed time. Its onset of action is one hour and duration of action is 10-12 hours. Its longer duration of action may cause hangover the next day. It is also used in children as sedative hypnotic.

Promethazine: **AVOMINE, PHENERGAN** *is available as 10 mg, 25 mg tablet or 5 mg/5 ml syrup.*

4.4.2 Centrally Acting Skeletal Muscle Relaxants (Spasmolytics)

These drugs reduce skeletal muscle tone by a selective action in the cerebrospinal axis without altering consciousness. Spasticity is characterised by an increase in tonic stretch reflexes and flexor muscle spasm along with muscle weakness. It is associated with disease like cerebral palsy and multiple sclerosis. It involves abnormal function of bowel, bladder and skeletal muscle. Antispastic drugs control the symptoms of spasticity either by enhancing the activity of inhibitory neurons of the reflex arc (e.g. diazepam, baclofen) or by interfering directly with skeletal muscle excitation-contraction coupling (e.g. dantrolene). Components

involved in these processes and sites of action of drugs are shown in Fig. 4.9. Mephenesin group drugs are also used to relieve acute local muscle spasm. Their mode of action is non-specific and is described as depressants of polysynaptic reflexes at spinal level. Both spinal and supra-spinal polysynaptic reflexes are involved in the regulation of the muscle tone. Monosynaptic pathways mediate stretch reflex. All these drugs have some sedative side effects.

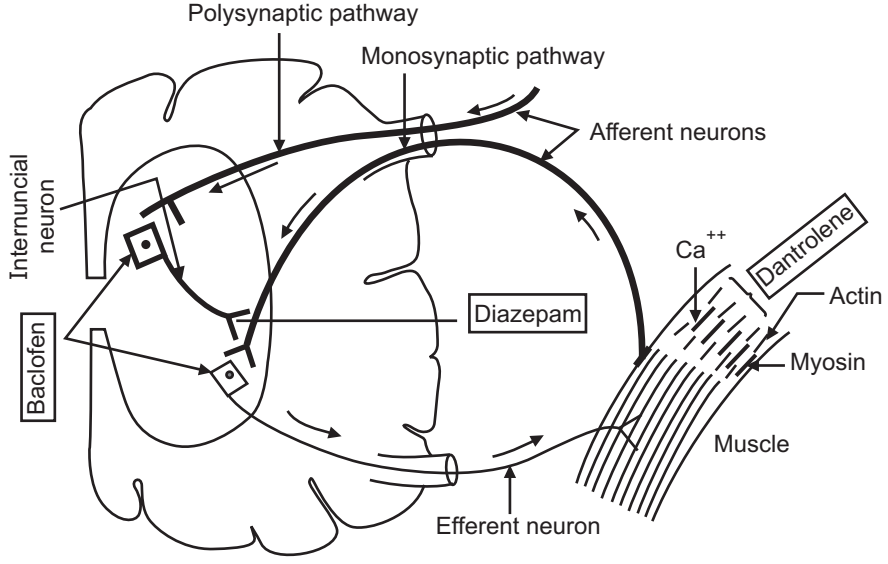


Fig. 4.9: Cross-section of spinal cord showing components involved in stretch reflex arc with postulated sites of action of diazepam, baclofen and dantrolene

[I] Mephenesin Group

It involves drugs like Carisoprodol, Chlorzoxazone, Chlormezanone and Methocarbamol. These drugs are spinal neuron blocking agents at the level of brain stem. They preferentially inhibit polysynaptic reflexes without affecting monosynaptic tendon reflexes like knee jerk. They are used to treat muscle spasm of local origin such as resulting from spondylitis, sprains and lumbago. Sedation and GIT upset are the most common side effects.

Chlorzoxazone has longer duration of action (8-12 hours) and a slower onset of action (1.5 hour). It is well tolerated orally. Carisoprodol has duration of action of 4-6 hours. It is also analgesic, antipyretic and has antimuscarinic action. It causes blurred vision. It is converted to meprobamate, as an active metabolite. Hence, tolerance and dependence may develop after prolonged use. Chlormezanone has some hypnotic action as well. Methocarbamol is preferred by parenteral route because of extensive first pass metabolism.

Carisoprodol: **CARISOMA** *is available as 350 mg tablet. Chlorzoxazone:* **NEW PANAZOX, UNIDIC-MR** *is available as 500 mg tablet. Methocarbamol:* **ROBINAX FLEXINOL** *is available as 500 mg tablet.*

These drugs are usually combined with paracetamol and anti-inflammatory drug like diclofenac or ibuprofen.

[II] Benzodiazepine Group

Diazepam and chlorazepam have antispastic action. They enhance GABA-ergic transmission in brain as well as other GABA synapses. They inhibit both monosynaptic as well as polysynaptic reflexes and produce marked sedation. They reduce muscle spasm of almost any origin including local muscle trauma. They are particularly useful in spinal injuries, tetanus and rheumatic disorders associated with muscle spasm. Sedation is their major side effect.

Diazepam is available as 2 mg, 5 mg tablet. Clonazepam is available as 1 mg, 2 mg and 5 mg tablet.

[III] GABA Derivative

Baclofen is an orally active GABA-mimetic drug which acts as a agonist on $GABA_B$ receptors. The receptors are G-protein coupled receptors which hyperpolarise neurons by increasing potassium ion conductance and reducing calcium ion conductance. At spinal level, it inhibits both monosynaptic and polysynaptic responses. Activation of $GABA_B$ receptors in brain results in hyperpolarisation which interferes with release of excitatory neurotransmitters. It also reduces pain associated with spastic conditions.

It is used to relieve painful spasticity in multiple sclerosis. It is not much useful in cerebral palsy. It can be used to treat trigeminal neuralgia and tardive dyskinesia.

Its adverse reactions are sedation, drowsiness, muscle weakness and ataxia. Sudden withdrawal may precipitate anxiety, tachycardia and hallucination. It is teratogenic and should be avoided during pregnancy.

Baclofen is available as 10 mg and 25 mg tablet: **LIOFEN, LIORESAL, BACMAX.**

[IV] Central α_2- agonist

Tizanidine is a α_2-agonist with action on CNS and alters neuronal activity in the spinal cord. It antagonises spasticity at doses which have minimal effect on blood pressure in comparison to clonidine. It inhibits release of excitatory amino acids in spinal interneurons. It is widely used to treat spasticity in multiple sclerosis. It is effective in patients with amyotrophic lateral sclerosis. It is useful in spasticity due to neurological disorders and painful muscle spasm of spinal origin. Adverse effects include drowsiness, dry mouth, asthenia and hypotension. It is well tolerated orally but undergoes first-pass metabolism.

Tizanidine is available as 2 mg and 4 mg Tablet.

4.5 ANTI-EPILEPTICS

Epilepsy is a common neurological abnormality characterised by occurrence of seizures. A seizure means a paroxysmal abnormal discharge at high frequency, from an aggregate of neurons in cerebral cortex. Epilepsy involves recurrent seizures. Convulsions are involuntary, violent and spasmodic or prolonged contractions of skeletal muscle. A patient may have epilepsy without convulsions.

4.5.1 Classification of Seizures

Broadly, the seizure activity is either generalised or partial. In addition, there is one more category of unclassified seizures.

(i) Generalised Seizures

These seizures arise from both cerebral hemispheres and diencephalon simultaneously, involving the entire body, and have characteristic bilateral pattern in EEG recording. These are of following types:

(a) Grand mal or Tonic-Clonic Seizures

These are usually associated with an aura prior to seizures. The patient falls to the ground in stiff tonic phase (legs extended) with an epileptic cry, caused by tonic contraction of laryngeal muscles. This is followed by clonic convulsions (repeatitive bilateral muscle jerking) and then to coma which may last for 15-30 minutes. Recovery is associated with stupor, amnesia, mental confusion and post-ictal depression, incontinence and exhaustion. EEG shows a bilateral diffused pattern of high voltage polyspikes of 10-30 Hz/sec in tonic-clonic phase.

(b) Petit mal or Absence Seizures

There is no aura associated with this disorder and attack appears without warning. There is no loss of consciousness. The seizure lasts for few seconds without loss of postural control. There is no post-ictal confusion or amnesia. The seizures are characterised by subtle bilateral symptoms such as rapid blinking of eyelids, chewing movements or small amplitude clonic jerks of hands for few seconds. EEG shows generalised symmetric 3 Hz spikes and wave pattern of discharge per second which begins and ends suddenly. These are responsive to pharmacotherapy.

Atypical absence seizures are of slower onset and of longer duration. These are non-responsive to pharmacotherapy and are associated with other neurologic complications like mental retardation.

(c) Myoclonic Seizures

These are bilateral epileptic myoclonus characterised by sudden and brief skeletal muscle contraction which may involve the entire body or one part of the body. Most commonly the patient complains of sudden jerking movements appearing during sleep. EEG shows 2 Hz spikes and wave pattern per second.

(d) Akinetic (Atonic) Seizures

These are characterised by sudden loss of postural tone. The head may sag to oneside or the patient may fall all of a sudden. The consciousness may be impaired for a brief period but there is no post-ictal confusion. EEG shows brief generalised spike and wave discharge followed by diffused slow waves which correlate with loss of muscle tone.

(e) Clonic Seizures

These are characterised by repetitive muscle jerks. EEG shows fast activity (10 Hz or more) slow waves.

(f) Tonic Seizures

These are characterised by rigid, violent muscular contraction with stiff and fixed extended limbs. EEG shows low-voltage fast-activity waves.

(ii) Partial Seizures (Localised/Focal)

These are the most common seizures. The seizure activity is restricted to a discrete area belonging to one cerebral hemisphere only. These are of three types:

(a) Simple partial seizures (Jacksonian seizures)

These are characterised by unilateral clonic movements which begin in one group of muscles and spread gradually to adjacent group reflecting the march of epileptic activity (e.g. mouth, thumb, great toe). Alternatively, the patient may have somatosensory symptoms such as auditory, visual or olfactory hallucinations. There is no loss of consciousness in simple partial seizures.

(b) Complex partial seizures (Psychomotor Epilepsy)

These originate in the temporal or the frontal lobe and are accompanied by partial loss of consciousness. It is a dreamy state of psychic seizures where the patient behaves as partially conscious with automatism. The patient may get up, put on his clothes, start walking or even driving a vehicle but does not follow your commands and does not recollect the events after the attack is over. The attack is usually associated with auditory, visual or olfactory aura. Sometimes patient shows other types of automatisms like lip smacking, fumbling and searching of which the patient has no memory.

(c) Partial seizures evolving to secondary generalised seizures

These are the type when partial seizures progress to generalised/tonic/clonic/tonic-clonic seizures. Patients usually report aura before the event.

(iii) Unclassified Seizures

It covers undetermined epilepsies and epileptic syndromes like febrile seizures or infantile spasm. In febrile seizures, young children frequently develop seizures with illness accompanied by hyper-pyrexia. In infantile spasm, there is progressive mental retardation. These are generalized tonic-clonic convulsions of short duration which may appear frightening but are usually benign.

4.5.2 Mechanism of Action of Anti-Epileptic Drugs

Anticonvulsant drugs act by different mechanisms to suppress repetitive firing action potentials by an epileptic focus in the brain. The mechanisms are classified in two types:

(i) Mechanisms in Grand mal and Partial Seizures:

They are further sub-classified into following sub-types:

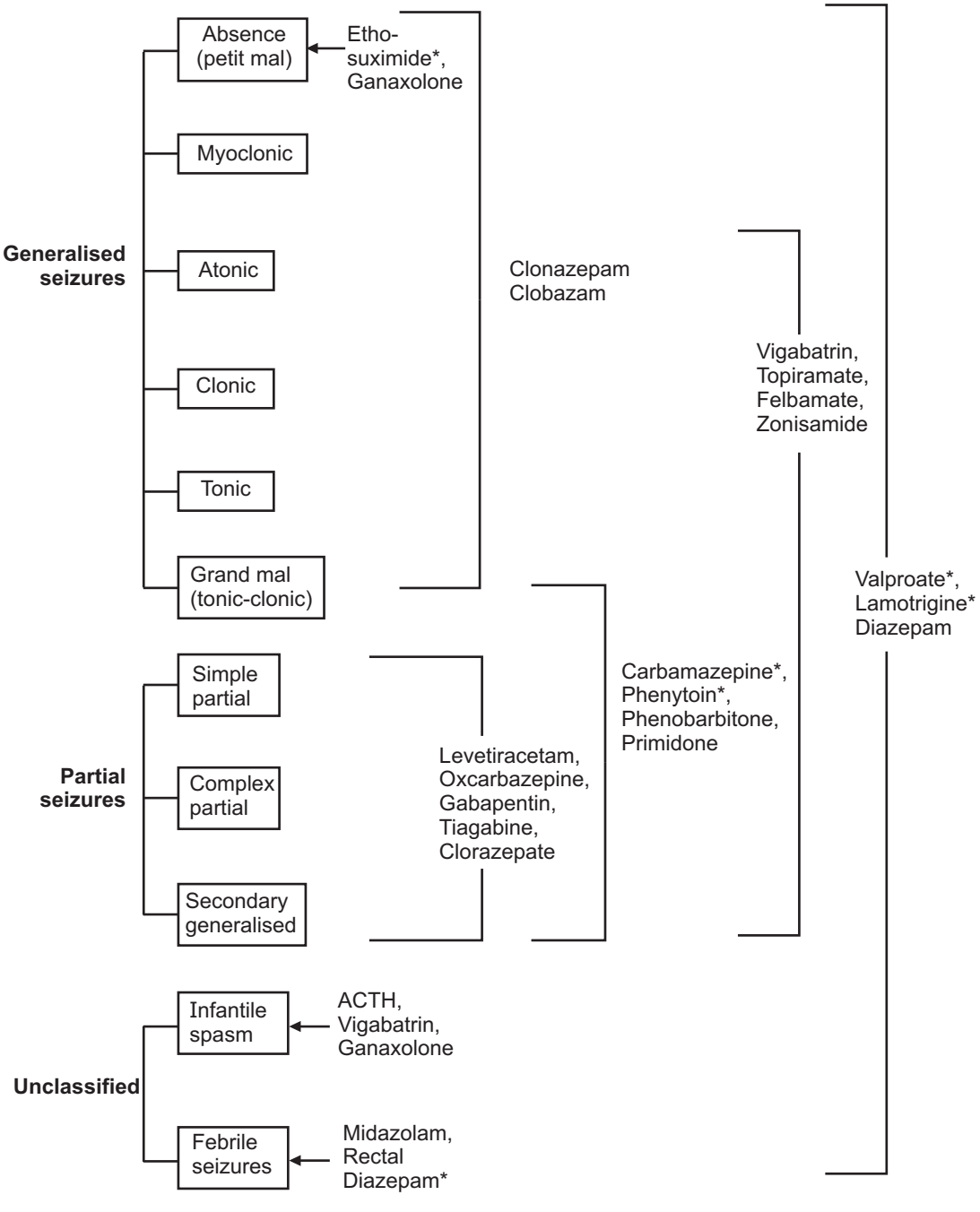
- Inhibition of Use-Dependent Sodium Ion Channels. Drugs like Phenytoin, Carbamazepine, Valproate, Lacosamide and Lamotrigine block voltage-gated sodium channels.
- Enhancement of GABAergic action. Drugs like Phenobarbital and Benzodiazepines activate $GABA_A$ receptors to facilitate opening of chloride channels.
- Blockade of NMDA or AMPA receptors. Drugs like Felbamate block NMDA receptors. Drugs like Phenobarbital, Topiramate and Lamotrigine block AMPA receptors.
- Blockade of voltage-gated N type calcium channels. Drugs like Lamotrigine and GABApentin decrease synaptic release of glutamate.
- Selective blocking of synaptic vascular protein. Drug like Levetiracetam decrease synaptic release of glutamate and increase release of GABA.
- By blocking effects of neurotropic factors, drug like Lacosamide inhibit specific proteins involved in genesis of epilepsy.

(ii) Mechanisms in Petit mal (Absence Seizures)

It involves inhibition of T-type calcium channels. Drug like Ethosuximide inhibit calcium channels. Valproic acid also shows this kind of action.

4.5.3 Individual Drugs

Following drugs are used to treat epilepsy. Types of epilepsy and drugs used to treat them are depicted in Fig. 4.10.



* Drugs of first choice, rest are 'add-on' drugs

Fig. 4.10: Therapeutic spectra of antiepileptic drugs

(i) Phenytoin

It is an oldest non-sedative antiepileptic drug. Chemically, it is diphenylhydantoin. It provides a good example of application of pharmacokinetics for successful prescribing.

- **Mechanism of action**

  In therapeutic plasma levels of 10-20 µg/ml, it blocks use-dependent sodium channels and thus inhibits generation of repetitive action potentials. At higher doses it also reduces influx of calcium and suppresses repetitive firing of neurons. Both these actions decrease glutamate release.

- **Therapeutic uses and plasma levels**
  - **Antiepileptic use**

    It is the drug of choice for psychomotor seizures. As a second choice, it is used to treat generalised tonic-clonic and status epilepticus. Fosphenytoin is its pro-drug. Phenytoin is contraindicated in Petit mal (absence) and myoclonic seizures.
  - **Non-antiepileptic use**

    It is used to treat trigeminal neuralgia, ventricular arrhythmia and also for wound healing.

- **Pharmacokinetics**

Its oral absorbtion is slow but complete (80-90%). Phenytoin is not given by IM or IV route. Its pro-drug Fosphenytoin is administered by slow IV route. IM phenytoin precipitates in muscle and causes intense pain. IV phenytoin causes thrombophlebitis and hypotension.

It is 90-92% protein bound. It is a potent enzyme inducer both for CYP3A4 and glucuronyl transferase. Metabolites are eliminated through urine. The drug is excreted through saliva. Its elimination is dose-dependent and follows saturation kinetics. Up to 10-20 µg/ml, its elimination obeys first order kinetics. Hence, its plasma levels remain steady, up to 20 µg/ml. Beyond 20 µg/ml, its elimination follows zero-order kinetics and hence a slight increase in dose results in to larger increase in plasma concentration leading to toxicity.

Periodic assessment of plasma concentrations and subsequent dose adjustments are necessary in neonates and in patients with kidney disease, liver disease and hypoproteinaemia. Its plasma half-life is about 24 hours. Five days are needed to attain steady state.

- **Adverse reactions**

  Following adverse effects are observed with chronic toxicity:

  - Gingival hyperplagia and coarsening of facial features.
  - Megaloblastic anaemia
  - Vitamin K deficiency
  - Vitamin D deficiency
  - Hirsutism (in females) and acne
  - Hyperglycemia, decrease of ADH release

- Congenital malformation like cleft lip, cleft palate and heart disease
- Hypersensitivity reactions like skin rashes, fever, hepatitis, vertigo, nausea, tremors
- Withdrawal seizures, if discontinued abruptly

- **Drug interactions**
  - It increases metabolism of Corticosteroids, Oral contraceptives, Doxycycline, Rifampicin, Theophylline, Levodopa, Vit. K and Vit. D due to enzyme-induction.
  - Enzyme-inhibitors like Disulfiram, Cimetidine, Isoniazid and Chloramphenicol decrease metabolism of Phenytoin leading to increase in plasma concentration.
  - Carbamazepine and Phenytoin or Phenobarbital and Phenytoin increase each other's metabolism.
  - Sodium valproate displaces protein bound Phenytoin and inhibits its metabolism. Hence, plasma level of phenytoin increases.

Phenytoin: **DILANTIN, EPSOLIN, EPTOIN** *is available as 100 mg capsule, 100 mg tablet, 150 mg tablet, 300 mg ER tablet, 25 mg/ml suspension, 30 mg/5 ml suspension and 50 mg/ml injection. Fosphenytoin:* **FOSOLIN** *is available as 75 mg/ml injection.*

(ii) Phenobarbital and Primidone

Barbiturates having an aromatic ring at position-5 exhibit anticonvulsant action. Primidone is a deoxyphenobarbital. It is metabolised to Phenobarbital and phenylethyl malonamide and all these three agents have anticonvulsant action.

- **Mechanism of action**

  Phenobarbital binds to GABA receptor and enhances GABA-mediated inhibitory effect by increasing the duration of chloride channel opening. It also inhibits glutamate mediated excitatory effects by blocking AMPA receptor. Both the increase in GABA-mediated inhibition and decrease in glutamate mediated excitation are observed with Phenobarbital and primidone. At higher doses they block calcium and sodium channels.

- **Therapeutic uses**

  Both are effective against partial seizures and generalised tonic-clonic seizures but are less effective than Phenytoin and Carbamazepine. Combination of them works better than individual drugs alone. Both are enzyme inducers. They competitively inhibit each other's metabolism. Tolerance develops to its sedative action but not anticonvulsant action. Phenobarbital, if discontinued suddenly, precipitates withdrawal seizures. These drugs are contraindicated in Petit mal (absence) seizures and in porphyria.

- **Pharmacokinetics**

  Oral absorption is slow but almost complete (85-90%). It is metabolised by liver and is potent enzyme inducers for CYP2A, CYP2B, CYP2C, CYP3A and CYP6A isoforms of cytochrome P450 and also for glucuronyl transferase enzyme. Plasma half-life of Phenobarbital is around 100 hours; hence after steady state, there is less fluctuation in plasma for 24 hours.

  Therapeutic levels for Phenobarbital range from 10-40 µg/ml. In febrile seizures, levels below 15 µg/ml are ineffective. Usual doses for Phenobarbital are 60-180 mg daily orally at night. For Primidone initially, 125 mg daily at night can be slowly increased to 250 mg twice a day.

- **Adverse effects**

  Adverse effects due to enzyme induction are same as that of phenytoin. Phenobarbital does not cause gingival hyperplasia, coarsening of facial features and hirsutism. It can cause irritability and hyper-excitability in children. The chances of dependence are less. It is less teratogenic; but when given with phenytoin, teratogenecity increases.

Phenobarbital: **GARDENAL, PHENOBARB, PHENYTAL** *is available as 30 mg, 60 mg tablet or 20 mg/5 ml syrup. Primidone:* **MYSOLINE** *is available as 250 mg tablet.*

(iii) Carbamazepine and Oxcarbazepine

Carbamazepine is structurally related to tricyclic antidepressants and Oxcarbazepine is a derivative of Carbamazepine.

- **Mechanism of action**

  Like Phenytoin, Carbamazepine blocks sodium channels and inhibits high frequency-repetitive firing.

Like Phenytoin, Carbamazepine blocks sodium channels and inhibits high frequency-repetitive firing of the neurons in brain, at therapeutic levels.

- **Therapeutic uses**
  - **Antiepileptic use**

    It is a drug of choice for partial and generalised tonic-clonic seizures. It is contra-indicated in absence seizures.
  - **Non-antiepileptic use**

    It is a drug of choice for trigeminal neuralgia and in other neuropathic pain. It is not an analgesic. It is also effective in treating manic depressive psychosis.

- **Pharmacokinetics**

Oral absorption is slow. It should be given after meals. It is distributed mainly in brain, liver and kidneys. It is metabolised by CYP3A4 and is its enzyme inducer. It also induces glucuronyl transferase. Its metabolites are excreted through kidney. Oxcarbazepine is a poor enzyme inducer. It is converted to hydroxyl-metabolite which has itself anticonvulsant action.

Optimum therapeutic levels are 4-8 µg/ml. The usual adult oral dose is 100-200 mg twice or thrice daily which can be increased to maximum of 200-400 mg twice or thrice daily. For Oxcarbazepine usual oral dose is 300 mg twice daily which can be increased to 450 mg twice daily.

- **Adverse effects**
  - Dose-dependent adverse effects start with drowsiness followed by dizziness, headache, slurred speech, vertigo, ataxia and diplopia.
  - Allergic reactions like rashes and fever are observed. Other idiosyncratic reactions are blood dyscrasias, aplastic anaemia, leukopenia, hepatitis and systemic lupus erythematosis.
  - It stimulates ADH secretion and can cause water retention and hyponatremia.

- Risk of teratogenecity is low, but can induce finger nail hypoplasia and delayed development of foetus.
- Oxcarbazepine shows lesser hypersensitive reactions and has milder side effects.

- **Drug interactions**
  - Erythromycin, Fluoxetine and Isoniazid inhibit metabolism of Carbamazepine and precipitate toxicity.
  - Carbamazepine and Phenytoin increase each other's metabolism.
  - It is an enzyme inducer and reduces plasma concentration of Haloperidol and Oral contraceptives.

Carbamazepine: **MAZETOL, TEGRITAL, TEGRITOL** *is available as 100 mg, 200 mg, 400 mg tablets; 200 mg and 400 mg SR tablets; 100 mg chewable tablet; 100 mg/5 ml syrup. Oxcarbazepine:* **OXCARB, OXETOL, OXEP** *is available as 150 mg, 300 mg and 600 mg tablets.*

(iv) Ethosuximide

It belongs to succinimide group of anticonvulsants. It is a drug of choice for Petit mal (absence) seizures. It inhibits the low threshold T-type calcium channels. The therapeutic plasma levels are 60-100 µg/ml. For this purpose, oral dose of 20-30 mg/kg/day is adequate. It is secreted in saliva and can reflect plasma concentration effectively.

Its absorption is almost complete after oral administration. It is metabolised in liver and the metabolites are excreted in urine. It follows first order elimination kinetics.

It causes GIT distress, headache, dizziness, hiccups, lethargy and euphoria. Idiosyncratic adverse effects include skin rashes, fever, eosinophilia and bone marrow depression. It is lesser teratogenic and can be given during pregnancy.

Valproic acid inhibits Ethosuximide metabolism and clearance and increases its plasma levels.

(v) Trimethadone

It is similar to Ethosuximide. It is no longer used now. It is a serious teratogenic drug.

(vi) Valproic acid (sodium valproate)

It is used either as valproic acid or as its sodium salt.

- **Mechanism of action**

It is known to block sodium channels, increase GABA activity by activating the enzyme glutamic acid decarboxylase (GAD) and by inhibiting the enzyme GABA transaminase. It decreases release of glutamate and blocks T-type calcium channels.

- **Therapeutic uses**
  - **Antiepileptic use**

    It is effective against absence seizures. It is preferred if the patient has con-committent generalised tonic-clonic attacks and myoclonic seizures. It is used in combination with clonazepam to treat cortical myoclonus. It is used for infantile spasm. It should be withdrawan gradually.

- **Non-antiepileptic use**

  Enteric coated tablet of Semi-sodium valproate is used to treat manic depressive bipolar disorder. It is also used for prophylaxis of migraine and tension type cluster headache. It is used with Metyrapone in the treatment of Cushing's syndrome. Due to its GABAergic action it is used to treat tardive dyskinesia. It is also useful to treat trigeminal neuralgia as an alternative to Carbamazepine.

- **Pharmacokinetics**

  It is well absorbed (80%) following oral dose. Food delays its absorption, but the toxicity is reduced if the drug is given after meals. It is 90-95% bound to plasma proteins. It is a potent enzyme inhibitor and can inhibit its own metabolism as well as that of Phenobarbital. The therapeutic plasma concentration of 50-100 µg/ml can be attained by an oral dose of sodium valproate as 300 mg twice a day. It can be slowly increased to 500 mg to 1 gm twice a day.

- **Adverse effects**

  Adverse effects include weight gain, increase in appetite, GIT distress, tremors and reversible alopecia. Idiosyncratic toxicity is limited to fatal hepatotoxicity. The risk is greater in children below 3 years and those taking a combination of Valproate with Phenobarbital. Rarely, it may cause pancreatitis and thrombocytopenia. Its use in pregnancy results in a higher risk of spina bifada.

- **Drug interactions**
  - It is not a CNS depressant, but it potentiates depressant actions of Phenobarbital and BZDs.
  - It increases plasma concentration of Phenobarbital.
  - It decreases metabolism as well as displaces Phenytoin resulting in toxicity of phenytoin.

Valproic: **ENCORATE, TORVATE, VALTEC** *acid/sodium valproate is available as 200 mg, 300 mg, 500 mg, 750 mg, 1000 mg tablets or 200 mg/5ml syrup. It is also available as 500 mg CR tablet and 300 mg capsule.*

(vii) Benzodiazepines (BZDs)

Although BZDs have anticonvulsant action, it has two limitations: pronounced sedative effects and development of tolerance to anticonvulsant action. They enhance the frequency of GABA-mediated chloride channel opening. At higher doses they block sodium channels which have an advantage in controlling generalised status epilepticus.

Diazepam as a slow IV injection in a dose of 20-30 mg is used to treat seizures. It is also useful for controlling local anaesthetic induced seizures. In addition, Clonazepam, Clorazepate and Clobazam are also used for treating convulsions.

Clobazam: **COBAZAM, CLOBA, CLOBATOR** *is used as 5 mg, 10 mg and 20 mg tablet. Diazepam and Clonazepam formulations are listed under BZDs.*

(viii) Vigabatrin

It is an irreversible inhibitor of GABA transaminase and thus elevates GABA levels in brain. It is useful in the treatment of simple and complex partial seizures as well as generalised seizures. It is also useful in treating drug-refractory epilepsy and infantile spasm. It should not be used in cases of absence epilepsy or myoclonic seizures. The usual dose is 2 gm per day, to be taken in equally divided doses.

Adverse effects include behavioural changes, sedation, amnesia and weight gain. Rarely, it may cause irreversible visual field defects due to peripheral retinal atrophy. It should be used with caution in patients with visual field defects and in children suffering from infantile spasm, in whom visual field monitoring is difficult.

(ix) Tiagabine

It inhibits GABA uptake by neurons and increases its content in brain. It is used for treatment of partial complex seizures, and as an adjunct for refractory complex epilepsy. Adverse reactions include dizziness, fatigue, sedation, tremors and confusion. Usual doses for adults are 20-60 mg/day in 3-4 equally divided doses.

(x) Gabapentin and Pregabalin

Both are GABA analogs and can cross BBB and increase GABA concentration in brain. They inhibit calcium channels and decrease synaptic release of glutamate. They also function as $GABA_B$ receptor agonist.

The absorption of Gabapentin from the intestine depends on carrier system and shows saturation. Hence increasing dose may not increase absorption proportionately. It is neither metabolised nor bound to plasma proteins and is excreted unchanged by kidneys. Drug interactions are minimal.

It is useful in treating drug resistant partial seizures and generalised tonic-clonic seizures. Usual adult dose is 200-300 mg orally three times a day. It is useful in treating diabetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia and pain associated with multiple sclerosis in doses of 1800 mg/day in divided doses. Adverse reactions include drowsiness, fatigue, dizziness, weight gain and ataxia. Dose of Pregabalin is 200-600 mg three times a day orally.

Gabapentin: **GABANTIN, GABAPIN, GABATOR, GABANEURON** *is available as 100 mg, 300 mg, 400 mg capsule. Pregabalin:* **MAXGALIN, NEUGABA, PREGEB, PREEGA-M** *is available as 50 mg, 75 mg and 150 mg capsule.*

(xi) Topiramate

It is a broad spectrum anticonvulsant drug acting by multiple mechanisms like blockade of sodium channels, activation of $GABA_A$ receptor and inhibition of AMPA receptors for glutamate. It is most useful for generalised tonic-clonic, partial and absence seizures. Usual adult oral dose is 300-600 mg/day in divided doses. Adverse reactions include sedation, somnolence, amnesia, urolithiasis and teratogenic risk.

Topiramate: **TOPEX, TOPIROL** *is available as 25 mg, 50 mg or 100 mg tablet.*

(xii) Zonisamide

It is a broad spectrum anticonvulsant drug with multiple actions including blockade of sodium channels and inhibition of calcium channels. It has good bioavailability, linear elimination kinetics, negligible protein binding and renal excretion. It is effective against partial, generalised tonic-clonic and myoclonic seizures. It is also useful against infantile spasm. Usual adult oral dose ranges from 100-600 mg/day in 2-3 equally divided doses. Adverse reactions include drowsiness, amnesia, skin rash and kidney stones.

Zonisamide: **ZONISEP, ZONICARE, ZONIMID** *is available as 50 mg, 100 mg capsule.*

(xiii) Lamotrigine

It is a broad spectrum antiepileptic drug. It blocks voltage-gated sodium channels as well as calcium channels and inhibits release of glutamate. It is effective in treating partial, generalised tonic-clonic, secondary generalised, absence and atonic seizures. It is effective in myoclonic seizures in children. Usual adult oral dose is 100-300 mg/day in divided doses. It is effective in treating bipolar disorder as a additional drug. Adverse reactions include dizziness, ataxia, diplopia and skin rash, especially in children. Enzyme inducers like Phenytoin and Carbamazepine decrease while enzyme inhibitors like Valproic acid increase the half-life of Lamotrigine.

Lamotrigine: **LAMITOR, LAMOGIN, LAMEPIL, LAMETEC** *is available as 25 mg, 50 mg and 100 mg tablet.*

(xiv) Felbamate

It is a wide spectrum of antiepileptic activity. It is less preferred because of unpredictable toxicity. It is useful in drug refractory epilepsies. It is also useful in atonic seizures, atypical absence seizures, partial seizures and generalised tonic-clonic seizures. Usual adult oral dose is 2000-4000 mg/day in 3-4 equally divided doses. It has been withdrawn from some countries due to aplastic anaemia and hepatotoxicity.

(xv) Levetiracetam

It is used specifically for treating partial seizures. The elimination kinetics is linear and hence drug interactions are minimal. Usual adult oral dose is 500 mg twice daily. Adverse reactions include somnolence, asthenia and dizziness.

Levetiracetam: **LEVROXA, TORLEVA, LEVTAM** *is available as 250 mg, 500 mg and 750 mg tablet and 100 mg/ml syrup.*

(xvi) Lacosamide

It is useful for treatment of partial seizures. Usual oral dose is 50 mg twice daily and can be increased by 100 mg every week till 300 mg. Adverse reactions include headache, nausea and dizziness. Oral bioavailability is 100%. It is neither enzyme inducer nor inhibitor. No clinically important drug interactions are reported.

4.6 ALCOHOL AND DISULFIRAM

4.6.1 Alcohol (Ethyl Alcohol/Ethanol)

The pharmacological effects of alcohol on different organs are to be considered as acute and chronic.

4.6.1.1 Pharmacological Effects (Acute)

- **Pharmacokinetics**

Ethanol is rapidly absorbed from GIT. Food, especially milk delays absorption of alcohol by slowing gastric emptying. Distribution is rapid with Volume of distribution (Vd) of 0.5-0.7 litres/kg. It crosses BBB as well as placental barrier; but the concentration in brain is very close concentration to that in blood. It is because the brain receives large proportion of blood flow.

About 95% of absorbed alcohol is metabolised and remaining 5% is excreted through breath, urine and sweat. Alcohol in alveolar air is in equilibrium with that in pulmonary capillary blood and this ratio is relatively constant. 80 mg/100 ml of ethanol in blood is equivalent to 35 µg/100 ml of ethanol in expired air.

A sizable fraction of ethanol is cleared by first-pass hepatic metabolism, which follows zero-order kinetics. A fixed amount of 8-12 ml or 7-10 gm of alcohol is metabolised per hour irrespective of its blood concentration. Hence, when stomach is empty, greater absorption produces higher pharmacological effects.

Ethanol is metabolised first to acetaldehyde and then to acetic acid. Two major pathways of alcohol metabolised to acetaldehyde, which take place in liver have been identified. (Fig. 4.11)

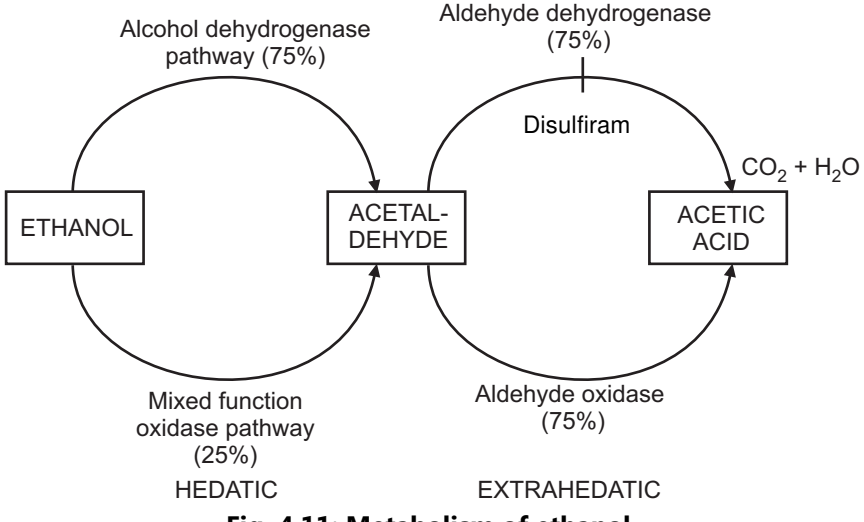


Fig. 4.11: Metabolism of ethanol

- **Metabolism of alcohol to acetaldehyde**

  The enzyme alcohol dehydrogenase, found mainly in liver, stomach and intestine oxidises about 75% ethanol to acetaldehyde (Fig. 4.10). The metabolism follows zero order kinetics.

  Another enzyme, mixed function oxidase (CYP450) system is responsible for remaining 25% of ethanol metabolism. At concentration of ethanol above 100 mg/dl, this pathway is more important for metabolism. During chronic alcohol use, there is induction of this enzyme system and therefore metabolism of steroids, oral anticoagulants and paracetamol is increased.

- **Metabolism of acetaldehyde to acetic acid**

  About 75-80% of acetaldehyde is converted to acetate in the liver by enzyme aldehyde dehydrogenase (ALDH). Only 20-25% of acetaldehyde is converted to acetic acid outside liver by an enzyme aldehyde oxidase. This leads to formation of acetate which is further metabolised to CO_2 and water.

- **CNS**

  Alcohol enhances the action of GABA at $GABA_A$ receptors similar to that of benzodiazepines (BZDs). BZDs also intensify acute effects of alcohol. BZD antagonist, Flumazenil reverses CNS depressant action of alcohol; however it is not used to reverse ethanol intoxication. Ethanol also inhibits ability of glutamate to activate NMDA receptor and thus inhibit opening of calcium channel linked to NMDA receptor.

  The acute effects of alcohol on CNS are sedation, relief from anxiety, loss of inhibitions and impaired judgement as well as driving skills. These effects occur at alcohol blood levels between 50-100 mg/dl. Blood levels of 120-160 mg/dl lead to effects like ataxia, slurred speech, mental clouding and grossly impaired motor functions. These effects are identified as "gross drunkenness". Levels between 200-300 mg/dl produce emesis and stupor, while levels above 300 mg/dl lead to coma, respiratory and cardiovascular depression. Levels above 500 mg/dl are lethal. Concommittent administration of drugs like BZDs, Phenothiazines, Tricyclic antidepressants and opiates causes additive depression.

- **Heart**

  At blood concentrations of 100 mg/dl, ethanol decreases myocardial contractility. Acetaldehyde may cause cardiac abnormalities by altering myocardial stores of catecholamines. Large doses depress vasomotor centre leading to fall in BP.

- **Smooth muscles and other effects**
  - Ethanol causes cutaneous vasodilatation, which leads to feeling of warmth, but actually increases heat loss.
  - It produces relaxation of uterus only at high doses.
  - Diuresis is associated with alcohol intake. It is caused by inhibiton of antidiuretic hormone secretion and partly because of increased water intake. However, tolerance develops rapidly to diuresis.

- Aggressive sexual behaviour is due to loss of inhibitions; however performance of the sexual act is hampered.
- Moderate amounts of ethanol causes catecholamine release and reduce glucose uptake by the tissues resulting in hyperglycemia. However inhibition of gluco-neogenesis can also cause hypoglycaemia.
- It requires no digestion and instantly supplies 7 cal/gm. This energy cannot be stored or utilised for body building. Thus, alcohol serves as an expensive as well as nutritionally worthless food.

4.6.1.2 Pharmacological Effects (Chronic)

Chronic ethanol intake adversely affects functions of several vital organs.

(a) Nervous system

Tolerance and dependence are major effects on CNS. Tolerance develops to the subjective and behavioural effects of alcohol. Chronic alcoholics may function normally even above 180 mg/dl levels as compared to occasional drinkers. The reduced rate of absorption and faster metabolism is responsible for pharmacokinetic tolerance.

Chronic alcohol drinkers, if forced to abstain, experience distressing withdrawal symptoms with physical dependence. The symptoms include hyper-excitability, toxic psychosis, delirium tremens and seizures. The withdrawal effects are observed around 8-24 hours after abstinence. The symptoms are tremors, nausea and sweating. This phase is followed by seizures and in next three days delirium tremens develop, which is characterised by confusion, agitation, aggressiveness and hallucination. Psychological dependence is characterised by compulsive desire to drink.

(b) Neurotoxicity

Chronic/heavy drinkers show ataxia, demensia and peripheral neuropathies. It is associated with thiamine (vitamin B_1) deficiency. The syndrome is characterised by ataxia, confusion and paralysis of extra-occular muscles. Prompt treatment with IV/IM thiamine is necessary. Alcohol also impairs visual acuity with painless blurring of vision on chronic consumption.

(c) Liver and GIT

Chronic excessive ethanol consumption causes fatty liver with inflammation. It leads to irreversible hepatic necrosis, fibrosis and failure. Another factor causing liver damage is malnutrition. Women appear to be more susceptible to alcohol hepatotoxicity. It is one of the most common causes of chronic pancreatitis. Irritation, inflammation, bleeding, scaring or even induration of gut mucosa occurs after chronic alcohol use. Defective absorption leads to deficiency of water soluble vitamins.

(d) Cardiovascular system

Chronic alcohol consumption leads to dilated cardiomyopathy, ventricular hypertrophy and fibrosis. Alcohol also interferes with therapeutic benefits of β-blockers and ACE inhibitors. It is also associated with ventricular arrhythmia, which may lead to syncope. It is also a contributory factor for hypertension.

(e) Blood lipoprotein and platelet functions

Moderate alcohol intake increases HDL and decreases LDL, which may account for observed protective effect against ischaemic heart disease. Alcohol inhibits platelet aggregation; it results from inhibition of arachidonic acid formation from phospholipids. Chronic alcoholics show megaloblastic anaemia due to alcohol related folic acid deficiency. Iron deficiency anaemia may be caused by gastro-intestinal bleeding.

(f) Endocrine effects and electrolyte balance

Chronic alcoholism can produce testicular atrophy, gynaecomastia and impotence. "Pseudo-Cushing's syndrome" is observed in chronic alcoholics. Alcoholics with cirrhotic liver may show ascites, edema and effusions due to decreased protein synthesis and portal hypertension. Secondary aldosteronism in chronic alcoholics can cause hypokalemia and muscle weakness. Some alcoholics may exhibit ketosis caused by increased lipolytic factors like cortisol and growth hormone.

(g) Effects on foetal development

Consumption of about 6-10 units of alcohol per day during pregnancy causes foetal alcohol syndrome. It is characterised by microcephaly, mental retardation, flattened face, retarded growth and cardiac or other malformations of eyes and ears as congenital abnormalities.

Another lesser degree of impairment is "alcohol-related neuro-developmental disorder". It is characterised by behavioural as well as cognitive and motor defects.

(h) Miscellaneous effects

- There are effects on immune system. Chronic alcoholics are pre-disposed to lung infections and may suffer from pneumonia.
- Its chronic use is associated with increased incidence of neoplastic disease like breast and liver carcinoma.
- Ethanol alters uric acid metabolism by increasing uric acid metabolism and decreasing renal secretion. Hence, gout may be precipitated due to hyperuricaemia.

4.6.1.3 Treatment of Acute and Chronic Alcoholism

Intoxication due to acute intake of ethanol is managed by maintainence of vital signs and prevention of aspiration of vomitus. Treatment of hypoglycaemia and ketosis can be made by giving IV glucose. IV/IM thiamine and correction of electrolytes may also be required.

The abstinence syndrome is managed by administration of a long acting sedative – hypnotic like Chlordiazepoxide or Diazepam. Intensity of withdrawal syndrome may be reduced by Clonidine and Propranolol. Once the withdrawal phase is over, BZDs may be withdrawn with gradual reduction of dose. Several months may be needed for restoration of normal sleep, and decrease of tremors and anxiety.

Alcohol dependence is followed by following means:

(a) The first effort is to render ethanol consumption unpleasant. It is discussed under use of Disulfiram.

(b) Another approach is to reduce craving or to blunt the pleasurable outcome of renewed drinking. Naltrexone, an opioid antagonist in a dose of 50 mg once a day is used to treat alcohol dependence. It reduces craving for alcohol.

Another approach is to use anticonvulsant drug like Topiramate. The drug potentiates inhibitory effects of GABA but acts at a site different than BZDs or barbiturates.

(c) Selective serotonin uptake inhibitors (SSRIs) like Fluoxetine can increase serotonergic activity in CNS. Alternatively, Ondansetron, a 5-HT_3 antagonist has been successfully used to treat alcohol dependence.

(d) To reduce craving for alcohol Acamprosate has been tried. It reduces excitatory effect of glutamate on NMDA receptor and also facilitates GABA neurotransmission. It also possesses some opioid antagonist activity and increase serotonin levels in synapses.

4.6.2 Drug Interactions

- Chronic consumption of alcohol increases risk of hepatotoxicity by Paracetamol. It involves CYP2E1 mediated conversion of paracetamol to reactive hepatotoxic metabolite N-acetyl-p-benzo-quinone imine.
- All cerebral depressants like hypnotics, sedatives, phenothiazines and anti-histamines can have synergistic effect with ethanol. It can have serious consequences during driving.
- Chronic alcoholics are relatively tolerant to use of general anaesthetics like halothane.
- Alcohol enhances the hypoglycaemic effects of insulin and sulfonylureas.
- Some alcoholic drinks like beer or wine contain tyramine, which is sufficient to cause hypertensive crisis in patients taking MAO inhibitors.

4.6.3 Clinical Uses of Ethanol

It is used for following purposes:

- As a skin antiseptic (76% v/v), alcohol is most effective.
- It has astringent action and hardens the skin to prevent the bed sores.
- It is used to treat methanol poisoning.

4.6.4 Disulfiram

The enzyme aldehyde dehydrogenase is inhibited by Disulfiram and by other drugs including metronidazole, oral hypoglycemics, some cephalosporins like Cifotetan and Cefoperazone and urinary antiseptics like Nitrofurantoin. When alcohol is consumed in presence of Disulfiram, conversion of acetaldehyde to acetic acid is significantly reduced.

Hence, acetaldehyde accumulates to cause effects like facial flushing, nausea, vomiting, dizziness and headache. The reaction is extremely unpleasant, but not life threatening. Hence, Disulfiram can be used as an aversion therapy to discourage people from consuming alcohol. Disulfiram is rarely used as an aversion therapy of alcohol dependence. Adverse reactions of Disulfiram include skin rashes, metallic taste and abdominal upset. Its dose is 1 gm on first day which is to be reduced by 250 mg daily until 250 mg once daily maintainence dose is adjusted.

Disulfiram: **ANTADICT, SUFITAL, ESPERAL** *is available as 250 mg tablet.*

QUESTIONS

Long Answer Questions:

1. Describe neurohumoral transmission in CNS.
2. Comment on distribution, biosynthesis, release and metabolic degradation of 5-HT.
3. Describe various pharmacological actions of 5-HT.
4. Comment on actions of GABA on its receptors.
5. Comment on different agonists for 5-HT receptor.
6. Describe different stages of anaesthesia.
7. What are pharmacokinetic principles for using general anaesthetics.
8. Compare and contrast Benzodiazepines with Barbiturates.
9. Comment on pharmacokinetics of Benzodiazepines with reference to interrelation of their metabolites.
10. Comment on adverse reactions and drug interactions of Benzodiazepines.
11. Write pharmacological effects, pharmacokinetics and therapeutic uses of Barbiturates.
12. Elaborate on centrally acting skeletal muscle relaxants.
13. Classify types of seizures.
14. Comment on mechanism of action of antiepileptic drugs.
15. Give detailed account of Phenetoin.
16. Write pharmacological actions and pharmacokinetics of ethanol.
17. Discuss chronic effects of alcohol consumption.

Small Answer Questions:

1. Write short notes on:
    - GABA
    - Glutamate
    - Glycine
    - Serotonin (5-HT)
    - Dopamine
    - MAC value of anaesthetic
    - Halothane
    - Isoflurane

- Thiopental
- Pre-anaesthetics
- Non-benzodiazepine hypnotics
- Melatonin
- Ticlophos
- Promethazine
- Mephenesin
- Daclofen
- Adverse reactions to Phenetoin
- Pharmacokinetics of Phenobarbitone
- Carbamazepine
- Ethosuximide
- Sodium valproate
- Vigabatrin
- Gabapentin
- Lamotrigine

2. List three adverse reactions to Benzodiazepines
3. List three drug interactions of Benzodiazepines with other drugs.
4. Classify Barbiturates.
5. Name three adverse effects of Barbiturates.
6. Enlist contraindications of Barbiturates.
7. Comment on drug interactions of Barbiturates with other drugs.
8. How does Disulphuran act?
9. What are clinical uses of ethanol.
10. What are interactions of ethanol with other drugs.

■■■

Unit ... 5

PHARMACOLOGY OF CENTRAL NERVOUS SYSTEM - II

♦ LEARNING OBJECTIVES ♦

After completing this chapter, student should be able to understand:

- *Pharmacology of Psychopharmacological Agents like Antipsychotics, Antidepressants, Antianxiety Agents, Antimaniacs and Hallucinogens*
- *Pharmacology of Drugs used in Parkinson's and Alzheimer's Disease*
- *Pharmacology of CNS stimulants and Nootropics*
- *Pharmacology of Opioid Analgesics and Antagonists*
- *Drug Addiction, Drug Abuse, Tolerance and Dependence*

Drugs acting on CNS are classified in different categories. The first category belonging to psychopharmacological agents is discussed below.

5.1 PSYCHO-PHARMACOLOGICAL AGENTS: ANTI-PSYCHOTICS, ANTI-DEPRESSANTS, ANTI-ANXIETY AGENTS, ANTI-MANIACS AND HALLUCINOGENS

Psychopharmacological agents are the drugs used to treat CNS – conditions related to behaviour of a person. They are further sub-classified as antipsychotics, antidepressants, antianxiety agents, antimaniacs and hallucinogens. Each sub-category is discussed below.

5.1.1 Antipsychotics

Antipsychotics are used to treat schizophrenia. Although, genetic predisposition is considered to be one of the causes of schizophrenia, there are three hypotheses, based on neurotransmitters used to explain pathogenesis of schizophrenia.

(a) Dopamine (DA) hypothesis

It is argued that DA abnormality is the basis for most of the manifestations of schizophrenic patients. Excess of dopamine in some areas of brain is considered responsible for schizophrenia. Typical antipsychotic drugs like Haloperidol bind to D_2 receptors of DA. However, dopamine antagonists are not a cure for all schizophrenics. Probably, other neurotransmitters are involved.

(b) 5-HT/Serotonin hypothesis

The role of 5-HT in schizophrenia is based on the finding that LSD, a central 5-HT_2 receptor agonist produce hallucinations and sensory disturbances, which are symptoms

observed in psychosis. Atypical neuroleptics like Clozapine and Olanzapine are potent 5-HT_{2A} receptor antagonists. These receptors modulate release of DA in some areas of brain. Hence, both 5-HT and DA hypotheses for schizophrenia are compatible.

(c) Glutamate hypothesis

Involvement of glutamate is based on the finding that glutamate-NMDA receptor antagonists like Phencyclidine and Ketamine when administered to normal subject, produces psychotic symptoms like hallucinations and thought disorders. In addition, reduced glutamate densities have been reported in brains of schizophrenics. Drugs which may enhance NMDA receptor activity may be useful in treating schizophrenia.

5.1.1.1 Classification of Antipsychotics

Antipsychotics are broadly classified as typical and atypical antipsychotics.

(i) Typical antipsychotics are further classified in to four categories as follows:

- **Phenothiazenes:** They are further sub-classified based on side chains attached to phenothiazenes.
  - **Aliphatic side chain:** Chlorpromazine
  - **Piperidine side chain:** Thioridazine
  - **Piperazine as side chain:** Trifluoperazine, Perfenazine, Fluphenazine
- **Thioxanthenes:** Flupenthixol, Thiothixene, Zuclopenthixol
- **Butyrophenones:** Haloperidol, Benperidol, Droperidol.
- **Miscellaneous:** Pimozide, Penfluridol, Molindone, Loxapine, Sulpiride, Amisulpride, Remoxipride.

(ii) Atypical antipsychotics: Clozapine, Olanzapine, Quetiapine, Zotepine, Risperidone, Ziprasidone, Paliperidone, Aripiprazole, Sertindole, Asenapine.

5.1.1.2 Mechanism of Action

All typical antipsychotic drugs act as antagonists at D_2 and/or D_3/D_4 dopamine receptors. Atypical antipsychotics block other monoamine receptors, especially 5-HT_{2A} receptors.

Typical antipsychotics produce competitive blockade of post-synaptic D_2 receptors in mesolimbic system. Atypical antipsychotics have a high affinity for 5-HT_{2A} receptors, but they have antagonistic action on α_1, ACh M_1, Histamine H_1 and Dopamine D_2 receptors.

All antipsychotic drugs exhibit a latent period of 2-3 weeks for attaining therapeutic effects. Majority of them are given orally; however their bioavailability increases ten fold when given by IM route.

5.1.1.3 Therapeutic Uses

They are primarily used for three types of indications:

(a) Psychiatric indications

They are primarily used to treat schizophrenia. In addition, they are also used to treat drug-induced psychoses like delusions associated with LSD, Amphetamine-induced psychoses and delirium following infectious psychoses. They are also used to treat shizo-affective disorders in which schizo refers to schizophrenia and affective refers to mania.

(b) Neuro-psychiatric indications

It involves use in Tourette's syndrome which is marked by tics, grunts and vocalisations which are frequently obscene. Haloperidol and Pimozide are preferred for this condition.

In addition, they are also useful for Huntington's disease which involves progressive choreoathetosis and dementia. Haloperidol and Chlorpromazine are preferred for this condition.

(c) Non-psychiatric indications

All antipsychotics have antiemetic effects of varying degree. It is due to blockade of D_2 receptor in CTZ as well as in GIT. Prochlorpromazine is preferred for this purpose.

Antipsychotic like Promethazine is used as pre-operative sedative since it has antihistaminic, anticholinergic and antiemetic effects also. Droperidol is a short acting antipsychotic with antiemetic, sedative and anticonvulsant effects.

Parenteral acaholrpromazine or Haloperidol is useful in controlling intractable hiccups.

5.1.1.4 Adverse Effects

Adverse effects to antipsychotics are categorised into following five types:

(a) CNS side effects

It involves behavioural effects, tolerance and dependence. Behavioural effects depress the sensory inputs to reticular activating system and cause sedation as well as psychomotor impairment in high doses. Toxic confusional states may occur with higher doses of drugs having anticholinergic effects.

Tolerance develops to sedative and autonomic effects but not to antipsychotic action. Withdrawal symptoms are manifested as dyskinesias. Physical dependence is not observed.

(b) Neurological side effects

Dystonias, akathisia, parkinsoniasm and a rare neurolept-malignant syndrome appear during treatment. Tardive dyskinesia and a rare peri-oral tremor appear later following prolonged treatment for about a year.

Dystonia is characterised by spasm of muscles of tongue, face, neck and back.

Akathisia is characterised by uncontrollable motor restlessness without anxiety.

Parkinsoniasm is due to imbalance in dopamine-acetyl choline in basal ganglia due to D_2-receptor blockade.

Neurolept-Malignant Syndrome (NMS) is a life-threatening disorder observed in extremely sensitive patients. It leads to hyperpyrexia, muscle rigidity, autonomic instability with fluctuating BP, increased myoglobin and increased creatinine kinase reflecting muscle damage.

Peri-oral tremors (Rabbit syndrome) shows rapid chewing movements just like that of rabbits.

Tardive dyskinesia shows involuntary oro-buccal-lingual dyskinesia; as if the patients are chewing gum.

(c) Autonomic side effects

It involves α-adrenergic blockage and anti-muscarinic effects. α-blockade leads to postural hypotension and tachycardia. It also involves loss of libido and delayed ejaculation. Anti-muscarinic effects cause dryness of mouth, constipation, urinary retention, disturbed accommodation but no pupillary dilation.

(d) Endocrinal side effects

It results in hyperprolactinamia which is manifested as galactorrhea in females and gynaecomastia in males. These drugs also inhibit release of FSH and LH leading to amenorrhoea and inhibition of ovulation.

(e) Miscellaneous side effects

Drugs belonging to Phenotiazine groups are also known to cause jaundice, photosensitivity, corneal opacity, epileptogenic effects and poikilothermic effects.

5.1.1.5 Drug Interactions

Drug interactions of antipsychotic drugs are presented in table 5.1.

Table 5.1: Drug interactions with antipsychotic drugs

Sr. No.	Drug	Effects
1.	Antacids	Decreased absorption of antipsychotic drugs
2.	Anticholinergics	Increased anticholinergic effects
3.	Alcohol	More sedation
4.	Antithyroid drugs	Increased risk of agranulocytosis (with Clozapine)
5.	Barbiturates	Decreased antipsychotic effects, more sedation
6.	Carbamazepine/Phenytoin	Decreased antipsychotic effects and lowering of seizure threshold
7.	Chloroquinine	May precipitate extra-pyramidal symptoms with Phenothiazines
8.	Lithium	Enhancement of neurotoxicity and precipitation of NMS (Haloperidol)
9.	Levodopa	Decreased efficacy of neuroleptics
10.	Oral contraceptives	May potentiate hyperprolactinaemia
11.	Cigarette smoking	Increased metabolism of antipsychotics; higher dose needed

Preparations of various antipsychotics are presented in table 5.2.

Table 5.2: Available preparations of antipsychotic drugs

Sr. No.	Drug	Formulations and strength	Trade name
1.	Chlorpromazine	25 mg, 50 mg, 100 mg, 200 mg tablet; 25 mg/ml injection	Megatil, sunprazin
2.	Fluphenazine	25 mg/ml injection	Anatensol decanoate, Prolinate
3.	Trifluoperazine	5 mg, 10 mg tablet	Neocalm, Talecalm, Trazine
4.	Thioridazine	10 mg, 25 mg, 50 mg, 100 mg tablet	Melleril, Ridazin, Thioril
5.	Flupenthixol	0.5 mg, 1 mg, 3 mg tablet; 20 mg/ml depot injection	Fluanxol
6.	Zuclopenthixol	200 mg/ml injection	Clopixol depot
7.	Haloperidol	1.5 mg, 5 mg, 10 mg, 20 mg tablet; 2 mg/ml, 5 mg/ml injection, 50 mg/ml depot injection	Serenace, Trancodol, Senorm – LA, Gendol – LA
8.	Penfluridol	20 mg tablet	Flumap, Semap
9.	Pimozide	2 mg, 4 mg tablet	Mozep, Orap, Larap
10.	Loxapine	10 mg, 25 mg capsule; 25 mg/ml liquid	Loxapac
11.	Sulpiride	100 mg, 200 mg, 400 mg tablet	Stride
12.	Amisulpiride	50 mg, 100 mg, 200 mg tablet	Sulpitac, Amipride, Zulpride
13.	Levosulpiride	25 mg tablet	Lesuride
14.	Clozapine	25 mg, 50 mg, 100 mg tablet	Sizopin, Lozapin, Skizoril
15.	Olanzapine	2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg tablet	Oleanz, Olexar, Oliza, Tolaz
16.	Risperidone	1 mg, 2 mg, 3 mg, 4 mg tablet; 1 mg/ml syrup	Sizodon, Risnia, Risdone
17.	Ziprasidone	20 mg, 40 mg, 80 mg tablet	Zipsydon, Azona
18.	Paliperidone	3 mg, 6 mg, 9 mg ER tablet	Palica – OD
19.	Aripiprazole	10 mg, 15 mg, 20 mg, 30 mg tablet	Arpizole, Schizopra, Aripra – MT
20.	Quetiapine	25 mg, 50 mg, 100 mg, 200 mg, 300 mg tablet	Placidin, Qutipin, Qutan, Q-pin

5.1.2 Anti-Depressants

Depression is a disorder of mood and hence it is classified as affective disorder. There are two major types of depression: unipolar depression and bipolar depression. Unipolar depression is further sub-divided as reactive depression and endogenous depression.

About 80% of depressed patients experience unipolar depression in which the mood swings in one direction only i.e. either depression with a feeling of worthlessness or depression with irritability. About 60% of unipolar depressed patients show reactive depression manifested by feeling of sadness or grief and anxiety due to reasons like death of a loved one, unemployment, physical illness or social problems. It is self-limiting and responds to antianxiety drugs. About 25% of unipolar patients are having endogenous depression with suicidal thoughts. It is not self-limiting, unless treated with an anti-depressant drug or by electro convulsive therapy (ECT). It results either due to genetic causes or due to disturbed neurotransmission of NE, 5-HT or DA in certain areas of brain.

5.1.2.1 Classification

Classification of antidepressant drugs is based on their mechanism of action.

Antidepressants are classified in to following seven sub-types:

- Drugs which block both NE and 5-HT reuptake: Tricyclic antidepressants (TCAs): Imipramine, Clomipramine, Amitriptyline, Doxepin
- Selective 5-HT-NE reuptake inhibitors (SNRIs): Duloxetine, Venlafaxine, Milnacipram
- Drugs which block NE reuptake: Desipramine, Nortriptyline, Protryptyline, Maprotiline, Amoxapine, Reboxetine
- Selective serotonin reuptake inhibitors (SSRIs): Sertraline, Fluoxetine, Fluvoxamine, Paroxetine, Citalopram, Escitalopram
- Atypical antidepressants: Trazodone, Nefazodone, Bupropion, Mirtazapine, Mianserin
- Antidepressants of natural origin: St. John's wort (Active principle: Hyperforin)
- MAO inhibitors: Non-selective: Tranylcypromine; Selective: Moclobemide

5.1.2.2 Mechanism of Action

A brief account of mechanism of action is presented below:

(a) Drugs which block NE and 5-HT reuptake: These are tricyclic antidepressants. They block reuptake of NE and 5-HT into their neuron by inhibiting respective transporters. It leads to more availability and a longer stay of NE and 5-HT at their respective receptor sites. (Fig. 5.1).

(b) SNRIs: Besides the effects shown by tricyclic antidepressants, SNRIs lack α_1-adrenergic, histamine H_1 and cholinergic receptor blocking properties of TCAs. Hence, they have fewer side effects.

(c) Drugs blocking NE reuptake: These drugs predominantly inhibit NE reuptake which results in increased concentration of NE in synaptic cleft.

(d) SSRIs selectively increase levels of serotonin in synaptic cleft. They are most commonly prescribed antidepressant drugs.

All antidepressants described above exhibit a lag of 2-3 weeks to produce desirable clinical effects.

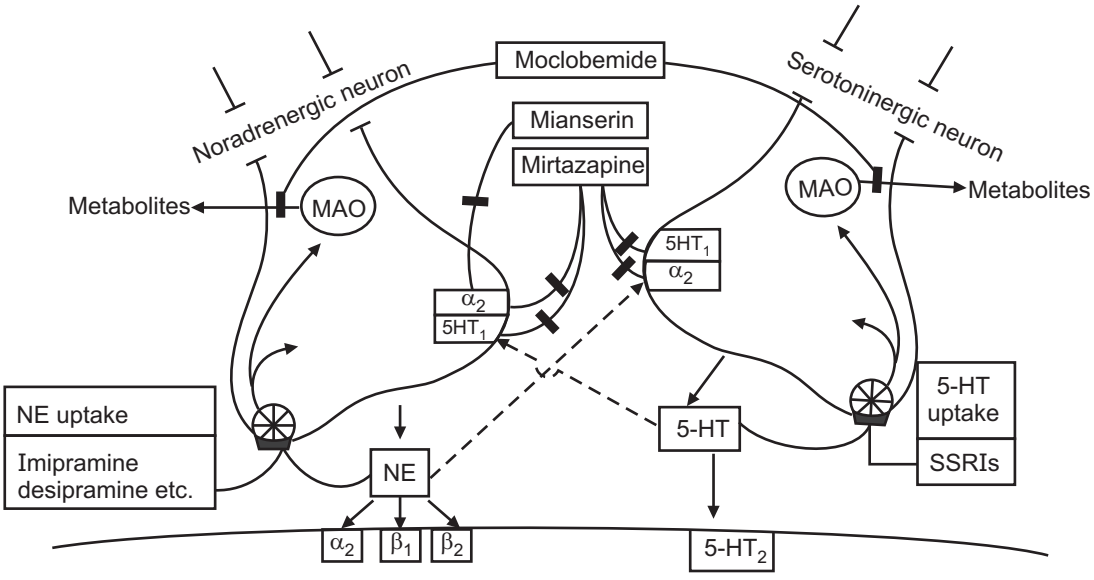


Fig. 5.1: Potential sites of action of some antidepressant drugs

(e) Atypical antidepressants have different mechanisms of action. Trazodone/ Nefazodone inhibit uptake of 5-HT, blocks 5-HT_{2A} receptor and desensitizes presymaptic 5-HT receptor. Mianserin blocks presynaptic α_1-receptors and increase release of NE in brain. Mirtazapine acts by increasing both NE and 5-HT release. Bupropion is a weak inhibitor of neuronal reuptake of 5-HT, NE and DA.

(f) Active ingradients of St. John's wort (*Hypericum perforatum*) are monoamine reuptake inhibitors, mild MAO inhibitors and stimulants at GABA receptors.

(g) MAO inhibitors increase brain amine levels by inhibiting their metabolism, resulting in increase of NE and 5-HT. There are two isoforms of MAO: MAO-A and MAO-B. MAO inhibitors need a biological lag of 2-3 weeks to exert clinical effects.

5.1.2.3 Pharmacokinetics

Oral absorption of most antidepressant drugs is good; still the bioavailability is uncertain because of their first pass metabolism. Bioavailability of Citalopram and Protryptyline is > 90%. The plasma half-life of most antidepressants is long, hence plasma concentration is built-up slowly. After reaching steady state, one daily dose at bed time is enough. Plasma half-life for some antidepressants is low. Amoxapine (8 hours), Nefazodone (2-4 hours), Trazodone (4-8 hours) and Venlafaxine (4-9 hours) are some of the examples. The half-life is longer due to their metabolites except for Fluvoxamine, Paroxetine and Protriptyline. Among MAO inhibitors, Moclobemide is readily absorbed but its first pass metabolism reduces bioavailability; its half-life is 1-3 hours.

5.1.2.4 Therapeutic Uses

They are broadly classified as psychiatric uses and non-psychiatric uses.

(a) Psychiatric uses

The drugs are useful to treat endogenous depression. There are three phases of treatment: acute phase, continuation phase and maintainence phase. In the initial phase, objective is to resolve symptoms followed by prevention of relapse and prevention of recurrence in the last phase. SSRIs like Mirtazapine, Nefazodone, Duloxetine and Venlafaxine are considered best drugs of choice.

SSRIs like Paroxetine, Fluvoxamine and Fluoxetine, alone or with Alprazolam, can be used to treat panic disorders. They need several weeks for stabilisation.

SSRIs like Fluvoxamine are useful for treating Obsessive-Compulsive Disorders (OCDs). Alternatively, Clomipramine or Citalopram may also be used for the purpose.

Drugs like Imipramine or Desipramine are preferred to treat Attention Deficit Hyperkinetic Disorders (ADHD). Alternatively, Atomoxetine is also used for the purpose.

SSRIs like Paroxetine or reversible MAO-A inhibitor Moclobemide are preferred for school phobia and social phobia. Paroxetine with Alprazolam are preferred for post-traumatic stress disorder. SSRIs are helpful in controlling impulse control disorder like gambling.

(b) Non-psychiatric uses

Antidepressants with anticholinergic side effects like Amitriptyline, Desiprimine and Imipramine are preferred for treating enuresis and bed-wetting in children. Older patients are more sensitive to anticholinergic effects of TCAs.

TCAs like Imipramine, Amitriptyline or nortriptyline are preferred in treating neuropathic chronic pain.

TCAs like Amitriptyline in low doses (10 mg at night), followed by increase in dose up to 50 mg within 2-3 weeks is effective in treating migraine headache.

5% topical Doxepin cream relieves itching in atopic dermatitis.

SSRIs like Fluoxamine and Fluoxetine are useful in treating bulimia nervosa.

Bupropion is used to treat nicotine dependence and smoking caessation.

Citalopram is used to treat ethanol abuse syndrome.

5.1.2.5 Adverse Effects

Adverse effects are dependent on the type of anti-depressant based on its mechanism of action.

(a) TCAs which block uptake of NE or NE + 5-HT

TCAs with histamine H_1 receptor blocking actions (Amitriptyline, Doxepin and Trimipramine) cause more sedation. Drugs like Maprotiline, Bupropion and Clomipramine lower seizure threshold and precipitate epileptic seizures. Drug like Amoxapine can induce extrapyarmidal effects, gynacomastia (in males) and galactorrhoea (in females).

Antidepressants with anticholinergic effects cause blurred vision, urinary retension, constipation and increase in intra-occular pressure. Antidepressants with α-blockade cause postural hypotension and tachycardia.

Some antidepressants altering endocrinal responses cause weight gain and sexual disturbances. Some TCAs can cause QT-prolongation leading to arrhythmia.

(b) SNRIs

These drugs have serotonergic side effects like discontinuation syndrome.

(c) SSRIs

Some patients complain of agitation, anxiety and insomnia. Few others complain of sexual dysfunction including decreased libido and delayed ejaculaton. Nausea and loose stools are also experienced by few patients. Sudden withdrawal causes discontinuation syndrome leading to dizziness, paresthesias and headache.

(d) MAO inhibitors

Their adverse effects include postural hypotension (in elders), weight gain, dizziness and sexual dysfunction.

(e) Atypical antidepressants

Trazodone causes nausea, sedation, postural hypotension and priapism leading to impotence. Bupropion causes agitation and insomnia. Mirtazapine and Mianserin cause sedation due to histamine H_1-blockade. Hepatotoxicity and blood dyscrasias have also been reported.

5.1.2.6 Drug Interactions

They are classified under three categories:

(i) Interactions with TCAs and related drugs:

(a) TCAs potentiate effects of directly acting sympathomimetics causing rise in BP and arrhythmias; but inhibit effects of indirectly acting sympathomimetics.

(b) Anticholinergic drugs aggravate toxicity of TCAs.

(c) Phenytoin, Chlorpromazine and Aspirine displace TCAs from their protein binding sites leading to increased effect of TCAs.

(d) MAO inhibitors have synergistic action with TCAs causing hypertension, arrhythmias and seizures.

(ii) Interactions with MAO inhibitors:

(a) Food articles containing tyramine, like cheese, beer, red wine, banana, yoghurt and pickled meat when used with MAO inhibitors can cause hypertensive crisis.

(b) MAO inhibitors with TCAs or with directly/indirectly acting sympathomimetics can cause hypertension, arrhythmias and seizures.

(c) MAO inhibitors inhibit degradation of DA. This can result in hypertension.

(d) MAO inhibitors retard metabolism of drugs like morphine causing severe respiratory depression. It also retards metabolism of sulfonylureas causing hypoglycaemia and that of chloroquinine causing toxicity of chloroquine.

(iii) Interactions with SSRIs:

(a) SSRIs inhibit metabolising enzymes like CYP2D6 and CYP3A4. As a result, plasma levels and toxicity of TCAs, Haloperidol, Clozapine, Warfarin, Dextromethorphan, Terfenadine, Astemizole and Cisapride are increased. Elevated levels of Terfenadine, Astemizole and Cisapride can precipitate arrhythmias.

(b) SSRIs with MAO inhibitors result in elevated levels of 5-HT causing "serotonin syndrome" leading to hyperthermia, muscle rigidity, tremors and rapid changes in mental status along wirth cardiovascular collapse.

Preparations of various antidepressants are presented in table 5.3.

Table 5.3: Preparations of antidepressant drugs

Sr. No.	Drug	Formulations and strength	Trade name
1.	Amoxapine	50 mg, 100 mg tablets	Demolox, A-pine
2.	Amitriptyline	10 mg, 25 mg, 75 mg tablets	Amitone, Tryptomer, Tadamit
3.	Clomipramine	10 mg, 25 mg, 50 mg tablets	Clonil, Clofranil
4.	Doxepin	10 mg, 25 mg, 75 mg capsule	Doxetar, Doxin, Spectra
5.	Imipramine	25 mg, 75 mg capsule	Depsonil, Depsonil PM, Imipramine
6.	Nortriptyline	25 mg tablet	Sensival, Nordep, Primox
7.	Trimipramine	10 mg, 25 mg tablets	Surmontil
8.	Reboxetine	2 mg, 4 mg tablets	Rebotin, Reboot
9.	Duloxetine	20 mg, 30 mg, 40 mg capsule	Delok, Dulane, Duzac
10.	Venlafaxine	25 mg, 37.5 mg, 75 mg tablets; 150 mg ER capsule	Dalium, Venlift, Veniz-XR, Venlor-XR
11.	Citalopram	10 mg, 20 mg, 40 mg tablets	Citopam, Zetalo, Cytop
12.	Escitalopram	5 mg, 10 mg, 20 mg tablets	Articalm, Stalopam, S-Zetalo, Nexito
13.	Fluoxetine	10 mg, 20 mg, 60 mg tablet; 20 mg/ 5ml suspension	F-udac, Prodep, hoftil, Flutinol
14.	Paroxetine	10 mg, 20 mg, 30 mg, 40 mg tablets; 12.5 mg, 25 mg, 37.5 mg CR tablets	Parotin, Pexep, Pari, Paxidep-CR
15.	Sertraline	25 gm, 50 mg, 100 mg tablets	Zosert, Sertil, Inosert, Serlift
16.	Moclobemide	150 mg, 300 mg tablet/ capsule	Rimarex, Trima

contd. …

17.	Bupropion	150 mg tablet, 150 mg SR tablet	Zyban, Smoqit-SR, Bupron-SR
18.	Mianserin	10 mg, 30 mg tablets	Depnon, Tetradep, Seridac
19.	Mirtazepine	7.5 mg, 15 mg, 30 mg tablets	Mirtaz, Mirtee, Mirazep
20.	Trazodone	25 mg, 50 mg, 100 mg tablets	Depryl, Trazonil, Tazodac, Trazalon
21.	Hypericum (St. John's wort)	300 mg capsule	J-Wort, Jovin

5.1.3 Anti-anxiety Agents

Anxiety is an adaptive response which prepares a person to face the challenges of life. It is characterised by psychological symptoms like tension, fear, apprehension and lack of concentration. In addition, sympathetic somatic symptoms like tachycardia, tremors, sweating and GIT distress are also observed. Fatigue and sleep disturbances are also common. If anxiety persists, it impairs person's ability to perform the job and often leads to visceral organ dysfunction and neurological problems.

Anxiety neurosis is characterised by uneasiness, easily provoked irritable behaviour and disproportionate concern and fear for future. It can result due to problems related to examination, interview to performance related to sexual act or even problems at work place. Manifestations of such anxiety are sweating, epigastric distress, tremors, dizziness, congestion in chest and hyperventilation.

There are two types of drugs used to treat anxiety: typical and atypical.

[I] Typical antianxiety drugs are BZDs and are discussed under section 4.4.1.

[II] Atypical antianxiety drugs (anxiolytics) are Buspirone, Ipsapirone and Gepirone. These drugs act through non-GABAergic system and have low chances of side effects in comparison to BZDs. These drugs exert their anxiolytic effects by acting as a partial agonist primarily at brain 5-HT_{1A} receptors. By selective activation of the inhibitory presynaptic 5-HT_{1A} receptor, they suppress 5-HT neurotransmission through neuronal system.

Useful anxiolytic effects of Buspirone are delayed for more than two weeks, which makes it unsuitable for treating acute anxiety states. It has no muscle relaxant, anticonvulsant or hypnotic action. It has minimal abuse liability and causes no withdrawal reactions on abrupt discontinuation. It causes lesser impairment of psychomotor skills and does not potentiate CNS depressant effects of alcohol. It can cause tachycardia, nervousness, GIT distress and paresthesias. It causes dose-dependent papillary constriction.

Buspirone is available as 5 mg, 10 mg tablet: **TAMSPAR, BUSCALM, BUSPIDAC**.

Non-specific β-adrenergic blocker like Propranolol is also used to treat anxiety. Worrying situations and apprehensions associated with examinations, job interviews or public address may lead to palpitation, tremors, GIT upset or even hypertension die to sympathetic

overactivity. These symptoms, in turn, reinforce anxiety and thus the visicous cycle continues. Propranolol breaks the visicious cycle. Through its β-blocking action, it decreases palpitation, tremors, GIT upset, hypertension and blood lactic acid levels. However, because of its cardiovascular actions, it is not a potential preferred anxieolytic.

Propranolol is available as 10 mg, 20 mg tablet in combination with 0.25 mg Alprazolam: **ALLTOP-P, ZOPAX PLUS.**

5.1.4 Anti-maniacs

Mania is characterised by an excessive desire and too much of euphoria. Majority of patients of mania experience cyclic episodes of mania followed by severe depression with periods of normal mood in between. Thus, the patient's condition moves between mania and depression. Hence, it is called as manic-depressive psychosis (MDP).

Excessive NE/DA related activity precipitates mania and the drugs which reduce NE/DA relieve mania. Balanced neurotransmitter levels help in stabilisation of mood. While manic episode is believed to result from elevated NE, depressive phase is associated with decrease in NE.

Lithium carbonate is considered to be a drug of choice for treating MDP. In addition, Carbamazepine, valproate or olanzapine can be used as alternatives to Lithium carbonate. Details about Lithium carbonate are presented here.

(a) Mechanism of Action

The mechanism of action of Lithium is related to second messenger involved in α-adrenergic and muscarinic neurotransmission. Inositol triphosphate (IP_3) is inactivated to inositol diphosphate (IP_2), inositol monophosphate (IP_1) and then to inositol. Lithium selectively inhibits signal transduction in overactive neurons by blocking conversion of IP_2 to IP_1 and then to inositol. As a result, the supply of free inositol to regenerate phosphatidyl inositol-diphosphate (PIP_2) in hyperactive neurons is interrupted and ultimately release of IP_3 and diacyl glycerol (DAG) is also reduced which decreases neuronal response to NE, DA and 5-HT.

In addition, Lithium may uncouple receptors from their G-proteins. Sodium ions are so common for neurotransmission. Competition of lithium ions with sodium is also said to contribute to the action of lithium.

(b) Pharmacokinetics

Lithium carbonate is readily absorbed from GIT. Distribution occurs throughout extracellular fluid and body water with no evidence of either protein binding or metabolism. The elimination half-life is 24 hours but the doses are given at 8 hourly interval. 96% of the drug is excreted through kidney and remaining 4% through saliva and sweat. Na^+ loading enhances Li^+ clearance while Na^+ depletion promotes Li^+ retention. This interrelation explains association of lithium toxicity with diuretics and diarrhoea. Li^+ has a low margin of safety with a therapeutic window of 0.5-1.5 mEq/L. Frequent measurements of serum steady state concentration are essential for optimum outcome. Toxicity appears when serum levels exceed 1.5 mEq/L.

(c) Therapeutic Uses

Lithium is used as Lithium carbonate or citrate. Both are less hygroscopic and less irritant to GIT than lithium chloride. However, in stomach any salt of lithium is converted to lithium chloride. Usual dose is 300-600 mg three times a day. The dose should be adjusted based on serum levels of lithium.

Lithium is primarily used for manic depressive bipolar psychoses. Abrupt discontinuation can lead to rebound effect. Persistent long term treatment is of importance.

Leucocyte counts are increased with Lithium therapy. This property is used to treat leukopenia and agranulocytosis associated with cancer chemotherapy.

Lithium is occasionally used to treat cluster headache and as an adjuvant to TCAs for treating recurrent unipolar depression.

(d) Adverse Effects

- Tremors, confusion and slurred speech.
- Sub-clinical hypothyroidism is reported on long-term use. Lithium inhibits TSH –activated adenylate cyclise causing lesser cAMP which in turn decreases T_3 and T_4 secretion.
- On long-term use some patients develop nephrogenic diabetes insipidus characterised by polyuria and polydipsia.
- Lithium causes diarrhoea. Diarrhoea causes sodium loss and the cycle continues.
- Oedema is a frequent adverse effect of lithium.
- Renal clearance of lithium increases during pregnancy but decreases immediately after delivery. Dose adjustment is essential. Lithium is also secreted through breast milk and should be avoided in lactating mothers.

(e) Drug Interactions

- Phenothiazine and Butyrophenone group of antipsychotics, when combined with lithium may aggravate risk of extrapyramidal effects.
- Thiazide or loop diuretics lead to rise in lithium plasma levels.
- Except aspirin or paracetamol, other NSAIDs reduce renal clearance of lithium.

Lithium carbonate is available as 250 mg, 300 mg, 350 mg tablet; 150 mg, 350 mg capsule and 400 mg SR/ER tablets: **LITHOSUN, LITHOSUN – SR, LICAB, LICAB – XL, LITHOCAP**.

Alternatives to Lithium

Nearly 50% of patients show incomplete or poor response to lithium. Hence, following drugs are used as an alternative to treat MDP: Olanzapine, Risperidone, Quetiapine, Ziprasidone, Lorazepam, Clonazepam, Bupropion, Paroxetine, Valproic acid, Carbamazepine, Lamotrigine, Gabapentine or Topiramate. Alternative drugs have been discussed earlier.

5.1.5 Hallucinogens

Hallucinogens are also termed as psychedelics or psychotomimetics. After the use of these drugs, a person feels that there is no boundary between him and the cosmos and that

his mind is able to see more than what he can tell. Drug abusers glorify them by the term "mind expanders". Pharmacologically, these drugs produce changes in sensory perceptions (visual, auditory and olfactory), thoughts, behaviour and mood. Their actions mimic psychoses.

Mood simply means a state of feeling at particular time. Percepts are such thoughts or messages, which though originate from outside, have a high degree of agreement with external reality or signals. These signals are not fantasies. If a fantacy is generated during sleep, it is called as a dream. However, if a fantasy occurs during wakeful state, it is called as hallucination. Thus, hallucination is a false perception without a true sensory stimulus. In hallucination, the images are vague and disproportionate.

The drugs under this category are as follows:

(i) Lysergic Acid Diethylamide (LSD)

It is a lysergic acid derivative which occurs in the cereal fungus ergot. The drug produces strong psychedelic effects in doses less than 1 µg/kg. It works as agonist of 5-HT_2 receptors and suppresses electrical activity in serotonergic raphe neurons which tonically inhibits the visual and sensory inputs. As a result, the excitation threshold of retina is decreased and its spontaneous electrical activity increases leading to visual hallucinations. Similarly, the excitation threshold of mid-brain RAS is decreased producing a hyper-arousal state. The drug also displays agonistic activity at 5-HT_{1A} and 5-HT_{1C} receptors.

A dose of 25-50 µg produces all effects of LSD. The onset of effect is fairly rapid but the duration varies with the user and the dose. Effects normally vanish within 8 hours. The effects start with somatic symptoms like tremors, blurred vision amd tachycardia. After one hour, they are followed by perceptual symptoms. Visual perceptions are expressed as distorted shapes with brilliant colours of changing intensities. Auditory perceptions include sharp hearing with difficulty in locating the source of sound. Further auditory sense gets fused with visual to provoke a strange feeling where one starts seeing the sound and hearing the colours. Olfactory perceptions also get fused with auditory and visual senses. The mood fluctuates in between joyous, sad to frightening. The sense of time is lost. After two hours, psychic symptoms start appearing. They are characterised by dreamy state and depersonalisation, as if the soul has come out of the body. A sense of union with cosmos is felt. All such experiences are either terrifying or hilarious depending on the user's personality traits. Further flash backs of hallucinatory experiences can appear within a week or month and may be precipitated by stress, fatigue or alcohol.

Adverse effects include hyper-pyrexia, nausea and muscular weakness. Hallucinatory experiences may be accompanied with paranoid delusions, which may lead to homicide or suicide. There is no physical dependence. Even psychic dependence is mild. Higher rate of absorption is observed in women. Animal experiments have shown teratogenic effects. Treatment of toxicity includes Diazepam for sedation and Haloperidol for psychotic symptoms.

(ii) Mescaline

It is derived from a Mexican cactus and has a low potency. It has marked sympathomimetic effects. It is less active than LSD and is lesser in use.

(iii) Phencyclidine (PCP; Angel dust)

It is an anticholinergic with mild hallucinatory effects like disorientation, distorted body images, loss of the sense of time and impairment of the thought processes. Like LSD, it also causes occasional bad experiences and recurrent psychotic episodes. Hence, it is less abused. Ketamine is an annalog of PCP with much low hallucinogenic potential and is used to produce anaesthesia. PCP may be smoked, mixed with tobacco, snorted or taken orally or injected intravenously.

(iv) Cannabinoids (Δ^9-Tetrahydrocannabinol; Δ^9 THC)

It is the active principle of the extracts of the hemp plant (*Cannabis sativa and Cannabis indica*). It is the most popular drug of abuse and is used in following forms:

- The dried leaves are powdered, made a paste and then used as a drink called Bhang.
- The dried leaves and flowering tops of the plant are referred to as *marijuana* (grass, pot, weed or reefer) and is smoked in pipes or rolled as cigarettes.
- *Charas or hashish* are resinous exudates of flower tops or leaves. It is very potent and is usually smoked in a pipe.

The major psycho-active constituent is TCH. The TCH content in hashish is more than that of marijuana. Its metabolite, 11-hydroxy-THC is also highly active.

(a) Pharmacokinetics

THC is readily absorbed when marijuana is smoked. The effects appear within 30 minutes of the onset of smoking. On oral administration THC is absorbed more slowly. The terminal half-life ranges from 18 hours to 3 days. The behavioural and physiological effects return to normal within 6-8 hours. Being highly lipophilic, THC and its metabolites are sequestered in body fat and adipose tissue. Hence, excertion continues several days after single dose.

(b) Pharmacological Actions

Initially there is CNS stimulation followed by sedation. During stimulatory phase there is euphoria, increased talkativeness, increase in appetite and a feeling of confidence, relaxation and well being. Many may laugh in an uncontrolled manner. During sedative phase, there are mild LSD type effects. There is retention of fixed unnatural posture. Ability to concentrate is impaired; sleepiness prevails. There is impairment of short term memory, simple learning task and of motor co-ordination. The peripheral effects include tachycardia, vasodilatation with reddening of conjunctiva, reduction in intraocular pressure and bronchodilatation. Other CNS effects are analgesia and anti-emetic action. It has inhibitory effects on immune function.

(c) Mechanism of Action and Clinical Use

Two types of cannabinoid receptors are known: CB_1 and CB_2. CB_1 receptors are located in brain while CB_2 receptors are located in periphery. Both are G-protein coupled receptors linked to inhibition of adenylate cyclise.

Anandamide, an arachidonic acid derivative, is an endogenous cannabinoid ligand for CB_1 receptor. Dronabinol and Nabilone are synthetic analogs of THC. They are used to increase appetite in patients of AIDS. Dronabinol is used to prevent emesis caused by cancer therapy. Rimonabant is approved for obesity. It is antagonist to CB_1 receptor. It is also used for smoking cessation.

CB_2 receptors are located in lymphoid system and accounts for inhibitory effects on the immune system.

(d) Adverse Effects

Cannabis is relatively safer than most abused substances like opioids and alcohol.

Psychological dependence is mild. There is no physical dependence. There are no reports of fatal overdose. Withdrawal effects are mild and include irritability, decrease in appetite and insomnia. Some tolerance may develop in heavy marijuana users.

Cannabinoids do impair cognitive and motor skills. They do not affect retrieval of previously learned facts. THC causes impairment of short term memory. Heavy marijuana smokers suffer with bronchitis. Endocrinal side effects include notable decrease in plasma testosterone and a reduction in sperm count. THC produces teratogenecity in rats and mutagenecity in white cells of human beings. Risk of foetal malformation is negligible.

Rimonabant is available as 20 mg tablet.

5.2 DRUGS USED IN PARKINSON'S DISEASE AND ALZHEIMER'S DISEASE

5.2.1 Drugs for Parkinson's Disease

Parkinson's disease is a slowly progressive neuro-degenerative disease characterised by following symptoms:

- Pill rolling tremors
- Akathesia: Inability to sit still
- Rigidity
- Kinesias (akinesia, bradykinesia)
- Instable (stooped) posture
- No arm swinging in rhythm with legs
- Sialorrhea: profused salivary secretion
- Masked facial expression

During functioning of brain, there is a functional balance between dopaminergic and cholinergic system. In Parkinson's disease (PD), there is a loss of dopaminergic neurons. It indirectly leads to hyperactivity of cholinergic neurons. The mechanism of action of drugs used in treating PD is shown in Fig. 5.2.

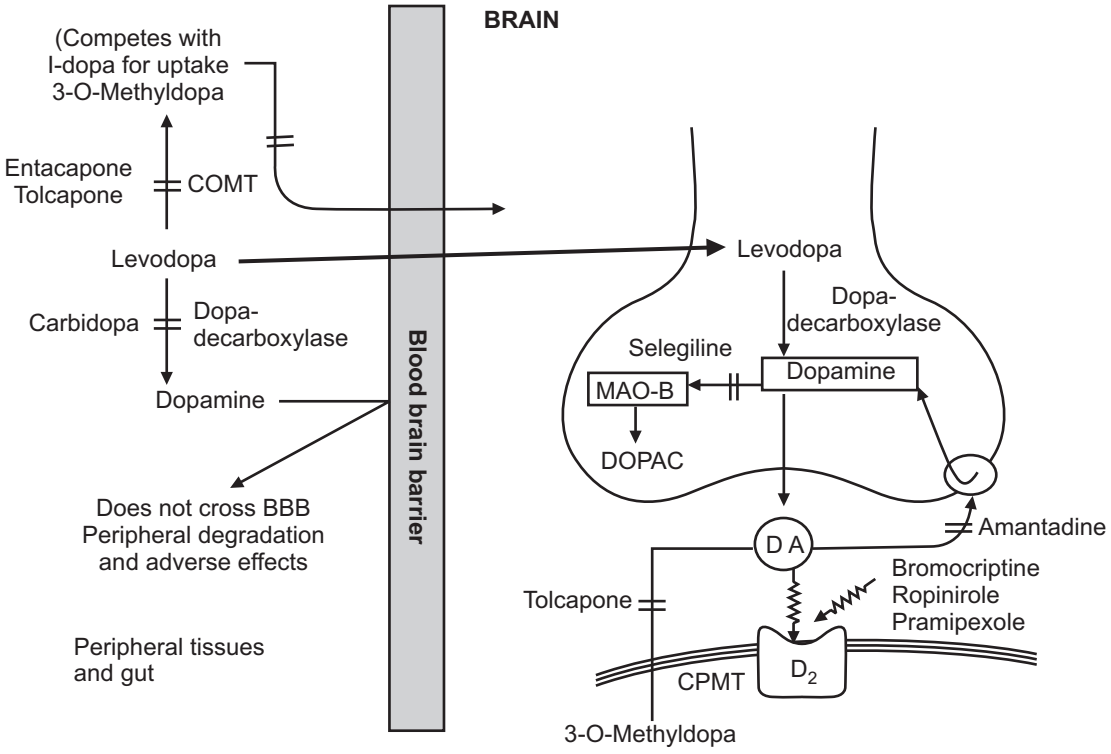


Fig. 5.2: Mechanism of action of dopaminergic drugs used for treatment of PD

Drugs used for treating Parkinson's disease are classified in to following four categories:

5.2.1.1 Drugs Which Increase Dopamine Levels

1. Levodopa with Carbidopa

DA itself does not cross BBB. Its peripheral effects do not provide any advantage to patients of Parkinson's disease. Levodopa is the precursor of DA. Levodopa can cross BBB and it is decarboxylated to DA in brain. If administered alone, only about 1% of Levodopa actually enters the brain. Remaining 97-99% Levodopa gets metabolised in GIT and peripheral tissues by the enzyme dopa decarboxylase to DA, which cannot enter brain because of its inability to cross BBB. To prevent its peripheral degradation, Levodopa is usually coadministered with either Carbidopa or Benserazide, a peripheral dopa decarboxylase inhibitor. This combination lowers the dose of Levodopa and reduces incidence of peripheral side effects.

Levodopa is widely used for treatment of all types of Parkinsoniasm, except the one which is associated with antipsychotic therapy. All clinical manifestations respond to the combination of Levodopa with Carbidopa. Rigidity, bradykinesia, abnormalities of posture and locomotion respond well to the combination while tremors are less responsive. The therapy started with small dose of Carbidopa 25 mg + Levodopa 100 mg (1:4 ratio) three times a day, 1 hour before meals. The dose of Levodopa is increased up to 250 mg (1:10 ratio) gradually. If necessary, a dopamine agonist like Bromocriptine may be added.

(a) Adverse effects

The response to combination of Levodopa + Carbidopa is not constant if the therapy is continued for a long time. There is decrease of effect indicating reduction in duration of benefit progressively. The treatment is characterised by "on-off phenonmenon" which indicates positive and negative effects of the therapy.

During therapy, there are excessive and abnormal choreiform movements of limbs, trunk, face and tongue. These effects are termed as dyskinesias, which disappear if the dose of Levodopa is reduced; but this causes rigidity to return. The variation in response is probably due to fluctuating levels of DA.

Other adverse reactions related to CNS are vivid dreams, delusions, hallucinations, confusion and sleep disrturbances, especially in elderly people. Prolonged therapy of Carbidopa + Levodopa may cause schizophrenia-like symptoms in elderly.

Postural hypotension may occur, but tolerance develops to this effect later. Occasionally, cardiac arrhythmias may occur due to stimulation of adrenoceptors by DA.

Anorexia, nausea and vomiting may be caused due to accumulation of DA. It is much less with the combination than with Levodopa alone. Tolerance develops to these effects later.

Levodopa may cause mydriasis and may precipitate an attack of glaucoma in some patients. Abnormalities in smell/taste, hot flushes and precipitation of gout may occur. Mild but transient increase in blood urea, serum transaminases, alkaline phosphatise and bilirubin may also be observed.

(b) Contraindications

Levodopa is contraindicated in psychoses, narrow angle glaucoma, cardiac arrhythmias and melanoma.

(c) Drug interactions

- Pyridoxine (vitamin B_6) enhances the extracerebral metabolism of Levodopa and decreases its therapeutic effects.
- MAO-A inhibitors potentiate toxicity of Levodopa leading to hypertensive crisis.
- Proteins ingested with meals may produce sufficient amount of amino acids, which compete with Levodopa transport both in GIT and brain; hence Levodopa should be given 30 minutes before meals.
- TCAs decrease the absorption of Levodopa leading to hypertensive episodes.

Levodopa + Carbidopa: **SYNDOPA, TIDOMET-FORTE, TIDOMET LS, SINEMET PLUS, SYNDOPA PLUS, TIDOMET PLUS** *is available as a combination as either 250 mg/25 mg or 100 mg/10 mg. It is also available as 100 mg/25 mg combination. Levodopa + Benserazide:* **BENSPAR** *is available as a combination of 200 mg/50 mg (tablet) or 100 mg/28.5 mg capsule.*

2. COMT Inhibitors

COMT metabolises DA and its precursor Levodopa, producing the inactive metabolite. Hence, inhibition of peripheral COMT will result in increase in plasma half-life of Levodopa. Selective COMT inhibitors like Tolcapone and Entacapone, not only diminish metabolism of Levodopa but also increase its bioavailability in brain. Pharmacological effects of Tolcapone and Entacapone are similar. However, Tolcapone has both central and peripheral effects while Entacapone is only peripheral blocker of COMT. Tolcapone is occasionally associated with severe hepatotoxicity and death. Hence, Entacapone is preferred because of lack of hepatotoxicity. Common side effects are dyskinesia, nausea, diarrhoea, postural hypotension and sleep disturbances.

Tolcapone is available as 100 mg tablet; Entacapone is available as 200 mg tablet. Both are given three times a day.

3. Amantadine

It is an antiviral drug. It prevents DA uptake, facilitates presynaptic DA release, possesses weak antimuscarinic action and blocks glutamate NMDA receptor. The first two actions help in treating Parkinson's disease. Blocking of NMDA receptor contributes in reducing excitation-induced neurotoxicity and dyskinesia. Amantadine alone or in combination with Levodopa and Carbidopa is used to treat PD. Adverse effects include nausea, dizziness, insomnia, confusion hallucinations, anke odema. Its anti-muscarinic actions are additive to CNS effects.

Amantadine is available as 100 mg tablet: **AMANTREL, COMANTREL.**

5.2.1.2 Drugs Which Prevent Dopamine Degradation

Inhibitors of the enzyme MAO-B are useful to treat PD. Selegiline is an irreversible inhibitor of MAO-B, an enzyme in dopaminergic neurons responsible for metabolism of DA. It makes more DA available for stimulation of its receptors. Initially, Selegiline may be used alone. Later, it is used along with Levodopa + Carbidopa to minimise problem of dyskinesia associated with long term use of Levodopa. Selegiline may retard progression of PD by reducing oxidative damage due to formation of free radicals produced during metabolism of DA. It may cause insomnia. It should not be coadministered with TCAs and SSRIs for the risk of acute toxic reactions like hyperpyrexia, agitation, delirum and coma.

Selegiline is available as 5 mg tablet: **SELGIN, SALERIN, ELEGELIN**.

5.2.1.3 Drugs Which Stimulate Dopamine Receptors

1. Dopamine agonists

These drugs directly stimulate DA recptors and do not depend on the formation of DA from Levodopa. They have following advantages:

(a) They do not require metabolic conversion to DA.
(b) They do not depend on the functional integrity of dopaminergic neurons.
(c) They have longer duration of action and lesser on-off phenonmenona as compared to Levodopa.

(d) They are more selective than Levodopa on DA receptors.
(e) They are less likely to generate damaging free radicals.

Bromocriptine and Cabergoline are amine ergot derivatives. Ropinirole and Pramipexole are synthetic non-ergot DA receptor agonists. Bromocriptine is a potent D_2 receptor agonist and a weak D_1 antagonist. Cabergoline is similar to Bromocriptine, but with a longer duration of action (half-life > 80 hours). Ropinirole and Pramipexole have more selective action on D_2-receptors. Pramipexole is excreted by kidney while Ropinirole is metabolised by CYP1A2. Ciprofloxacin, which inhibits CYP1A2 can increase plasma concentration of Ropinirole.

Bromocriptine and Cabergoline, being ergot derivatives cause following adverse reactions: anorexia, nausea, vomiting, vertigo, postural hypotension, painless peripheral vasospasm, peripheral oedema, pleural fibrosis and erythromelalgia. Erythromelalgia consists of red, tender, painful swollen joints of feet and hands. These symptoms are less frequent with Pramipexole and Ropinirole. Synthetic drugs are preferred. Pramipexole is given in a dose of 0.125-0.75 mg once a day while Ropinirole is given as 0.25 mg once a day. One more addition is of Rotigotine, which is used as a transdermal patch.

Bromocriptine: **PROCTINAL SICRIPTIN, PARLODEL, BROM, ENCRIPT** is available as 1.25 mg, 2.5 mg tablet. Cabergoline: **CABGOLINE** is available as 0.25 mg and 0.5 mg tablet. Ropinirole: **ROPITOR, ROPARK** is available as 0.25 mg, 0.5 mg, 1 mg and 2 mg tablet. Pramipexole: **PARPEX** is available as 0.5 mg, 1 mg and 1.5 mg tablet.

5.2.1.4 Drugs Which Restore DA-ACh Balance

The drugs under this category are centrally acting antimuscarinic drugs. In the absence of inhibitory control of DA, the activity of cholinergic system becomes dominant. Blockade of central muscarinic receptor by these drugs reduces cholinergic activity. The muscarinic antagonists are most commonly used to treat following conditions:

(a) Early stages of the disease
(b) Late-stage PD as an adjunct to Levodopa + Carbidopa therapy
(c) Neuroleptic-induced extrapyrimidal side effects

The drugs in this category include: Trihexyphenidyl (benzhexol), Procycliydine, Orphenadrine and Benztropine. These drugs correct tremors and rigidity of PD more effectively than other symptoms. The adverse effects are related to their anticholinergic action and include: dry mouth, blurred vision, urinary retention and constipation. In high doses they cause confusion, delirium and hallucinations.

Trihexiphenidine is reported to have some abuse potential. The antihistamine Diphenhydramine has anticholinergic action and is used to treat mild PD.

Trihexiphenidine: **PACITANE, PARKITANE, PARKIN** *is available as 200 mg tablet. Procyclidine:* **KEMADRIN, PRODINE** *is available as 2.5 mg and 5 mg tablet and Orphenadrine:* **ORPHIPAL** *is available as 50 mg tablet.*

5.2.2 Drugs for Alzheimer's Disease (AD)

It is the most prevalent form of dementia which does not have any previous cause like stroke, brain trauma or alcohol toxicity. The symptoms of AD are progressive loss of memory and disordered cognitive functions, with loss of short-term memory that usually preceeds loss of long-term memory. Patients of AD may not recognise their own family members. Other signs include reduced verbal fluency and impairment of speech due to failure of arranging words in proper sequence. Ultimately, patient may fall in to a vegetative state. Death is usually associated with complications of immobility; e.g. pneumonia or pulmonary embolism.

The loss of cholinergic activity in brain or patients with AD led to the use of cholinesterase inhibiting drugs which can cross BBB. These drugs block degradation of ACh and increase availability of ACh in synaptic cleft. The drugs used to treat AD are: Tacrine, Donepezil, Rivastigmine and Galantamine. Tacrine is a long-acting reversible anticholine-sterase. It can be used for treatment of mild to moderate patients of AD. It is orally active and provides improvements in memory, cognition and general well being soon after initiation. It facilitates release of ACh from cholinergic nerve ending. However, it produces significant hepatotoxicity hence its use is restricted. Donepezil, Rivastigmine and Galantamine have better penetration in CNS. They are less toxic and better tolerated in comparison to Tacrine. Their clinical results are modest and temporary.

Their dosages are as follows:

- **Donepezil:** 5 mg once daily in evening increased maximum upto 10 mg once daily after 4 weeks.
- **Rivastigmine:** 1.5 mg initially twice a day increased upto 3 mg twice a day after two weeks.
- **Galantamine:** 4 mg twice initially, increased upto 8 mg twice a day after one to two weeks. Transdermal Rivastigmine patch, to be applied once in a day is available. Use of these drugs is not associated with hepatotoxicity except for peripheral cholinergic side effects like disrrhoea, nausea, vomiting and increased urination.

It is also postulated that enhanced glutamate transmission via NMDA receptors also contributes to Pathophysiology of AD. Memantine is a non-competitive antagonist of NMDA receptor. It is better tolerated and less toxic than cholinesterase inhibitors. The drug is given 5 mg once daily, slowly increased to 10-20 mg /day which can be given in two divided doses.

Donepezil: **ALZIL, DONECEPT, DOPEZIL** *is available as 5 mg, 10 mg tablet. Rivastigmine:* **RIVASMINE, RIVAMER, EXELON** *is available as 1.5 mg, 3 mg, 4.5 mg and 6 mg capsule. Galantamine:* **GALAMER** *is available as 4 mg, 8 mg and 12 mg tablet. Memantine:* **ADMENTA, MENTADEM** *is available as 5 mg, 10 mg tablet.*

5.3 CNS STIMULANTS AND NOOTROPICS

5.3.1 CNS Stimulants

The drugs in this category have a marked influence on mental functions and behaviour to produce excitement, euphoria, increase in motor activity and reduction in fatigue. They are sub-classified as follows:

(I) Amphetamines/Non-amphetamines

- Amphetamine group: e.g. Amphetamine, Dexaamphetamine, Methamphetamine, Methylenedioxy methamphetamine (MDMA), Methylphenidate and Fenfluramine.
- Non-amphetamine group: e.g. Modafinil, Atomoxetine, Sibutramine and Pemoline.

(II) Methylxanthines:

- Pharmacological effects of amphetamins and Non-amphetamines are almost same. Hence, only methylxanthines are discussed separately.

(a) Mechanism of Action

These drugs enter the nerve ending by active transport and displace DA/NE from storage vesicles by altering their pH. They have some property to inhibit DA metabolism by inhibiting MAO-B in the nerve ending. Due to inhibition of the enzyme, concentration of intraneuronal DA increases. This reverses the direction of transport mechanism so that DA is now released in to synapse by reverse transport rather than by usual exocytosis. This further increases DA concentration in the synaptic cleft.

(b) Pharmacological Effects

Following are main central effects of Amphetamine-like drugs:

- Increased motor activity
- Euphoria and excitement
- Anorexia
- Stereotyped and psychotic behaviour with prolonged administration.

In addition, their peripheral sympathomimetic actions include rise in BP and inhibition of GIT motility. Amphetamines increase the wakefulness, capacity to work and euphoria. Hence, there is unawareness of fatigue which can be dangerous. With large doses, stereotyped behaviour occurs which consists of characteristic repeated actions. Subjects become confident, talkative and hyperactive. Sex drive is said to be enhanced. Fatigue, both physical and mental, is reduced but the improvement can be offset by mistakes committed due to overconfidence. Amphetamine like drugs (Fenfluramine and Dexfenfluramine) cause marked anorexia; but the effect is short lived. The effect occurs due to enhancement of release of 5-HT.

If Amphetamine is taken repeatedly, psychoses can develop which resembles schizophrenia. It is associated with paranoid ideas and auditory as well as tactile hallucinations rather than visual. This is the main difference between Amphetamine and LSD. Since higher doses lead to aggressiveness and violent behaviour, death may occur due to violence, accident, murder or even suicide.

(c) Pharmacokinetics

All these drugs are well absorbed orally and freely penetrate BBB. A considerable portion of unmetabolised drug is excreted through urine. It is possible to trap this weakly basic drug by acidifying urine with ascorbic acid or ammonium chloride. Acidification reduces its absorption from renal tubules and enhances its clearance.

(d) Clinical Uses

(i) Attention deficit hyperkinetic disorder (ADHD) with minimal brain dysfunction: It is a childhood disease characterised by hyperactivity, inability to concentrate and impulsive behaviour. Dexamphetamine, Methylphenidate and Atomoxetine are quite effective in controlling hyperkinetic children. Atomoxetine is a non-stimulant, non-addicting drug which is inhibitor of reuptake of NE. It is quite safe but is contraindicated in glaucoma.

(ii) Narcolepsy: Narcolepsy is characterised by sleep attacks particularly during day time, vivid nightmares which may persist even in awakening state and sudden loss of muscle tone (catalepsy) which is usually reversible. Methylfenidate is particularly useful to treat narcolepsy. Another non-amphetamine derivative called Modafinil is useful to treat narcolepsy and is devoid of abuse liability.

(iii) Appetite suppression: Amphetamine has anorexic effect; but tolerance to this action develops within few weeks and food intake returns to normal. In addition, insomnia, pulmonary hypertension and abuse potentials are associated side effects. Hence, their use is restricted. Fenfluramine and Dexfenfluramine were used to treat obesity. Now, Sibutramine is used for the purpose. It blocks neuronal uptake of NE, 5-HT and DA which are involved in regulating food intake. It can be used in severely obese patients with diabetes and dyslipidaemia. Adverse effects include dry mouth, headache, insomnia, constipation, increase in heart rate and BP. It is contraindicated in any cardiovascular disease. It should not be taken along with SSRIs like Fluoxetine and 5-HT agonists like Sumatriptan.

(d) Adverse Effects

(i) Tolerance: Tolerance develops rapidly to peripheral sympathomimetic and anorexic effects.

(ii) Psychic dependence: Amphetamine produces high psychic dependence and rarely physical dependence. Withdrawal symptoms consist of prolonged sleep, extreme hunger, and fatigue with long phases of depression.

(iii) Effects of amphetamine overdose: The effects include euphoria, dizziness, tremors, hypertension, irritability and insomnia. Higher doses cause convulsions, psychotic manifestations, cardiac arrhythmia and coma.

(iv) Sudden death: Sudden deaths have occurred with Methylenedioxy metham-phetamine (MDMA) even after a single moderate dose. MDMA may cause rhabdomyolysis and renal failure. It also causes inappropriate secretion of ADH leading to water retention and hyponatraemia. It possesses hallucinogenic activity. Besides inducing release of NE and DA, it also releases endogenous 5-HT and activates 5-HT receptor.

(v) Psychotomimetic effects: Methylenedioxy amphetamine (MDA) is similar to MDMA in its pharmacological profile. However, 75 mg of MDA produces psychotomimetic effects with a feeling of closeness to each other. At a dose of 150 mg, it produces LSD-like effects and at 300 mg, it produces Amphetamine - like psychotic manifestations. Adverse effects include tachycardia and hypertension. It can cause arrhythmias at higher doses.

Modafinil: **PROVAKE, MODALERT, MODAPRO** *is available as 100 mg, 200 mg tablets. Atomoxetine:* **ATTENTROL, AXEPTA** *is available as 10 mg, 25 mg capsule. Fenfluramine:* **FLABOLIN** *is available as 20 mg tablet and 40 mg capsule. Sibutramine:* **OBEGO, OBESTAT, SIBUTREX** *is available as 5 mg, 10 mg capsule.*

5.3.1.1 Methylxanthines

- The popularity of xanthine - containing drinks such as coffee, tea and coke appears to be related to their CNS-stimulating effects. Xanthine derivatives are: Caffeine, Theobromine, Theophylline and its derivatives like Aminophylline, Etophylline, Acebrophylline and Enprophylline. Theophylline is found in tea, Theobromine in coca while caeffine is found in coffee, tea and cola drinks.

(a) Mechanism of Action

Three important mechanisms of actions for methylxanthines are as follows:

- Methylxanthines inhibit the enzyme phosphodiesterase (PDE) resulting in increased concentration of 3,5-c AMP causing bronchodilation.
- They inhibit the cell surface receptors for adenosine. Adenosine is a modulator. Its actions are inhibitory, leading to drowsiness, motor inco-ordination, cerebral vasodilation, CNS depression, anticonvulsant action and bronchoconstriction. Methylxanthines antagonise all these effects.
- They enhance deacetylation of histones and prevent transcription of inflammatory genes (acetylation of histones activate inflammatory genetranscription). It leads to inflammatory action.

(b) Pharmacological Actions

(i) CNS effects: They act as CNS stimulants. The rank order is caeffine > Theophylline > Theobromine. CNS stimulation causes wakefulness, alertness and increased capacity to do intellectual work with better association of ideas. They produce equal fatigue reduction, much less locomotor stimulation but produce no euphoria, stereotyped behaviour or psychotic manifestations.

(ii) CVS effects: They produce increase in heart rate, peripheral vasodilation. BP is not affected. Cardiac output is increased, which is an advantage in CHF patients. Coronary blood flow is increased. Cranial blood vesels are constricted; oxygen tension in brain is reduced. Caeffine is useful in migraine.

(iii) Kidney: They are mild diuretics, but the action is brief. The action is due to increased filtration pressure at glomerulus and also due to increased cardiac output.

(iv) Miscellaneous effects

- They stimulate medullary respiratory centre.
- They cause bronchodilation. Biliary spasm is reduced.
- They facilitate neuromuscular transmission by increasing release of ACh and enhance contractile power of skeletal muscles. They are useful in dyspnoea.
- They increase gastric acid and pepsin secretion leading to gastric irritation.
- Theophylline inhibits release of histamine and other mediators in mast cells. This is the basis of their action in bronchial asthma.

(c) Clinical Uses

- Caeffine is combined with aspirin for treatment of headache. It is also combined with ergot alkaloids for treatment of migraine.
- Oral Theophylline is used in the treatment of COPD and mild to moderate asthma.
- Ceaffine citrate or Theophylline is used for short term management of apnoea in premature infants in first few weeks of life.
- Aminophylline is useful in relieving paroxysmal dyspnoea, associated with ventricular failure.

(d) Adverse Effects

Theophylline has a narrow margin of safety with 8-15 µg/ml as optimum plasma level. Above 15 µg/ml, the adverse effects are: dyspepsia, headache, insomnia, restlessness, vomiting, palpitations, agitation, tachypnoea, flushing, hypotension, extra-systoles, arrhythmias, delirium, convulsions, coma leading to death. Children are more prone for the toxicity.

(e) Drug Interactions

- Agents which decrease Theophylline concentration are: Smoking, Phenytoin, Carbamazepine, Rifampin, Phenobarbital. Dose of Theophylline is to be increased when used along with the above mentioned drugs/smoking.
- Drugs which inhibit Theophylline metabolism are: Erythromycin, Ciprofloxacin, Cimetidine, Oral contraceptives and Allopurinol. Dose of Theophylline is to be reduced when used in combination with the mentioned drugs.
- Theophylline enhances the effects of sympathomimetics, Digitalis, Furosemide, Hypoglycemic agents and Oral anticoagulants.

(f) Abuse of Xanthenes

Caeffine-containing beverages cause habituation, but no dependence. Chronic coffee drinkers suffer from headache and a feeling of fatigue after sudden abstention. Tolerance to these drugs is not severe.

Theophylline: **BRONCORDIL, THEODAY, THEODER, DERIPHYLLINE** *is available as 400 mg, 600 mg ordinary/SR tablet. Doxofylline:* **DOXOBID, DOXFREE, BESTOFYLINE** *is available as 400 mg tablet or 100 mg/5 ml syrup. Aminophylline:* **MINOPHYL, AMINOPHYLLINE** *is available as 100 mg tablet or 25 mg/ ml injection. Acebrophylline:* **AB-PHYLLINE, BESTOPHYLLINE-A, UNOBRO** *is available as 100 mg capsule.*

5.3.2 Nootropics

Nootropics are psychotherapeutic agents which facilitate the acquisition of learning and enhance memory retention.

Learning is defined as, "the change in behaviour to a given situation brought about by repeated experiences in that situation". It is acquired when a stimulus or a sequence of stimuli are transmitted to the brain which is encoded in to a memory race. It involves formation of new synaptic connections in brain area involved in forming and storing the acquired information. The memory process involves three components: registration (acquirement of learning), retention (memory storage) and retrieval (recall). Cognition is defined as, "the process of acquiring, storing and utilising intellectual knowledge".

Impairment in memory, cognition, comprehension, problem solving, judgement and learning is a normal consequence of ageing and is seen in many mental illnesses. Several depressants including alcohol, scopolamine and hallucinogens can impair memory. There is a loss of memory in Alzheimer's disease. Nootropics can be useful to enhance memory.

Nootropics can overcome or retard cognitive decline occurring in old age and in some diseased conditions. They can prevent the disruption of the process of memory consolidation by hypoxia, trauma, seizures, hypoglycaemia and other aversive factors. Nootropics should possess following properties:

- They should facilitate learning acquisition and memory consolidation and prevent or mitigate impairment of memory induced by ageing, amnestic agents and other aversive factors.
- They should facilitate inter-hemispheric transfer of information.
- They should improve tonic cortical control over sub-cortical centres.
- They should not induce any overt behavioural or autonomic effects on long term administration.

Some nootropics may act mainly by improving cerebral citculation and cerebral metabolism which are retarded in cerebro-vascular disease. Their use may be limited to cognitive defects induced by cerebro-vascular insufficiency.

They belong to diverse chemical category. Some of them are listed below:

- Piracetam and its congeners: Aniracetam, Oxiracetam.
- Hydergine (dihydroergotoxin)
- Vincamine
- Meclofenoxate
- Pentoxifylline
- Pyritinol
- Cyclangate
- Nicergoline
- *Herpestis monniera (Brahmi)*
- *Ginkgo biloba extract*

(a) Mechanism of Action

Nootropics like Pentoxifylline, Pyritinol, Cyclandate and Nicergoline function like cerebral protectors improving cerebral circulation. Actions of other drugs are more complex. Improvement in brain metabolism and energy utilisation may be involved, as also effects on central neurotransmitters. There is evidence that central cholinergic synapses may be part of the intrinsic system controlling memory storage. Nootropics may induce environment of neurotransmitters condusive to learning acquisition and memory retention. The mechanism of action includes increase in central cholinergic, nonadrenergic and dopaminergic activity with concommittent reduction in serotonergic function.

Piracetam

Piracetam is a cyclised derivative of GABA. It was first introduced as a nootropic agent. It has been shown to be beneficial in cognitive deficit occurring in several types of brain disorders. Mental performance is improved in children and ageing individual with memory deficits. Piracetam is devoid of significant autonomic, motor or behavioural effects, even at relatively high doses.

Piracetam has been proposed to augment energy utilisation and to increase resistance to adverse cellular changes induced by anoxia. Changes induced by Piracetam on central neurotransmitters may also contribute to its nootropic action. Aniracetam and Oxiracetam are derivatives of Piracetam. The derivatives have actions similar to Piracetam. Dose of Piracetam is 2-3 gm daily in divided doses.

Therapeutic Uses

- In cognitive defects associated with presenility (Alzheimer's disease) and ageing.
- In children with learning and attention deficit.
- Amnesia following cerebral trauma, drug abuse including alcoholism, seizures.
- Coexisting memory deficits in neurological and psychiatric illnesses.

5.4 OPIOID ANALGESICS AND ANTAGONISTS

Pain is an ill-defined, disabling event associated with many medical conditions. It is often evoked by an external or internal noxious stimulus. The sensation of pain is called as algesia. Drugs which inhibit sensation of pain are termed as analgesics. Opium was the first natural analgesic. Derivatives of opium are termed as Narcotic/Opioid/Morphine like analgesics. Some background about pathophysiology of pain, endogenous opioid peptides and opioid receptors is desirable before discussing opioid analgesics.

5.4.1 Pathophysiology of Pain

There are two components in pain perception: the nociceptive and the affective. The nociceptive component is a disabling, unpleasant sensation evoked by noxious stimuli and conveyed to CNS by ascending pathways. The affective component is the psychological response towards the pain and is conveyed from CNS to dorsal horn by descending pathway.

The physiological basis of pain and sites of action of drugs which relieve pain are summarised in Fig. 5.3.

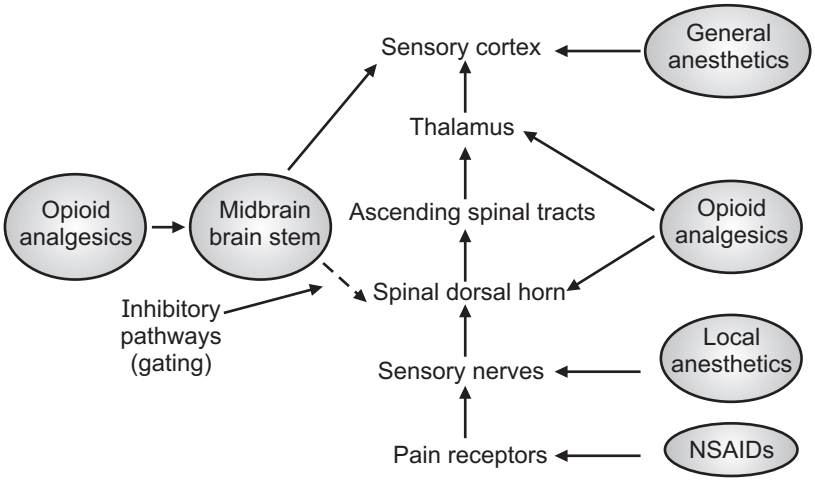


Fig. 5.3: Neural pathways of pain and sites of action of drugs relieving pain

- Noxoious stimuli stimulate nociceptive receptors of sensory nerve endings in pain sensitive tissues. The stimulation is mostly chemical in nature. The pain-inducing endogenous substances are released during inflammation, tissue injury, ischaemia and by thermal or mechanical stimuli. The endogenous substances include ACh, histamine, bradykinin and kallidin. Of these, bradykinin is the most powerful algesic substance. It acts by releasing prostaglandins (PGs). PGs do not induce pain themselves but they sensitize pain receptors to the action of other algesic chemicals.
- The sensations from pain receptors are transmitted through sensory afferent nerves to the dorsal horn of spinal cord. Substance P may be the neurotransmitter for relay of nociceptive impulses. The signals are processed and transmitted via ascending pathways in the spinal cord to different regions.
- The signals received in the thalamus, brain stem reticular formation and peri-ventricular grey matter (pain centres) are processed and transmitted to the sensory cortex where pain is finally perceived. These centres are depressed by opioid peptides.
- Pain processing by the dorsal horn is subject to modulatory influences by "gate" controlled mechanism. Thus, inhibitory influences are exerted by activity in other peripheral sensory neurons and the descending pathways from mid brain and brain stem.
- Opioid analgesics act on the spinal cord and brain, where they inhibit pain processing at the dorsal horn and increase the threshold for pain perception by the central pain centres. They may also act by altering the sensory cortical component of pain.

5.4.2 Endogenous Opioid Peptides

Three types of endogenous peptides with analgesic activity have been identified. They are endorphins, enkephalins and dynorphins. They are derived from distinct precursor polypeptides. They are involved in modulating pain and form part of the complex pain-inhibiting mechanisms in the brain and spinal cord. These peptides have also been involved in genesis of psychiatric disorders and in control of autonomic and neuroendocrine functions, both under normal and stressed conditions.

5.4.3 Opioid Receptors

Four major categories of endogenous opioid receptors have been identified. They are as follows:

- μ (mu)
- κ (kappa)
- δ (delta)
- σ (sigma)

Of these, the μ, κ and σ receptors mediate the main pharmacological actions of narcotic analgesics. μ and κ receptors are important for analgesia while sigma receptors are responsible for psychotomimetic effects. The δ-receptors inhibit excitatory neurotransmission in the brain and periphery. It is postulated that opioid receptor activation leads to decrease in c AMP production in the brain, opening up of K^+ channels and inhibition of intraneuronal Ca^{++} transport, all of which induce inhibiton of neuronal activity.

Based on receptor activity, drugs acting on opioid receptors can be categorised as follows:

- **Agonists**

  They are sub-classified based on chemical modifications in the structure of morphine.
  - Morphine analogs are: Heroin and Codeine.
  - Methadone derivative is Dextropropoxyphene.
  - Thebaine derivative is Etorphine.
  - Phenylpiperidine derivatives are Pethidine, Fentanyl, Sufentanil and Diphenoxylate.
- **Mixed agonists-antagonists**

  They are also sub-classified on chemical modifications in the structure of morphine.
  - Benzomorphan derivatives: Pentazocine, Cyclazocine.
  - Morphine analogs: Nalbuphine, Buprenorphine.
  - Morphinan derivatives: Levollorphan, Meptazinol.
- **Antagonists**

  These are discussed separately in section 5.4.6.

5.4.4 Opioid Analgesics

Drugs having agonistic activity, especially on μ-receptors are used as analgesics. Morphine is the prototype drug in this category. Other morphine agonists and mixed agonists-antagonists have actions similar to morphine with few modifications.

Actions of morphine are discussed below:

(a) Pharmacokinetics

Morphine is readily absorbed from GIT. However, because of extensive first-pass metabolism, bioavailability is poor. The drug is usually administered by intramuscular route. Half-life is 2.5 hours, peak effect is at 1 hour and duration of analgesia is 4 hours. Morphine is metabolised by N-dealkylation and oxidation followed by glucuronide or sulphate conjugation. It has relatively poor access through BBB. Its derivative, Heroin (diacetyl morphine) crosses BBB easily. It is 2-2.5 times more potent than morphine, and is preferred by addicts. Metabolites are excreted in urine.

(b) Mechanism of Action

Morphine acts through different receptors mentioned earlier. In addition, it influences the activity of some neurotransmitters in brain. It increases cholinergic and 5-HT activity; and inhibits nor-adrenergic, dopaminergic and GABAergic activity. It releases histamine but inhibits release of substance P. These wide-ranging effects contribute to various pharmacological actions.

(c) Pharmacological Actions

(i) Effects on CNS: Morphine has a wide variety of actions in CNS due to location of related receptors.

- **Analgesia:** Besides raising pain threshold, morphine reduces emotional reaction to pain. This eliminates distress caused by pain and helps the patients to tolerate pain better. The analgesic action is due to effect on opioid receptors.
- **Euphoria:** Morphine induces a marked sense of well-being and relief from anxiety which contributes to its analgesic action. Some patients may experience restlessness and anxiety, termed as dysphoria. Tolerance is noted both to euphoria (mu-receptors) and dysphoria (kappa receptors).
- **Sedation:** Morphine induces sedation in analgesic doses and is useful when pain is accompanied by insomnia.
- **Respiratory depression:** Morphine depresses respiratory centre resulting in increase in plasma carbon dioxide concentration. The sensitivity of respiratory centre to CO_2 is decreased, but the hypoxic drive is not affected. Morphine does not depress vasomotor centre. The action on respiratory centre is mediated by mu-receptors and is the cause of death in morphine poisoning. Some degree of tolerance to respiratory depressant effect is observed in morphine addicts.
- **Pupillary constriction:** Miosis is induced by action of morphine on mu and kappa receptors. Tolerance to pupillary constriction is not seen in addicts. Pin-point pupils are indicative of morphine abuse.
- **Nausea and vomiting:** Nausea and vomiting, observed along with analgesic effect of morphine are due to stimulation of CTZ. Higher doses of morphine inhibit CTZ. Morphine emesis is not blocked by DA antagonists like Prochlorperazine, but is inhibited by opioid antagonist, Naloxone.

- **Antitussive effect:** It depresses medullary cough centre. It is not used for clinical benefit because its derivative, codeine is more effective. Tolerance is noted for this activity.
- **Neuroendocrine effects:** It increases release of ADH, decreases release of ACTH, growth hormone and gonadotrophins, together with increased plasma prolactin levels.

(ii) Effects on GIT: It induces marked increase in tone and reduces motility in many parts of GIT. It results in severe constipation. Gastric emptying is delayed. Intra-biliary pressure is increased due to constriction of biliary sphincter and contraction of gall bladder. Gastric, intestinal, pancreatic and biliary secretions are decreased by morphine. The actions of morphine on GIT are blocked by Naloxone and Atropine.

(iii) Effects on CVS: Morphine causes hypotension and bradycardia. Hypotension is due to dilation of peripheral veins and arterioles, histamine release and reduced sympathetic activity. Bradycardia is due to vagal stimulation.

(iv) Other actions: Bronchoconstriction is due to release of histamine and increased vagal activity. In addition, contraction of uterus, ureters and urinary bladder occurs occasionally.

Immunosuppressant effect is probably due to actions on CNS. Morphine addicts may have risk of AIDS.

(d) Therapeutic Uses:

(i) For analgesia: For relief of acute severe pain in trauma, burns, post-operative pain, myocardial infarction, renal and intestinal colic. It may also be used in terminal cancer patients for analgesia and euphoria.

(ii) In left ventricular failure: Morphine helps relief of symptoms by inducing marked veno-dilatation and decrease in pre-load. In addition, reduced sensitivity of respiratory centre to stimuli from congested lungs and increased CO_2 levels also contribute to decreased dyspnoea.

(iii) In anaesthetic pre-medication: Morphine sulphate (8-12 mg) or Pethidine (50-100 mg) is given intramuscularly 1 hour before surgery to reduce pain during surgery.

(e) Contraindications

(i) Acute abdomen: Morphine can mask the symptoms; hence it should not be given in undiagnosed abdominal pain.

(ii) Head injury: Morphine induced respiratory depression and rise in intra-cranial tension, together with miosis and vomiting may interfere with diagnosis.

(iii) Bronchial asthma: Morphine may aggrevate bronchial spasm and respiratory depression.

(iv) Chronic lung disease: Respiratory insufficiency by morphine can aggrevate the symptoms.

(v) Hypothyroidism: Slow metabolism of morphine can cause increased toxicity.

(vi) **Hepatic failure:** Reduced metabolism can cause higher toxicity leading to hepatic coma.

(vii) **Biliary colic:** Morphine can cause constriction of biliary spincter. It is also to be avoided after cholecystectomy.

(viii) **Ulcerative colitis:** Production of colonic dilatation by morphine can complicate ulcerative colitis.

(ix) **Enlarged prostate:** Morphine may cause urinary retention.

(x) **In obstetrics:** There is a possibility of respiratory depression of neonate.

(f) Adverse Reactions

Acute toxicity symptoms are nausea, vomiting, drowsiness, sweating, prurites, piloerection, bradycardia, hypotension, bronchospasm, urinary retention, dysphoria and constipation. All these actions are related to pharmacological actions of morphine. Tolerance and dependence of morphine are discussed in section 5.5.3 and 5.5.4.

(g) Drug Interactions

The respiratory depression caused by morphine is potentiated by all CNS depressants, Chlorpromazine, TCAs and MAO inhibitors. Hypotension is aggrevated by anti-hypertensives. Cimetidine inhibits metabolism of morphine and Pethidine.

5.4.5 Morphine Related Drugs (Opioids)

(i) **Pethidine**: It is less potent than morphine as analgesic but causes equal respiratory depression and vomiting. It has shorter duration of action; it is less sedative, antitussive and constipating agent. It has spasmolytic, mydriatic and visual effects. It is used as an analgesic and preanaesthetic medicant.

(ii) **Heroin:** It is more effective than morphine as analgesic. It crosses BBB. It is metabolised to morphine in brain. It is most addictive and is not used clinically.

(iii) **Methadone:** It is equipotent to morphine with an advantage of being oral active and longer duration of action. It is used in the treatment of morphine deaddiction. Its withdrawal syndrome is mild and more prolonged. Levomethadyl acetate, a related agent has longer duration of action and is used for deaddiction from Morhine or Heroin.

(iv) **Fentanyl:** Fentanyl and its derivatives Sufentanil, Afentanil, Remifentanil are more potent than morphine but have shorter duration (30-60 minutes) of action. Their uncontrolled use may lead to marked respiratory depression. They are used in combination with Droperidol to induce neurolepanalgesia and in patient-controlled analgesia because of shorter duration of action.

(v) **Etorphine:** It is an analogue of morphine with 1000 times more potency than morphine. It is mainly used in veterinary medicine and for trapping wild animals.

(vi) Codeine: Codeine and its derivatives Oxycodone, Dihydrocodeine, Hydrocodone are less effective as analgesics. Large doses can induce excitement. Tolerance and physical dependence are less marked. It is mainly used for antitussive action. 10% of administered codeine is metabolised to morphine. It is a constituent of many cough syrups.

(vii) Buprenorphine: It is a partial agonist of morphine. It acts on mu receptors and can precipitate morphine withdrawal. It is a potent analgesic with long duration of action. It inuduces significant respiratory depression but is less euphoric than morphine and less dysphoric than Pentaziocine. Bioavailability following oral administration is unpredictable; hence sub-lingual route is preferred. In a dose of 0.4-0.6 mg IM, 0.3-0.6 mg IV, it is used as an analgesic and for treatment of morphine addiction.

(viii) Nalbuphine: It has Pentazocine like actions but includes less sympathomimetic effects. Hence, it is better tolerated in myocardial infarction. Respiratory depression is not reversed by Naloxone.

(ix) Pentazocine: It has replaced Phenazocine. Pentazocine is an intermediate beween morphine and Pethidine for its potency as an analgesic. It is an agonist at κ-receptor and antagonist at μ-receptor. Its potency is much less than that of Nalorphine or Naloxone. The importance of pentazocine in clinical medicine is primarily due to ready non-availability of either morphine or Pethidine.

(x) Dextropropoxyphene: It is a dextro-isomer of Propoxyphene. It has less analgesic, antitussive, respiratory depressant and addictive properties in comparison with its conginer Methadone. It is rapidly absorbed and in low dose, can induce respiratory arrest, severe hypotension and cardiac arrhythmia within one hour. It is usually combines with Paracetamol for use as an analgesic. Levopropoxyphene has no analgesic action; but is used as antitussive.

(xi) Nefopam: It is structurally different from known narcotic/non-narcotic analgesic. It is devoid of respiratory depressant, constipating, emetic and addictive properties of narcotic analgesics and is free from GIT-related side effects of NSAIDs. It involves central cholinergic activity.

(xii) Tramodol: Its analgesic activity is partly mediated through μ-receptors. It is useful in chronic neuropathic pain. Toxicity includes dependence, seizures and anaphylactoid reactions.

(xiii) Diphenoxylate/Loperamide: Both are derivatives of morphine and are used to control diarrhoea. Atropine is added to Diphenoxylate to enhance anti-diarrhoeal effects and to limit addictive potential.

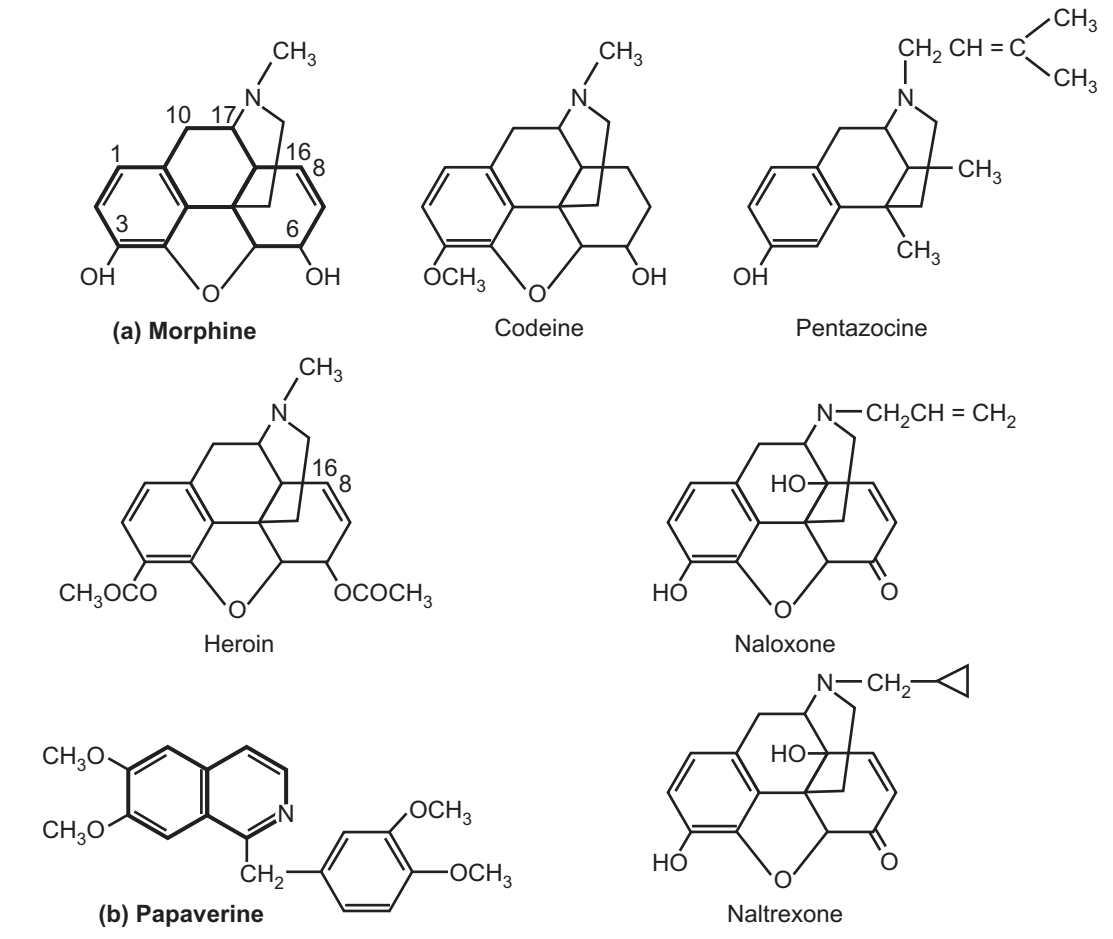
Preparations of morphine and its derivatives are listed in table 5.4.

Table 5.4: Preparations of Morphine and its Derivatives

Sr. No.	Drug	Strength and formulation	Trade name
1.	Morphine sulphate	10 mg, 20 mg, 30 mg, 60 mg tablet/SR tablet; 10 mg/ml injection	Vermor, Vermor – SR, Rilimore
2.	Pethidine	100 mg/2 ml injection	Pethidine hydrochloride
3.	Dextropropoxyphene	65 mg tablet in combi-nation with 400 mg/650 mg Paracetamol	Proxyvon, Dolopar plus, Walagesic, Sudhinol
4.	Fentanyl	25 µg/ml injection; 25 µg, 50 µg, 75 µg, 100 µg/hour transdermal patch	Fent, Durogesic
5.	Tramadol	50 mg capsule; 50 mg/ml injection	Domadol, Contramal, Dolotram, Esgipyrin-T, Domadol plus
6.	Codeine	15 mg tablet; 15 mg/5 ml syrup	Codine sulphate, Codin linctus
7.	Pentazocine	25 mg tablet; 30 mg/ml injection	Fortiwin, Fortstar, Zocin, Foracet, Fortagesic
8.	Butorphanol	1 mg/ml, 2 mg/ml injection	Butodol
9.	Buprenorphene	0.2 mg tablet; 0.3 mg/ml injection	Tidigesic, Norphin, Buprinor

5.4.6 Opioid Antagonists

The substitution of N-methyl by a bulkier N-allyl group at piperidine nitrogen (Fig. 5.4) changes an agonist to an antagonist. Naloxone, Naltrexone and Nalmefene are pure opioid antagonists at µ, κ and δ receptors. However, they block µ receptors at lower doses in comparison to doses required to block κ and δ receptors. Given alone to non-addicts or opioid-free person, these antagonists exhibit no pharmacological effects, there is no tolerance, dependence or withdrawal effects due to opioid antagonists. Individual opioid antagonists are discussed below:



Note: The phenanthrene moiety (a) and benzylisoquinoline moiety (b) have been highlighted with bold lines.

Fig. 5.4: Structures of morphine and related drugs

(i) Naloxone: Noloxone is a strong μ receptor antagonist; moderate antagonist at κ receptor and a weak antagonist at δ receptor. It has a fast onset of action (within minutes) with a plasma half-life of 1-2 hours. It has an extensive first-pass metabolism which reduces its bioavailability. It is primarily used for the treatment of opioid overdose. When given intravenously to a morphine toxicated person, it drastically reverses the opioid effects within minutes. It also normalises respiration, level of consciousness, pupil size, bowel activity and awareness of pain. However, because of its shorter duration of action, within 1-2 hours, the patient may show respiratory depression and coma, after immediate effects. Hence, it should be given in an intravenous dose of 0.4-0.8 mg every 5 minutes, till the desired parameters are normalised. Additional IV/IM doses may be given every 30-60

minutes till all the opioid is cleared from the body and no relapse is observed. It can also be used to reverse the agonistic actions of mixed agonist-antagonists overdose like that of Pentazocine. It also inhibits acupuncture analgesia because effects of acupuncture are associated with release of endogenous opioid peptides. If there is no response to respiratory depression, after administration of Naloxone, it indicates that the poisoning is not due to opioids.

It can also be used as a diagnostic test for a case of opioid addiction, because of instantaneous action. It is also used to revert neonatal respiratory depression, due to opioid use during labour. Adverse effects to Naloxone are minor.

Naloxone is available as 400 µg/ml injection: **NALOX, NARCOTAN, NEX.**

(ii) Naltrexone: It is a strong antagonist to µ and κ receprtors and a weak antagonist to δ receptors. It is 3-5 times more potent than Naloxone and has a longer duration of action. Its half-life is 10-12 hours. It exhibits significant first-pass metabolism in liver, but its major metabolite is equally active. It can be given orally. It can be used for treatment of opioid dependence in an opioid-detoxified, formerly addict patient. It is a good drug for treating morphine addicts. Before initiating treatment, an opioid free period of 10 days is essential. A great motivation is needed before starting the treatment. Doubts can be verified by performing a Naloxone challenge test. Naltrexone is also reported to decrease craving for alcohol in chronic alcoholics. Adverse reactions are minimal but high doses are hepatotoxic.

Naltrexone is available as 50 mg tablet: **NODICT, NALTIMA.**

(iii) Nalmefene: It is a derivative of Naltrexone, but can be used only intravenously. It has a quick onset of action (2 minutes), but plasma half life is longer than Naloxone (10 hours). It can be used like Naloxone to treat opioid overdose. It lacks hepatotoxicity. It is also approved for treatment of cholestatic pruritus with a dose of 20 mg twice a day.

(iv) Alvimopan: It predominantly blocks peripheral µ receptors in the gut and does not cross BBB. It has been approved for relieving constipation of an opium addict without risking the precipitation of opiate withdrawal. It is also used to treat post-operative paralytic ileus following bowel surgery.

5.5 DRUG ADDICTION, DRUG ABUSE, TOLERANCE AND DEPENDENCE

Whenever a person needs to take higher quantity of the same drug for its expected effect, it is termed as addiction. The reason for addiction may be tolerance. An addictive drug may cause dependence. All these causes lead to abuse of drugs, probably because of euphoria caused by the drug. Features of these drugs are discussed below.

5.5.1 Drug Addiction

Drug addiction has following features:

- The detrimental effects of drugs not only harm the individual but the society as well.
- There is always an intense craving to procure the drug by any means.
- There is development of tolerance and hence a need to increase the dose to get the same rewarding experience.
- There are life-threatening or alarming withdrawal effects after cessation of the drug and hence there is a physical need to continue with use of the drug for the fear of abstinence syndrome.

5.5.2 Drug Abuse

Drug abuse has following features:

- Recurrent substance use results in failure to fulfil his/her major obligations at work, school or home, e.g. poor performance at work, expulsion from school.
- Recurrent substance use even in situations where it should not be used, e.g. during driving, operating a machine or even operating on the patient.
- Recurrent substance use despite punitive action, e.g. punishment for disorderly conduct.
- Recurrent substance use despite having interpersonal or family problems, e.g. arguments or physical fight with spouse about consequences of abuse.

Drug abuse discards all other terms like misuse, habituation etc.

It does not apply to taking tea or coffee.

5.5.3 Drug Tolerance

Tolerance develops if, after repeated administration, a given dose of a drug produces a decreased effect than expected. Conversely, larger doses are needed to obtain the same effects with previous dose. It is classified as pharmacokinetic (e.g. Barbiturates) or pharmacodynamic (e.g. opioids). There is another related term: cross-tolerance. When tolerance to primary drug develops, the individual also exhibits cross-tolerance to related classes of drugs, e.g. a patient with tolerance to morphine may show cross-tolerance to heroin.

5.5.4 Drug Dependence

Dependence is a physiological state of neuroadaptation resulting from repeated administration of the drug, necessitating its continued use to prevent the appearance of distressing withdrawal syndrome which is manifested as opposite to the pharmacological effects of drugs.

Withdrawal or abstinence syndrome is a term used for the adverse (sometimes life-threatening) psychologic or physiologic reactions to an abrupt discontinuation of a dependence-producing drug.

Rebound means an exaggerated manifestation of the original disease symptoms experienced immediately after discontinuation of the drug providing clinical benefits. Rebound should not be confused with withdrawal syndrome as there is no craving or dysphoria after cessation of the drug.

Relapse refers to re-occurrence of the same disease symptoms, from which the patient suffered, after discontinuation of the treating drug. Detoxification means slow tapering of the drug that has caused dependence and would cause withdrawal if stopped suddenly.

The drugs of abuse which can endanger dependence are as follows:

- Drugs/agents having only mild psychological dependence. There are low withdrawal symptoms and no physical dependence, e.g. coffee, tea.
- Drugs/agents with moderate to severe psychological dependence. There are low withdrawal symptoms but slight physical dependence, e.g. Marijuana, Hashish, LSD, Amphetamine, Coccaine, Nicotine.
- Drugs/agents having moderate to severe psychological dependence with mild physical dependence, e.g. Benzodiazepines, Alcohol (moderate use).
- Drugs/agents having severe psychological and physical dependence, e.g. Opioids Barbiturates and Alcohol (heavy use).

5.5.5 Treatment of Drug Dependence

The pharmacological approaches to treat drug dependence and withdrawal include following:

- Short-term or long-term substitution of the abused drug by a similar drug having longer plasma half life.
- An aversive therapy by using a drug which produces unpleasant response after an intake of the abused drug.
- Use of a proper antagonist, to prevent relapse, once the drug free status is achieved.
- Use of such drugs which reduce craving for the abused drug.
- Rehabilitation and psychosocial interventions.

QUESTIONS

Long Answer Questions:

1. Comment on hypothesis for schizophrenia.
2. Discuss five interactions of anti-psychotics with other drugs.
3. Discuss mechanism of action and pharmacokinetics of tricyclic anti-depressants.
4. Write mechanism of action and interactions of other drugs with Tranylcypromine.

5. Comment on adverse effects and interactions with lithium carbonate.
6. Describe hallucinogens.
7. Write mechanism of action, contraindications and drug interactions of Livodopa.
8. What are symptoms of Parkinsoniasm?
9. Comment on pathophysiology of Alzheimer's disease.
10. What is the treatment for Alzheimer's disease.
11. Write mechanism of action, pharmacological effects and clinical uses of Amphetamine.
12. What are adverse reactions to Amphetamine.
13. What are pharmacological actions and mechanism of action of Theophyline.
14. What are adverse effects and drug interactions with Theophylline.
15. Elaborate on nootropics.
16. Write pharmacological actions of opium.
17. What are features of drug addiction and drug abuse.
18. What is drug dependence? Discuss treatment with a suitable example.

Small Answer Questions:

1. Classify anti-psychotics.
2. Write short notes on:
    - Chlorpromazine
    - Haloperidol
    - Selective serotonin reuptake inhibitors
    - MAO inhibitors
    - Mania
    - Manic depressive psychosis
    - LSD Cannabis
    - COMT inhibitors
    - Amantadine
    - Selegiline
    - Bromocriptine
    - Piracetam
    - Pethidine
    - Codeine
    - Pentazocine
    - Buprenorphine
    - Naloxone
    - Naltrexone

3. Classify anti-depressants.
4. Write clinical uses of Theophylline.
5. What is mechanism of action of nootropics.
6. List opioid receptors.
7. What are endogenous opioid peptides.
8. What are therapeutic uses of opium.
9. List contraindications to opium.

■■■

Appendix

Appendix I: Abbreviations

- **5-AMP:** Adenosine Mono Phosphate (Linear)
- **5-HT:** 5-Hydroxy Tryptamine (Serotonin)
- **A:** Adrenaline
- **AcCoA:** Acetyl Coenzyme A
- **ACE:** Angiotensin Converting Enzyme
- **ACh:** Acetyl Choline
- **AChE:** Acetyl Cholinesterase Enzyme (Enzyme)
- **ACTH:** Adreno Cortico Tropic Hormone
- **AD:** Alzheimer's Disease
- **ADH:** Anti Diuretic Hormone
- **ADHD:** Attention Deficit Hyperactivity Disorder
- **ADME:** Absorption, Distribution, Metabolism, Excretion
- **ADR:** Adverse Drug Reaction
- **AG:** Activation Gate
- **AIIMS:** All India Institute of Medical Sciences
- **ALA:** Amino Levulonic Acid
- **AMC:** ADR Monitoring Centre
- **AMPA:** Amino-3-Hydroxy-5-Methylisoxazole-4-Propionic Acid
- **ANF:** Atrial Natriuretic Factor
- **ANS:** Autonomic Nervous System
- **ASICs:** Acid Sensing Ion Channels
- **ASP:** Aspartate (Amoni acid)
- **ASV:** Anti-Snake Venom
- **ATP:** Adenosine Tri Phosphate
- **AUC:** Area Under Curve
- **AV:** Atrio-Ventricular
- **B:** Bronchoconstriction
- **BBB:** Blood Brain Barrier
- **BP:** Blood Pressure
- **BPH:** Beningn Prostatic Hypertrophy
- **BZDs:** Benzodiazepines
- **c AMP:** Cyclic Adenosine Mono phosphate
- **c GMP:** Guanosine Mono phosphate (Cyclic)
- **CDSCO:** Central Drug Standard Control Organisation
- **CDT:** Cholinergic Dependent Transporter
- **ChAT:** Choline Acetyl Transferase (Enzyme)
- **ChE:** CholinEsterase (Enzyme)
- **CHF:** Congestive Heart Failure
- **CIOMS:** Council for International Organisations of Medical Sciences

- **CNS:** Central Nervous System
- **COMT:** Catechol Ortho-Methyl-Transferase (Enzyme)
- **COPD:** Chronic Obstructive Pulmonary Disease
- **CPCSEA:** Committee for the Purpose of Control and Supervision of Experiments on Animals
- **CTZ:** Chemoreceptor Trigger Zone
- **CYP:** Cytochrome P450 enzymes, located in liver.
  - **Subclassified as** CYP1:/2/3; CYP1:A/B/C/D; CYP1A:1/2/3/4 etc.
- **CVS:** Cardio Vascular System
- **D/DA:** Dopamine
- **D:** Defaecation
- **DAG:** Diacyl Glycerol
- **DBD:** DNA-Binding Domain
- **DDT:** Dichloro Diphenyl Trichloroethane, (A synthetic insecticide)
- **DHR:** Decreased Heart Rate
- **DNA:** Deoxyribo Nucleic Acid
- **DRC:** Dose Response Curve
- **DRR:** Dose Response Relationship
- **d-TC:** d-Tubocurarine
- **DUS:** Drug Utilisation Study
- **EA:** Episodic Ataxia
- **ECG:** Electro Cardio Gram
- **ECT:** Electro-Convulsive Therapy
- **ED_{50}:** Effective Dose in 50% subjects
- **EEG:** Electro Encephalo Gram
- **EMA:** European Medicines Agency
- **ENS:** Enteric Nervous System
- **Erb:** Epidermal growth factor receptor
- **FHM:** Familial Hemiplegic Migraine
- **FSH:** Follicle Stimulating Hormone
- **GABA:** Gamma Amino Butyric Acid
- **GAD:** Glutamic-Acid-Decarboxylase (enzyme)
- **GDNF:** Glial Cell-Derived Neurotropic Factor
- **GEFS:** Generalised Epilepsy with Febrile Seizures
- **GERD:** Gastro-Esophageal Reflux Disease
- **GIT:** Gastro Intestinal Tract
- **GLP:** Good Laboratory Practice
- **GLU:** Glutamate
- **GPCR:** G-Protein Coupled Receptors
- **GPvP:** Good Pharmacovigilance Practices
- **GTF:** General Transcription Factor
- **GTg:** Glial Type Transporters

- **GTn:** GLU-Transporters
- **HDL:** High Density Lipoprotein
- **HR:** Heart Rate
- **HSF:** Heat Shock Factor
- **HVA:** Homovanillic Acid
- **Hz:** Hertz
- **ICH:** International Council for Harmonisation
- **IG:** Inactivation Gate
- **IM:** Intra-Muscular
- **IND:** Investigational New Drug
- **IOP:** Intra-Occular Pressure
- **IP_1:** Inositol Monophosphate
- **IP_2:** Inositol Diphosphate
- **IP_3:** Inositol Triphosphate
- **IPC:** Indian Pharmacopoeia Commission
- **ISA:** Intrinsic Sympathomimetic Activity
- **IV:** Intra-Venous
- **JAK:** Janus Kinase (enzyme)
- **JAK-STAT:** Involving JAK enzyme and STAT protein
- **L:** Lachrymation
- **LA:** Local Anaesthetic
- **LDL:** Low Density Lipoprotein
- **LH:** Luetinising Hormone
- **LSD:** Lysergic Acid Diethylamide
- **M:** Muscarinic (Cholinergic receptor)
- **MAC:** Minimum Alveolar Concentration
- **MAO:** Mono Amino Oxidase (Enzyme)
- **MDA:** Methylene Dioxy Amphetamine
- **MDMA:** MethyleneDioxy Methamphetamine
- **MFO:** Mixed Function Oxidase (Enzyme)
- **MI:** Myosis
- **NREM:** Non-rapid Eye Movement (Sleep)
- **N:** Nicotinic (Cholinergic receptor)
- **NA:** Nor Adrenaline
- **NDA:** New Drug Application
- **NMDA:** N-Methyl-D-Aspartate
- **NMJ:** NeuroMuscular Junction
- **NMS:** Neurolept-Malignant Syndrome
- **NO:** Nitrogen Oxide
- **NPR:** Natriuretic Peptide Receptor
- **NSAID:** Non Steroidal Anti Inflammatory Drug
- **NT:** NeuroTransmitter

- **OCD:** Obsessive-Compulsive Disorder
- **PABA:** Para-Amino-Benzoic Acid
- **PCP:** Phencyclidine
- **PD:** Parkinson's Disease
- **PDE:** Phospho Di Esterase
- **PDH:** Pyruvate Dehydrogenase Enzyme (Enzyme)
- **PGs:** ProstaGlandins
- **PIAS:** Protein Inihibitors of Activated STAT
- **PIP_2:** Phosphatidyl Inositol Diphosphate
- **PK:** Pharmacokinetic
- **PNS:** Peripheral Nervous System
- **PSNS:** Parasympathetic Nervous System
- **QSAR:** Quantitative Structure Activity Relationship
- **RAS:** Reticular Activating System
- **RBC:** Red Blood Cell
- **REM:** Rapid Eye Movement (Sleep)
- **RNA:** Ribo Nucleic Acid
- **S:** Salivation
- **SA:** Sino-Atrial
- **SC:** Sub-Cutaneous
- **Ser:** Serine (amino acid)
- **SNRIs:** Selective NE-Re-uptake Inhibitor
- **SNS:** Sympathetic Nervous System
- **SOCS:** Suppressors of Cytokine Signalling
- **SOP:** Standard Operating Procedure
- **SSRIs:** Selective Serotonin Re-uptake Inhibitor
- **STAT:** Signal Transducer and Activator of Transcription (Protein family)
- **$T_{1/2}$:** Half-life of a drug
- **TAL:** Transcription Activator Like
- **TCA:** Tricyclic Antidepressant
- **TD_{50}:** Toxic Dose to kill 50% subjects
- **TF:** Transcription factor
- **THC:** Tetra Hydro Cannabinol
- **Thr:** Threonine (amino acid)
- **TI:** Therapeutic Index
- **TLR:** Toll-Like Receptor
- **TM:** Trans-Membrane
- **TRH:** Thyroxine Releasing Hormone
- **TTX:** Tetrodo toxin
- **TYK:** Tyrosine kinase (Enzyme)
- **Tyr:** Tyrosine (Amino acid)
- **U:** Urination

- **UMC:** Uppsala Monitoring Centre
- **USFDA:** United State Food and Drug Administration
- **V_d:** Volume of Distribution
- **VIP:** Vasoactive Intestinal Polypeptide
- **VLDL:** Very Low Density Lipoprotein
- **WHO:** World Health Organisation

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Appendix II: Explanation of Terms

- **Abstinence syndrome:** Physiologic changes in patients who have become physically dependent on a drug.
- **Acne/Acne vulgaris:** Long term skin disease when hair follicles are clogged with dead skin cells and oil from skin.
- **Acute intermettant porphyria:** Heriditary hepatic porphyria causing higher porphyrin in blood.
- **Agitation:** A state of anxiety or nervous excitement.
- **Akathisia:** A feeling of internal motor restlessness.
- **Akinesia:** Inability to move.
- **Aldosteronism:** A condition with excessive secretion of aldosterone leading to high BP.
- **Alopecia:** Hair loss.
- **Alveolar wash-in:** A special procedure to treat a rare form of lung disease.
- **Amenorrhoea:** Absence of menstrual period in awoman of reproductive age.
- **Amnesia:** Deficit in memory caused by brain damage.
- **Amyotrophic lateral sclerosis (ALS) (Motor neuron disease (MND); Lou Gehring's disease):** Adisease causing death of neurons controlling voluntary muscles.
- **Analgesia:** Relief from pain.
- **Angina pectoris:** A condition marked by severe pain in chest.
- **Angioneurotic edema:** A genetic disease with lack of inhibitor protein (C1 esterase inhibitor) leading to swelling.
- **Anorexigenic:** Causing loss of appetite.
- **Antispasmodics:** A drug used to relieve spasm of involuntary muscle.
- **Aplastic anaemia:** Deficiency of all types of blood cells due to failure of bone marrow development.
- **Apnoea:** Temporary caessation of bleeding, especially during sleep.
- **Apocrine glands:** Sweat glands located in skin or eye lid.
- **Aqueous humor:** A transparent, watery fluid secreted from capillary epithelium in eye.
- **Ascites:** Abnormal accumulation of fluid in abdominal/peritoneal cavity.
- **Asthenia:** Abnormal physical weakness or lack of energy.
- **Ataxia:** Loss of full control of bodily movements.
- **Athetosis:** Repetitive involuntary, slow, gross movement.
- **Atony:** Loss of tone of a muscle.
- **Atrial fibrillation:** An irregular, rapid heart rate originating in atria.

- **Attention deficit hyperactivity disorder (ADHD):** A mental disorder of neuro developmental type with difficulty in paying attention and controlling behaviour.
- **Auditory hallucinations:** A hallucination involving hearing of one or more talking voices.
- **Aura:** A perceptual disturbance expected before seizures.
- **Autoimmune disease:** A condition in which immune system attacks own body.
- **Autoimmune disorder:** A disorder when body's immune system attacks/destroys healthy body tissue by mistake.
- **AV node:** Atrio-ventricular node controlling heart rate.
- **Benign prostatic hypertrophy:** Enlargement of prostatic gland caused by benign overgrowth of glandular tissue causing constriction of urethra.
- **Blood dyscrasia:** A pathological condition with abnormal blood cells.
- **Bradyarrhythmia:** Arrhythmia of heart showing slow heart rate.
- **Bradycardia:** Abnormally slow heart action.
- **Bradykinesia:** Reduced movements of body.
- **Bronchial asthma:** Chronic inflammatory disease of airways causing periodic attacks of coughing, wheezing, shortness of breath and chest tightness.
- **Bronchodilation:** Increase in calibre of bronchi and bronchioles due to drugs or autonomic nervous activity.
- **Bronchospasm:** Spasm of bronchial muscle, producing narrowing of bronchi.
- **Brugada syndrome:** A genetic disorder resulting in abnormal electrical activity in heart.
- **Bulimia nervosa:** A serious, potentially life-threatening eating disorder characterised by eating followed by purging.
- **Caesarean section:** Use of surgery to deliver a baby.
- **Cerebellum:** A part of brain performing co-ordination, precision and timing of body movement.
- **Cerebral haemorrhage:** Bleeding in and around the brain.
- **Cerebral ischaemia:** A condition in which there is insufficient blood flow to brain.
- **Cerebral palsy:** A group of movement disorders appearing in early childhood.
- **Chemokines:** A family of cytokines, or signalling proteins secreted by cells.
- **Chorea:** A nervous disease with involuntary and irregular movements.
- **Choreoathetosis:** A morbid condition characterised by choraic and athetoid movement.
- **Choroid plexus:** A plexus of cells which produces cerebrospinal fluid in the ventricles of brain.
- **Chromaffin granules:** Granules present in chromaffin cells of adrenal medulla
- **Chromogenin:** A substance which produces coloured pigments
- **Chronotropic:** A drug changing heart rate
- **Cleft palate:** Facial and oral malformation which occurs early in pregnancy while the baby is developing.
- **Coarsening of facial features:** Constellation of facial features present as inborn error of metabolism.
- **Congenital malformation:** A disorder which is present at or before birth.

- **Conjunctiva:** A clear thin membrane which covers part of the front surface of the eye and inner surface of the eyelids.
- **Constriction:** The action of making a lumen narrower.
- **Coombs test:** A blood test used in immunohematology to detect antibodies on surface of RBCs.
- **Corneal opacity:** A disorder of cornea which makes it appear clody or white.
- **Cortical myoclonus:** A type of epilepsy originating in cerebral cortex.
- **Cushing's syndrome:** A collection of signs and symptoms due to prolonged exposure to cortisol.
- **Cycloplegia:** Paralysis of ciliary muscle of the eye resulting in loss of accommodation.
- **Cystic fibrosis:** A genetic disorder causing difficulty in breathing and coughing of mucus due to frequent lung infections.
- **Cytochrome P450:** Enzymes present in liver microsomes, which metabolise potentially toxic compounds.
- **Cytokines:** A category of small proteins which are secreted by certain cells of immune system.
- **Dale's vasomotor reversal:** A phenonmena where prior administration of α-blocker leads to only fall in BP after giving adrenalin (it was first observed by Dale).
- **Delirium:** An acutely disturbed state of mind characterised by restlessness, illusions and incoherence.
- **Delirium tremens:** It shows rapid onset of confusion after withdrawal from alcohol.
- **Delusions:** An idiosyncratic belief or impression maintained despite being contradicted by reality or rational argument.
- **Dementia:** Achronic or persistent disorder of mental processes caused by brain disease or injury.
- **Dendrotoxins:** A class of pre-synaptic neurotoxins which block potassium channels in neurons.
- **Detrusor muscle:** A smooth muscle found in the wall of the bladder which remains relaxed to allow the bladder to store more urine.
- **Diaphragm:** A sheet of internal skeletal muscle separating thoracic and abdominal cavity.
- **Diastereomer:** A stearic isomer where compounds have different configurations at one or more asymmetric carbon atoms.
- **Diencephalon:** A part of forebrain containing thalamus, hypothalamus and the third ventricle of brain.
- **Dilatation:** The action of dilating a vessel or opening or the process of becoming dilated.
- **Diplopia:** Technical term for double vision.
- **Disorientation:** A condition of having lost one's sense of direction/a mental disorder.
- **Diverticulitis:** A condition in which pouches are formed in the wall of colon.
- **Dizziness:** The feeling of being light headed or unbalanced.

- **Duchenne muscular dystrophy:** A genetic disorder of voluntary muscles related to hips, pelvic area, shoulders and calves.
- **Dyskinesia:** Abnormality or impairment of voluntary movement.
- **Dyslipidemia:** Abnormal amount of lipids in blood.
- **Dyspepsia:** Indigestion.
- **Dyspnoea:** Difficult or laboured breathing.
- **Dyspraxia:** A developmental disorder of the brain in childhood causing difficulty in activities requiring co-ordination and movement.
- **Ejaculation:** Discharge of semen from the male reproductive tract.
- **Electro-convulsive therapy:** A procedure, done under general anaesthesia, in which small electric currents are psaased through the brain, intentionally triggering a brief seizure.
- **Enkephalin:** A pentapeptide involved in regulating nociception in the body.
- **Encephalitis:** An acute inflammation of the brain, often due to infection.
- **Endorphins:** Indeginous opioid neuropeptides and peptide hormones in humans.
- **Endotracheal tube:** A flexible plastic tube placed in trachea through mouth to help breathing.
- **Enterochromaffin cells:** A type of neuroendocrine cell in the gastric glands near parietal cells which aid in production of gastric acid via histamine.
- **Enuresis:** Involuntary urination, especially by children at night.
- **Episodic ataxia:** A genetic disorder characterised by sporadic events of ataxia (severe dis-co-ordination) with or without myokymia (continuous muscle movement).
- **Epistaxis:** Bleeding from nostril, nasal cavity or nasopharynx.
- **Erythromelalgia:** A condition characterised by intense burning pain of extremities, severe redness and increased skin temperature.
- **Esophageal variceal bleeding:** Bleeding from esophagus when swollen veins (varices) in lower esophagus rupture and bleed.
- **Ethanol abuse syndrome:** A condition in which an individual is physically and psychologically dependent on alcohol.
- **Euphoria:** A feeling or state of intense excitement or happiness.
- **Excitement:** A feeling of great enthusiasm and eagerness.
- **Excitotoxicity:** A pathological process by which neurons are damaged and killed by overactivations of NMDA/AMPA receptor.
- **Extra-pyramidal symptoms:** The symptoms including dystonia, akathesia, Parkinson, bradykinesia, tremor and tardive dyskinesia, caused by stimulation of nerve-tracts other than pyramidal pathways.
- **Extra-systoles:** A heart beat outside the rhythm.
- **Extravasation:** Leakage of fluid outside capillaries.
- **Familial hemiplegic migraine:** A genetic disease including weakness of half the body which can last for hours, days or weeks.
- **Familial hypercholesterolemia:** A genetic disorder with defect in removing LDL from blood.

- **Fasciculation:** A brief spontaneous contraction affecting a small number of muscle fibres.
- **Finger nail hypoplasia:** Underdevelopment or incomplete development of nail.
- **Flaccid paralysis:** A paralysis with weakness and reduced muscle tone without other obvious cause.
- **Floppy iris syndrome:** A complication which may occur during cataract extraction.
- **Flushing:** Becoming red and hot, as the result of illness or strong emotion.
- **Foetal alcohol syndrome:** Symptoms caused in children whose mothers consume alcohol during pregnancy.
- **Frostbite:** Adverse effects of low temperature causing freezing of skin or other tissues.
- **Galactorrhoea:** It is a milky nipple discharge unrelated to the normal milk production of breast feeding.
- **Ganglia:** A structure containing a number of nerve cell bodies, typically linked by synapses, and often forming a swelling on nerve fibre.
- **Gastro-esophageal reflux disease:** It occurs when stomach acid frequently flows back into esophagus.
- **Gingival hyperplagia:** Increase in the size of gingival (gums).
- **Glaucoma:** A disease of the eye in which fluid pressure in the eye rises.
- **Glioblastoma multiforme:** An aggressive cancer which begins within the brain.
- **Gluconeogenesis:** A metabolic pathway which results in generation of glucose from non-carbohydrate sources.
- **Glycogenolysis:** It is the breakdown of glycogen to glucose.
- **Glycolysis:** A sequence of reactions for breakdown of glucose to pyruvic acid.
- **Gout:** A form of arthritis characterised by severe pain, redness and tenderness in joints.
- **Grunts:** A low short sound made by the person.
- **Gynaecomastia:** Enlargement of male breast tissue.
- **Haemolytic anaemia:** A condition involving destruction and removal of RBCs from blood before their normal life span.
- **Haemophilia:** A genetic condition in which ability of the blood to clot is severely reduced.
- **Hallucination:** An experience involving the apparent perception of something not present.
- **Heteropodatoxin:** A peptide toxin from the venom of giant crab spider.
- **Hirsutism:** Unwanted male-pattern hair growth on a woman's face, chest and back.
- **Huntington's disease:** An inherited condition in which nerve cells in the brain breakdown over time.
- **Hyper excitability:** An excessive reaction to stimuli.
- **Hyperaemia:** An excess of blood in the vessels supplying to an organ or other part of the body.
- **Hyperalgesia:** Abnormally heightened sensitivity to pain.
- **Hyperexia:** Abnormally increased fever.
- **Hyperhidrosis:** Excessive sweating.

- **Hyperkalemic periodic paralysis:** Episodic muscle weakness caused due to elevated potassium.
- **Hyperprolactinaemia:** Elevated serum prolactin.
- **Hyperpyrexia:** Abnormally increased fever.
- **Hyperthyroidism:** Overproduction of thyroxine.
- **Hyperuricemia:** Excess of uric acid in blood.
- **Hypokalemia:** A condition when blood potassium levels are too low.
- **Hyponatremia:** A condition which occurs when the level of sodium in blood is too low.
- **Hypoxia:** Deficiency in the amount of oxygen reaching the tissues.
- **Iberiotoxin:** An ion channel toxin from Indian scorpion.
- **Impotence:** Inability in a man to achieve an erection or orgasm.
- **Impulse control disorder:** It is a psychiatric disorder leading to failure to resist temptation.
- **Incontinence:** Lack of voluntary control over urination or defaecation.
- **Integrins:** Proteins which function by attaching cell cytoskeleton to extracellular matrix.
- **Intractable hiccups:** A condition when hiccups last for more than a month.
- **Ionotropy:** Force of cardiac contraction.
- **Iridocyclitis:** Inflammation of the iris and ciliary body in eye.
- **Iritis:** Inflammation affecting coloured ring around the pupil of eye.
- **Irritability:** Excitatory ability to respond to the change in environment.
- **Ischaemic heart disease:** A heart disease caused by reduction of blood flow/oxygen to heart.
- **Islets of Langerhans:** Tiny cluster of cells in pancreas responsible for insulin production.
- **Jaundice:** Yellow discolouration of skin, mucus membranes and whites of eyes.
- **Juxta glomerular:** A specialised structure in glomeruli and distal convulted tubule of kidney.
- **Laryngospasm:** Sudden spasm of vocal cords.
- **Laxatives:** A substance which loosens stools.
- **Leucopenia:** Reduction in the number of white cells in the blood.
- **Libido:** Sexual desire.
- **Li-Fraumeni syndrome:** A genetic disorder which predisposes to cancer.
- **Limb girdle muscular dystrophy:** A group of disorders manifesting in proximal muscles around the hips and shoulders.
- **Lipolysis:** Breakdown of fats and other lipids by hydrolysis.
- **Lumbago:** Pain in the muscles and joints of the lower back.
- **Malignant hyperthermia:** A severe reaction causing muscle rigidity, high fever and a fast heart rate.
- **Manic depressive psychosis:** A mental disorder that causes periods of depression and periods of abnormally elevated mood.
- **Median eminence:** A part of hypothalamus from which regulatory hormones are released.
- **Medulla (medulla oblongata):** Apart of brain stem controlling ANS responses and motor functions.

- **Megaloblastic anaemia:** A macrocytic anaemia which results from inhibition of DNA synthesis during RBC production.
- **Mental confusion:** A change in mental staus in which a person is not able to think with usual level of clarity.
- **Mental retardation:** The condition of having mental IQ below 70-75. The person lacks in adaptive skills.
- **Mesolimbic system:** A dopaminergic pathway in the brain related to reward system.
- **Metabotropic receptors:** Receptors linked with ion channels through signal transduction mechanisms, often G-proteins.
- **Microcephaly:** A condition in which a baby's head is significantly smaller than expected.
- **Micturition:** The act of passing urine.
- **Migraine:** A headache of varying intensity, often accompanied by nausea and sensitivity to light and sound.
- **Miosis:** Excessive constriction of the pupil of the eye.
- **Mucosal vasoconstriction:** Blockage of vessels to mucosa, especially in nasal passages leading to nasal congestion.
- **Multiple sclerosis:** A disease in which the immune system eats away protective covering of nerves.
- **Muscarinic:** Relating to a type of ACh receptor in nervous system capable of responding to muscarine.
- **Myasthenia gravis:** Adisease causing weakness and rapid fatigue of muscles under voluntary control.
- **Mydriasis:** Dilation of the pupil of the eye.
- **Myocardial infarction:** A condition in which blood flow to heart decreases or stops, causing damage to heart muscle.
- **Myoclonic/petit mal seizures:** A kind of epilepsy when myoclonic jerks are associated with abnormal brain wave activity.
- **Myoclonus:** Spasmodic jerky contraction of groups of muscles.
- **Myoglobinuria:** Presence of myoglobin in urine.
- **Narcolepsy:** A chronic sleep disorder which causes overwhelming daytime drowsiness.
- **Neoplastic disease:** It refers to both malignant and benign growths.
- **Nephrogenic diabetes insipidus:** A kind of diabetes insipidus caused due to pathology of kidney.
- **Neurolept analgesia:** An intense analgesic and amnesic state.
- **Neurolept-malignant syndrome:** A rare, life-threatening condition characterised by fever, muscular rigidity, altered mental status, caused by antipsychotic drug.
- **Neuronal excitotoxicity:** Toxicity caused by excessive stimulation by glutamate/similar substances.
- **Nicotinic:** A channel protein which upon binding by ACh opens flow of cations, as in case of nicotine.
- **Nocturnal anuresis:** An involuntary urination which happens at night while sleeping.
- **Nystagmus:** A condition of involuntary eye movement resulting in limited vision.
- **Obsessive-compulsive disorders:** Excessive thoughts (obsessions) that lead to repetitive behaviours (compulsions).

- **Oedema:** A condition with excess of watery fluid in cavities or tissues of the body.
- **Pancreatitis:** An inflammation of pancreas causing abdominal pain.
- **Paralytic ileus:** Obstruction of intestine due to paralysis of intestinal muscles.
- **Paranoid delusions:** Fixed, false belief that one is being harmed or persecuted by a person.
- **Paranoid ideas:** Thought process believed to be heavily influenced by anxiety or fear.
- **Parasympatholytics:** A substance or activity which reduces the activity of PSNS.
- **Parasympathomimetics:** A substance which stimulates PSNS.
- **Paresthesia:** Burning or prickling sensation, usually felt in hands, arms, legs or feet.
- **Paroxysmal:** A sudden recurrence or intensification of symptoms.
- **Peptic ulcer:** A break in the lining of stomach or duodenum.
- **Phaeochromocytoma:** A hormone-secreting tumour which occurs in the adrenal gland.
- **Pheromones:** A chemical produced by a mammal or insect, affecting the behaviour or physiology of others of its species.
- **Photophobia:** A condition in which bright lights hurt eyes.
- **Photosensitivity:** An immune reaction triggered by Sunlight.
- **Pill rolling tremors:** A tremor in which index finger of hand tends to get in contact with thumb and they perform a circular movement together.
- **Piloerection:** Involuntary erection or bristling of hairs due to a sympathetic reflex triggered by cold, shock or fright.
- **Plasmapheresis:** A process which filters the blood and removes harmful antibodies.
- **Plasticity:** Ability of the brain to change throughout an individual's life.
- **Pleural fibrosis:** A restrictive lung disease with high morbidity/mortality.
- **Poikilothermic:** Ability to change body temperature with environment.
- **Polydypsia:** Abnormally great thirst.
- **Polyuria:** Production of abnormally large volumes of dilute urine.
- **Pons:** A part of brain stem including neural motor pathways from brain to cerebellum and sensory signals to thalamus.
- **Porphyria:** Disorder resulting from build up of porphyrin in blood.
- **Positive ionotropic:** Agents increasing strength of muscular contraction.
- **Post-ictal depression:** Feeling of depression before a seizure.
- **Post-traumatic stress disorder:** Stress observed after trauma.
- **Priapism:** Persistent and painful erection of the penis without sexual arousal.
- **Presenility:** Events earlier to mental deterioration associated with old age.
- **Progressive choreoathetosis:** Progressive movement disorder, cognitive and behavioural changes with a myopathy.
- **Prostatic hyperplasia:** Age-associated prostate gland enlargement that can cause difficulty in urination.
- **Pseudocholinesterase:** An enzyme present in blood and other organs which hydrolyses ACh more slowly than acetyl cholinesterase.
- **Pseudo-cushing's syndrome:** Cushing's syndrome which is not associated with hypothalamic-pitutary-adrenal axis.
- **Psychedelics:** Related to drugs which produce hallucinations and apparent expansion of consciousness.

- **Psychotomimetics:** Relating to drugs which are capable of producing an effect on the mind similar to a psychotic state.
- **Ptosis:** Grouping of the upper eyelid due to paralysis or disease.
- **Purgatives:** A medicine causing expulsion of unwanted waste from the body.
- **Raphe neurons:** Cluster of nuclei in brain stem, responsible for release of 5-HT to the rest of brain.
- **Raynaud's syndrome:** A condition in which spasm of arteries cause episodes of reduced blood flow.
- **Refractory complex epilepsy:** A type of epilepsy which cannot be controlled by several antiepileptics.
- **Restlessness:** The inability to rest or relax as a result of anxiety or boredom.
- **Resuscitation:** The process of correcting physiological disorders in an acutely unwell patient.
- **Rett syndrome:** A rare genetic mutation affecting brain development in girls (6-18 months).
- **Rhabdomyolysis:** A breakdown of muscle tissues that releases a protein in to blood which makes urine brown (myiglobinuria).
- **Rhinorrhoea:** A condition where the nasal cavity is filled with a significant amount of mucus fluid.
- **SA node:** The heart's natural pacemaker, located in upper part of right atrium.
- **Saxitoxin:** A potent neurotoxin from shell fish causing paralysis.
- **Schizophrenia:** A mental disorder that affects a person's ability to think, feel and behave clearly.
- **Serotonin syndrome:** A group of symptoms that may occur due to serotonergic drugs.
- **Sialorrhea (drooling):** Excessive salivation caused by poor oral and facial muscle control.
- **Sickle cell anaemia:** A group of disorders that cause RBCs to alter their shape and breakdown.
- **Sjogren syndrome:** An immune system disorder characterised by dry eyes and dry mouth.
- **Somnolence:** A state of strong desire for sleep or sleeping for unusually long periods.
- **Spasticity:** A condition in which certain muscles are continuously contracted.
- **Sphincter:** A circular muscle which normally maintains constriction of a natural body passage or orifice and which relaxes as per physiological need.
- **Spina bifida:** A birth defect in which a developing baby's spinal cord does not develop properly.
- **Spino-thalamic tract:** A sensory pathway from the skin to thalamus.
- **Splanchnic vasoconstriction:** Constriction of vessels supplying to spleen.
- **Spondylitis:** A form of arthritis which occurs in the spine.
- **Sprain:** A stretching or tearing of ligaments, the fibrous tissue which connects bones and joints.
- **Status epilepticus:** A dangerous condition in which epileptic feets follow one another without recovery of conscious between them.

- **Stupor:** A state of near-unconsciousness or insensibility.
- **Sympatholytics:** A drug which is antagonist to or inhbiting the transmission of nerve impulses in SNS.
- **Sympathomimetics:** A drug producing physiological effects characteristic of SNS.
- **Syncope:** Atemporary loss of consciousness due to insufficient blood flow to the brain.
- **Systemic lupus erythematosis (SLE):** An autoimmune disease in which the immune system mistakenly attacks healthy tissue in many parts of the body.
- **Tachycardia:** Increase in heart rate (> 100/minute).
- **Tachyphylaxis:** Rapidly diminishing response to successive doses of a drug, rendering it less effective.
- **Tachypnoea:** Abnormally rapid breathing.
- **Tactile hallucinations:** False perception of sensory input that creates a hallucinatory sensation of physical contact with an imaginary object.
- **Tardive dyskinesia:** A disorder which results in involuntary repeatitive body movements.
- **Tetanus:** A serious bacterial infection of *Clostridium tetani* spores causing painful muscle spasm and can lead to death.
- **Tetrodo toxin:** A potent neurotoxin from a fish which blocks sodium channel.
- **Thalassemia:** A genetic disorder characterised by abnormal haemoglobin production.
- **Theromogenesis:** Production of heat in human body.
- **Thrombocytopenia:** A condition characterised by abnormally low levels of thrombocytes/platelets.
- **Thrombophlebitis:** Inflammation of a vein (phlebitis) related to blood clot (thrombus).
- **Thymectomy:** Surgical removal of the thymus gland.
- **Tic:** An involuntary, spasmodic contraction of muscle fibres.
- **Tourette's syndrome:** A neuro-psychiatric condition showing tics, grunts and vocalizations.

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Appendix III: Receptors and their Subtypes

- **Dopamine (DA):** D_1, D_2, D_3, D_4.
- **Serotonin (5HT):** 5HT-1, 5HT-1A, 5HT-1C; 5HT-2A, 5HT-2B
- **Acetylcholine (AcH):** Muscarinic: M_1, M_2, M_3; Nicotinic: N_M, N_N
- **Histamine (H):** H_1, H_2.
- **Adrenaline (A):** α_1, α_2; β_1, β_2, β_3.
- **Noradrenaline (NA):** α_1, α_2; β_1, β_2, β_3.
- **Cannabis:** CB_1, CB_2.

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Appendix IV: Trade-Names of Few Drugs

DRUG (GENERIC NAME)		TRADE NAMES
Acebrophylline	:	**AB-PHYLLINE, BESTOPHYLLINE-A, UNOBRO**
Adrenaline	:	**VASOCON**
Alprazolam	:	**ALPRAX, ALZOLAM, RESTYL, TRIKA, ALLTOP-P, ZOPAX PLUS.**
Amantadine	:	**AMANTREL, COMANTREL**
Aminophylline	:	**MINOPHYL, AMINOPHYLLINE**
Asebutolol	:	**SECTRAL**
Atenolol	:	**BETACARD, TENORMIN**
Atomoxetine	:	**ATTENTROL, AXEPTA**
Atracurium	:	**ATRELAX TRACRIUIM**
Atropine	:	**ATROPINE SULPHATE, TROPINE**
Baclofen	:	**LIOFEN, LIORESAL, BACMAX**
Bambuterol	:	**BETADAY, BAMDULI, ROBUROL**
Benzocaine	:	**MUCOPAIN, ZOKEN**
Betaxolo	:	**OPTIPRESS, BULOL, IOBET, OCUBETA**
Bisoprolol	:	**ZAVESTA, CORLOIS, BISELECT**
Bromocriptine	:	**PROCTINAL SICRIPTIN, PARLODEL, BROM, ENCRIPT**
Bupivacaine	:	**MARCAIN, BUPIVAN**
Buspirone	:	**TAMSPAR, BUSCALM, BUSPIDAC**.
Cabergoline	:	**CABGOLINE**
Carbamazepine	:	**MAZETOL, TEGRITAL, TEGRITOL**
Carisoprodol	:	**CARISOMA**
Carvedilol	:	**ORICAR, CONPRESS, CEVAS, CARVIMED, CARDIVAS**
Celeprolol	:	**CELIPRES**
Chlordiazepoxide	:	**LIPRIUM, ODIP, LIBRAX**
Chlorpheneramine	:	**COZYPLUS**
Chlorzoxazone	:	**NEW PANAZOX, UNIDIC-MR**
Clobazam	:	**COBAZAM, CLOBA, CLOBATOR**
Clonazepam	:	**LONAZEP, RIVOTRIL, EPITRIL**
Clonidine	:	**ARKAMIN, CATAPRESS**
Cyclopentolate	:	**CYCLATE, CYCLOGIK, DILATE**
Diazepam	:	**VALIUIM, CALMPOSE**

Dicyclomine	:	**COLINET, CYCLOPAM**
Dipivefrine	:	**PROPINE**
Disulfiram	:	**ANTADICT, SUFITAL, ESPERAL**
Dobutamine	:	**DOBUTREX, DOBIER, DOBUCARD, KARDIA**
Donepezil	:	**ALZIL, DONECEPT, DOPEZIL**
Dopamine	:	**DOPACARD, DOPAR, DOPASOL, DOPINGA**
Doxasosin	:	**DOXACARD, DURACARD**
Doxofylline	:	**DOXOBID, DOXFREE, BESTOFYLINE**
Drotaverine	:	**DOTARIN**
Esmolol	:	**CARDESMO, NEOTACH, MINIBLOCK**
Eszopiclone	:	**FLUNITE**
Fenfluramine	:	**FLABOLIN**
Flavoxate	:	**FLAVOSPAS**
Flurazepam	:	**NINDRAL, FLURAZ**
Formoterol	:	**FORATEC**
Fosphenytoin	:	**FOSOLIN**
Gabapentin	:	**GABANTON, GABAPIN, GABATOR, GABANEURON**
Galantamine	:	**GALAMER**
Glycopyrrolate	:	**GLYCOP, VAGOLATE**
Halothane	:	**FLUOTHANE** or **HYPNOTHANE**
Homatropine	:	**HOMIDE**
Hydroxyzine	:	**MELOSET, ZYTONIN**
Hyoscine (scopolamine)	:	**BELLOID, BUSCOPAN, HYOSPAN**
Ipratropium	:	**IPRAVENT, IPRATOP**
Isoflurane	:	**FORANE, ISORANE, SOFANE**
Isoprenalilne	:	**ISOLIN, ISOPERIN, ISOSOL, NEO-EPININE**
Labetalol	:	**NORMADATE, LABESOL**
Levobunolol	:	**BETAGAN**
Levodopa + Benserazide	:	**BENSPAR**
Levodopa + Carbidopa	:	**SYNDOPA, TIDOMET-FORTE, TIDOMET LS, SINEMET PLUS, SYNDOPA PLUS, TIDOMET PLUS**
Lidocaine	:	**GESICAINE WITH ADRENALIN, XYLOCAINE WITH ADRENALIN, LIGNOCAINE, GESICAINE, XYLOCAINE**
Lithium carbonate	:	**LITHOSUN, LITHOSUN – SR, LICAB, LICAB – XL, LITHOCAP**
Lorazepam	:	**ATIVAN, LARPOSE, LORVAN, TRAPEX, LOPERZ**

Mefanamic acid	:	**MEFTAL-SPAS, BARALGAN-DM, DOTARIN-MF**
Melatonin	:	**ATARAX**
Memantine	:	**ADMENTA, MENTADEM**
Mephentermine	:	**MEPHENTINE**
Metaproterenol (orciprenaline)	:	**ALUPENT**
Methocarbamol	:	**ROBINAX FLEXINOL**
Metoprolol	:	**BETALOC, METOLAR, LOPRESOR**
Midazolam	:	**MIDAZ, MEZOLAM, FULSED**
Modafinil	:	**PROVAKE, MODALERT**
Naloxone	:	**NALOX, NARCOTAN, NEX**
Naltrexone	:	**NODICT, NALTIMA**
Naphazoline	:	**PRIVINE, OCUCEL, FENOX**
Nebivolol	:	**NEBICARD, NUBETA, NODON, NEBISTAR**
Noradrenaline (NE)	:	**ADRENOR, NODRESOL, NORAD, NOREPIRIN**
Orphenadrine	:	**ORPHIPAL**
Oxazepam	:	**SEREPAX**
Oxcarbazepine	:	**OXCARB, OXETOL, OXEP**
Oxprenolol	:	**TRASICOR**
Oxybutinine	:	**OXYSPAS, CYSTRAN**
Oxymetazoline	:	**XYNOSE, SYNAREST**
Pancuronium	:	**PANCURONIUM BROMIDE, PANCONIUM**
Phemylephrine	:	**DROSYN**
Phenobarbital	:	**GARDENAL, PHENOBARB, PHENYTAL**
phenobarbitone	:	**PIPLAR**
Phentolamine	:	**FENTANOR, FENTOSOL**
Phenylpropanolamine	:	**ALERID-COLD**
Phenytoin	:	**DILANTIN, EPSOLIN, EPTOIN**
Pindolol	:	**VISKEN**
Pipecuronium	:	**ARDUAN**
Pramipexole	:	**PARPEX**
Prazosin	:	**MINIPRESS, PRAZOPRESS**
Pregabalin	:	**MAXGALIN, NEUGABA, PREGEB, PREEGA-M**
Prilocaine	:	**PRILOX, ASTHESIA**
Primidone	:	**MYSOLINE**
Procyclidine	:	**KEMADRIN, DINE, PRODINE**
Promethazine	:	**AVOMINE, PHENERGAN**
Propantheline	:	**PROBANTHINE**

Propofol	:	**CRITIFOL, PROPOFOL, PROPOVAN**
Propranolol	:	**INDERAL, CIPLAR, BETACAP-TR**
Pseudoephedrine	:	**CHESTON**
Recuronium	:	**CUROMID**
Rivastigmine	:	**RIVASMINE, RIVAMER, EXELON**
Ropinirole	:	**ROPITOR, ROPARK**
Salbutamol	:	**ASTHALIN, VENTORLIN, DERIHALER**
Salmeterol	:	**SALMETER, SEROBID**
Selegiline	:	**SELGIN, SALERIN, ELEGELIN**
Sibutramine	:	**OBEGO, OBESTAT, SIBUTREX**
Sotalol	:	**SOTAGARD, SOLET**
Succinylcholine (ScA)	:	**SCOLINE, ENTUBATE, MIDARINE**
Tamsulosin	:	**CONTIFLO-OD, URIPRO, VELTAN, URIMAX**
Terazosin	:	**HYTRIN, TERAPRESS, TERALFA, OLYSTER**
Terbutaline	:	**BRICANYL**
Tetracaine	:	**AMETHOCAINE, ANETHANE**
Theophylline	:	**BRONCORDIL, THEODAY, THEODER, DERIPHYLLINE**
Thiopental	:	**INTRAVAL, PENTOTHAL**
Timolol	:	**OCUPRES, GLUCOMOL, IOTIM, TIMOLE**
Tiotropium	:	**TIATE, TIOVA**
Tolazoline	:	**FENOXENE**
Tolterodine	:	**TOLTER-OD, FLOWCHEK**
Topiramate	:	**TOPEX, TOPIROL**
Triclofos	:	**PEDICLORYL, TRICLORYL**
Trihexephenidyl	:	**PACITANE, PARKIN, PARKITANE**
Trihexiphenidine	:	**PACITANE, PARKITANE, PARKIN**
Triprolidine	:	**ACITIFIED**
Tropicamide	:	**OPTIMIDE, TROMIDE, TMIDE, DROSYN-T**
Valethamate	:	**EPIDOSIN**
Valproic	:	**ENCORATE, TORVATE, VALTEC**
Vecuronium	:	**VERUNIUM, VECURON**
Xylometazoline	:	**OTRIVIN**
Zaleplon	:	**ZAPLON, ZASO**
Zolpidem	:	**NITREST, ZOLPIGEM, ZOLPINITE**
Zonisamide	:	**ZONISEP, ZONICARE, ZONIMID**
Zopiclone	:	**ZOLINOX, ZOPICON, ZOLIUM**
α-methyldopa	:	**EMDOPA, ALFADOPA, ALDOPAM**

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