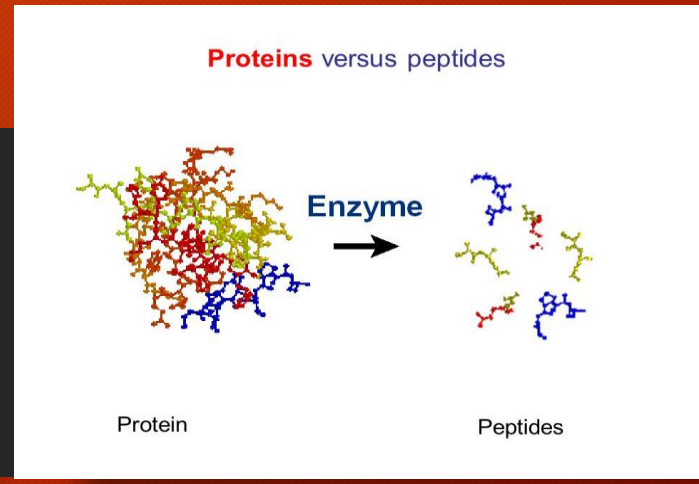
PROTEINS AND PEPTIDES



I M.PHARM (II Semester)
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CONTENTS

INTRODUCTION

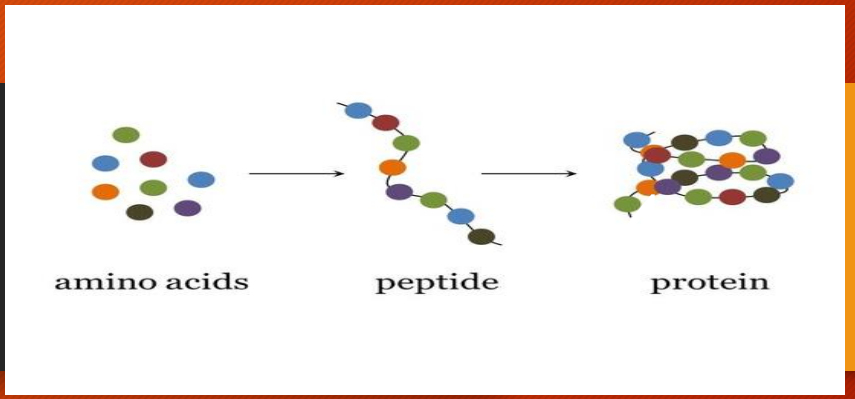
- Recently the armamentarium (i.e., the medicines, equipment and techniques available to a medical practitioner) pharmaceuticals almost completely comprised small organic molecules, the majority of which were synthesized in the laboratory

- Steady advances in cellular biology and in biotechnology have allowed scientists to create new therapeutic entities mimicking endogenous bioactive substances

- These new products include proteins, peptides, monoclonal antibodies, oligonucleotides, vaccines against microbiological and non-microbiological diseases, and gene therapy treatments

- Pharmacists need to understand the pharmacokinetics and pharmacodynamics of these therapeutic products of biotechnology, which will constitute an ever-increasing proportion of the medications that they will be called on to provide for patients.

PROTEINS & PEPTIDES



- Proteins- are the large organic compounds made of amino acids arranged in a linear chain and joined together by peptide bonds.

Protein > 50 amino acids

- Peptides- are short polymers formed from the linking in a defined order of amino acids.

Peptides< 50 amino acids

- The size range of these compounds that are in use ranges from 1 kDa to 320 kDa
- Smallest substance is oxytocin, a 9-amino-acid peptide which is produced by chemical synthesis
- Largest compound is the antihemophilic factor, a large glycoprotein produced by recombinant DNA technology

LIST OF PROTEIN AND PEPTIDE DRUGS

Compound	Molecular mass (kDa)	Volume of distribution (Lkg−1)	Elimination half life(h)	Administration (systemic availability)	Use
Becaplermin; Rh-platelet-derived growth factor (Regranex)	25	-	-	Topical gel (negligible)	Decubitus ulcer
Desmopressin (DDAVP, Stimate, Minirin)	1.18	-	1.5–2.5	Oral(0.0016);intra nasal (0.03)	Synthetic antidiuretic hormone
DNase; dornase alfa (Pulmozyme)	29.3			Inhalation (nebulizer) (negligible)	Breathing difficulty in cystic fibrosis
Coagulation factor VIIa (NovoSeven)	50	0.103	2.3	IV injection(1.0)	Haemophilia
Insulin, human	5.8	0.26–0.36	True half life0.08–0.12	SC(0.55–0.77)	Diabetes

ROUTE OF ADMINISTRATION

- Proteins and peptides of smaller size can only be administered orally. This is because large peptides and proteins are subject to degradation and inactivation in the gastrointestinal tract. There by systemic bioavailability will be negligible. **Desmopressin** (1.18 kDa)

- **Becaplermin**(25 kDa) is a drug that is administered topically as its site of action is on the surface of the skin, even though there are no protein drugs that can be administered transdermally due to their large molecular weight and thus interfering with systemic absorption.

ROUTE OF ADMINISTRATION

- They can also be administered through **nasal** route, for example: **DNase** (Pulmozyme). It is an enzyme used to break down thick mucus secretions in the respiratory tracts of cystic fibrosis patients. But for an inhaled protein that requires systemic absorption in order to exert its therapeutic effect is the inhalable form of human insulin, **Exubera** which have been showed better disposition and efficacy were comparable to those of subcutaneously administered insulin and also its absorption was somewhat faster

- The majority of these drugs are administered **parenterally**, either subcutaneously, intramuscularly, or systemically by intravenous injection or infusion

- Many of the drugs have very high systemic absorption from <u>subcutaneous</u> and <u>intramuscular</u> dosage forms.

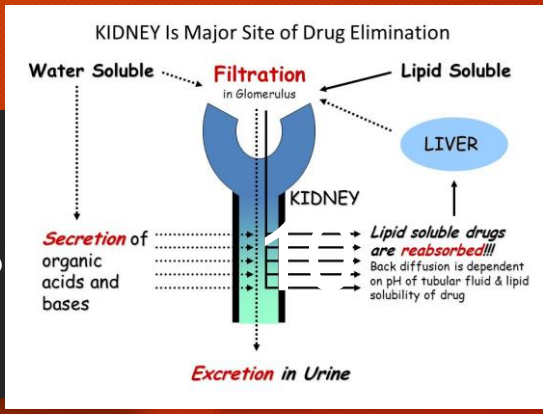
Pharmacokinetics & Pharmacodynamics of Protein & Peptide drugs

- Apparent volumes of distribution of these proteins and peptides are relatively small and roughly inversely correlated with their molecular weights
- However, irrespective of the value of the distribution volume, each protein is distributed to the tissue containing receptors for its therapeutic activity in an amount adequate to elicit effect. This specific distribution, though most important for effect, is often of too small a magnitude to affect the value of the overall volume of distribution
- For proteins, the total volume of distribution at steady state is usually not more than twice the initial volume of distribution
- Pegylation often decreases the volume of distribution of a protein drug.

Pharmacokinetics & Pharmacodynamics of Protein & Peptide drugs

- Most of the protein and peptide drugs have short elimination half lives, as recorded in intravenous studies. However, when these drugs are administered by subcutaneous or intramuscular injection, delayed absorption causes plasma drug levels to remain high for an appreciable period of time
- Proteins and peptide drugs are glycosylated or pegylated to increase their half life
- The desired therapeutic and pharmacokinetics of these drugs can be achieved by bioengineering such as by glycosylation, deglycosylation, pegylation, cyclization, or conjugation, etc.,
- The site and mechanism of elimination may be determined by charge, oil/water partition coefficient, the presence of sugars or other functional groups associated with the protein and to a large extent by molecular weight.

Pharmacokinetics & Pharmacodynamics of Protein & Peptide drugs



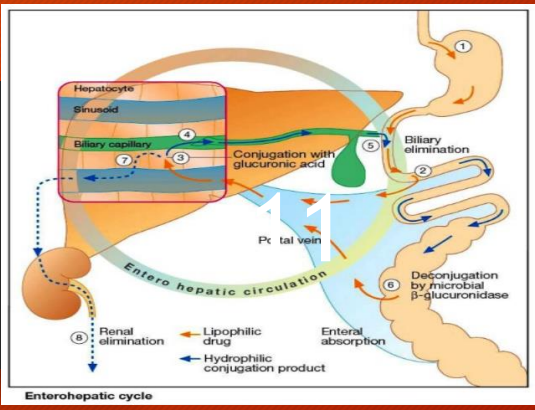
Elimination through kidney:

- ✓Proteins that are small enough to be filtered by the glomerulus in the kidney (<60 kDa) may either be absorbed by endocytosis into proximal tubule cells followed by lysosomal degradation (bradykinin) or may be metabolized by enzymes at the luminal brush border membrane

- ✓Proteins and peptides like insulin, parathyroid harmone and vasopressin are degraded by peritubular receptors.

- ✓Receptor-mediated endocytosis in the kidney is also an important mechanism of degradation of proteins that are too large to be filtered by the glomerulus

Pharmacokinetics & Pharmacodynamics of Protein & Peptide drugs



Enterohepatic cycle

Degradation in liver by intracellular catabolism:

- ✓ small polypepties (<1kDa): are transported to these cells by passive diffusion or carrier mediated uptake
- ✓ moderate size proteins (50-200kDa): receptor mediated endocytosis

Even though insulin has molecular weight of 5.8kDa, which is below the above mentioned range, insulin is eliminated to a considerable extent by receptor-mediated endocytosis in the liver

- ✓ largest proteins (200-400kDa): are opsonized by immunoglobulins followed by phagocytosis
- ✓ protein complexes (>400kDa): eliminated by phagocytosis

Pharmacokinetics & Pharmacodynamics of Protein & Peptide drugs

- For certain proteins, elimination through receptor mediated endocytosis occurs outside the liver.

For example:

--Granulocyte colony stimulating factor (GCSF) binds to receptor in bone marrow that can eliminate this protein by saturable process

--Macrophage colony stimulating factor (MCSF) is eliminated in part by binding to macrophages

- Elimination of these drugs may be complex process with dose-dependent, saturable pharmacokinetics.

Pharmacokinetics & Pharmacodynamics of Protein & Peptide drugs

- Plasma levels of the protein drugs may infact, correlate poorly with therapeutic effect. The drug may be cleared from blood not because of an elimination process but instead because it is taken up by a receptor where it may reside for some time exerting its therapeutic effect

- The curve of therapeutic effect as a function of time may be temporarily displaced with respect to the curve of plasma drug level over time, requiring the use of indirect PK and PD modelling

REFERENCE

- Basic Pharmacokinetics. Sunil S Jambhekar and Philip J Breen. Second edition 2012. Published:Pharmaceutical Press. Pg no.413-426.

THANK YOU!