College of Pharmacy
Fifth Stage

Pharmaceutical Biotechnology

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Lecture 7
Pharmacokinetics of Protein Products

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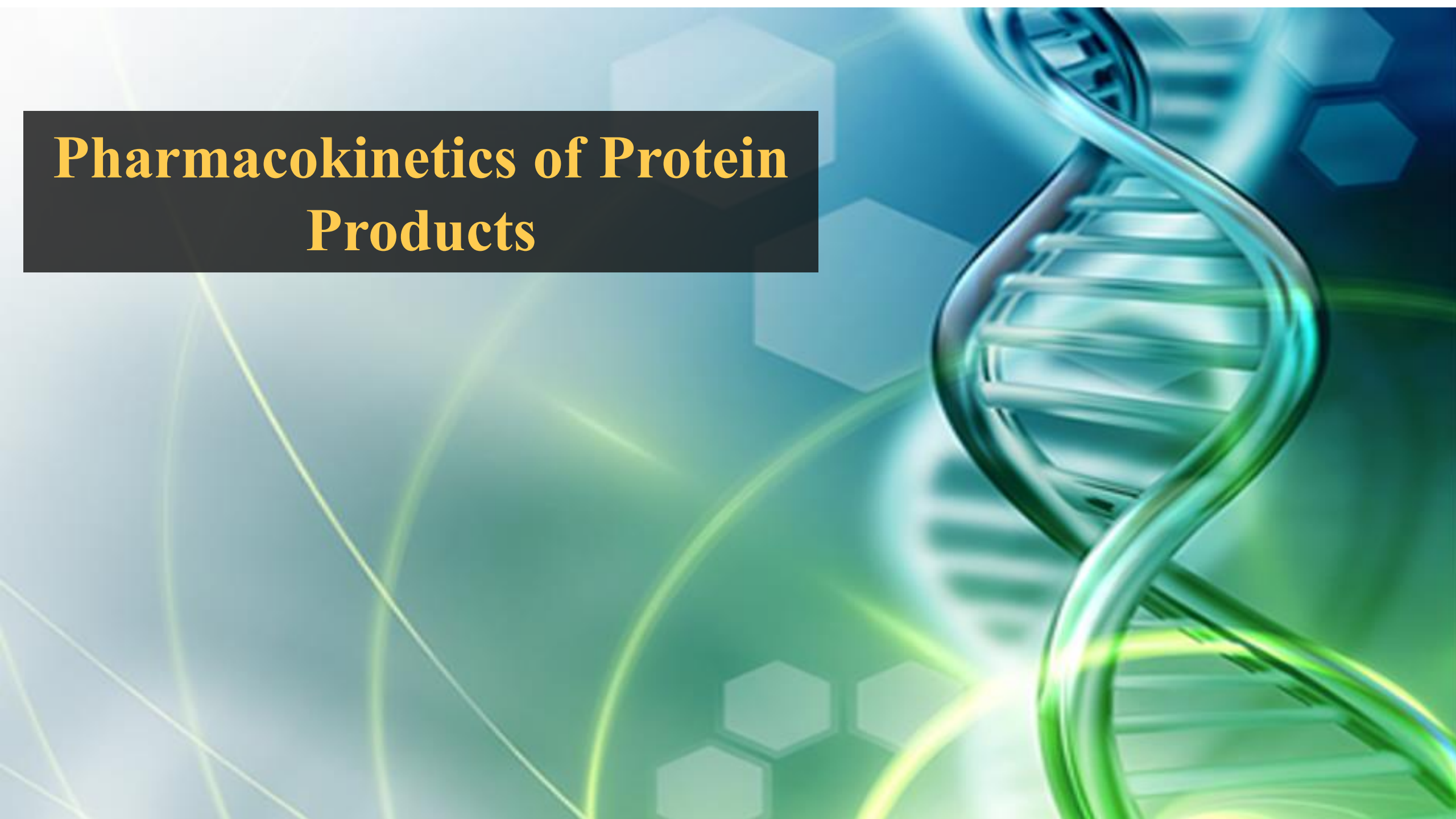
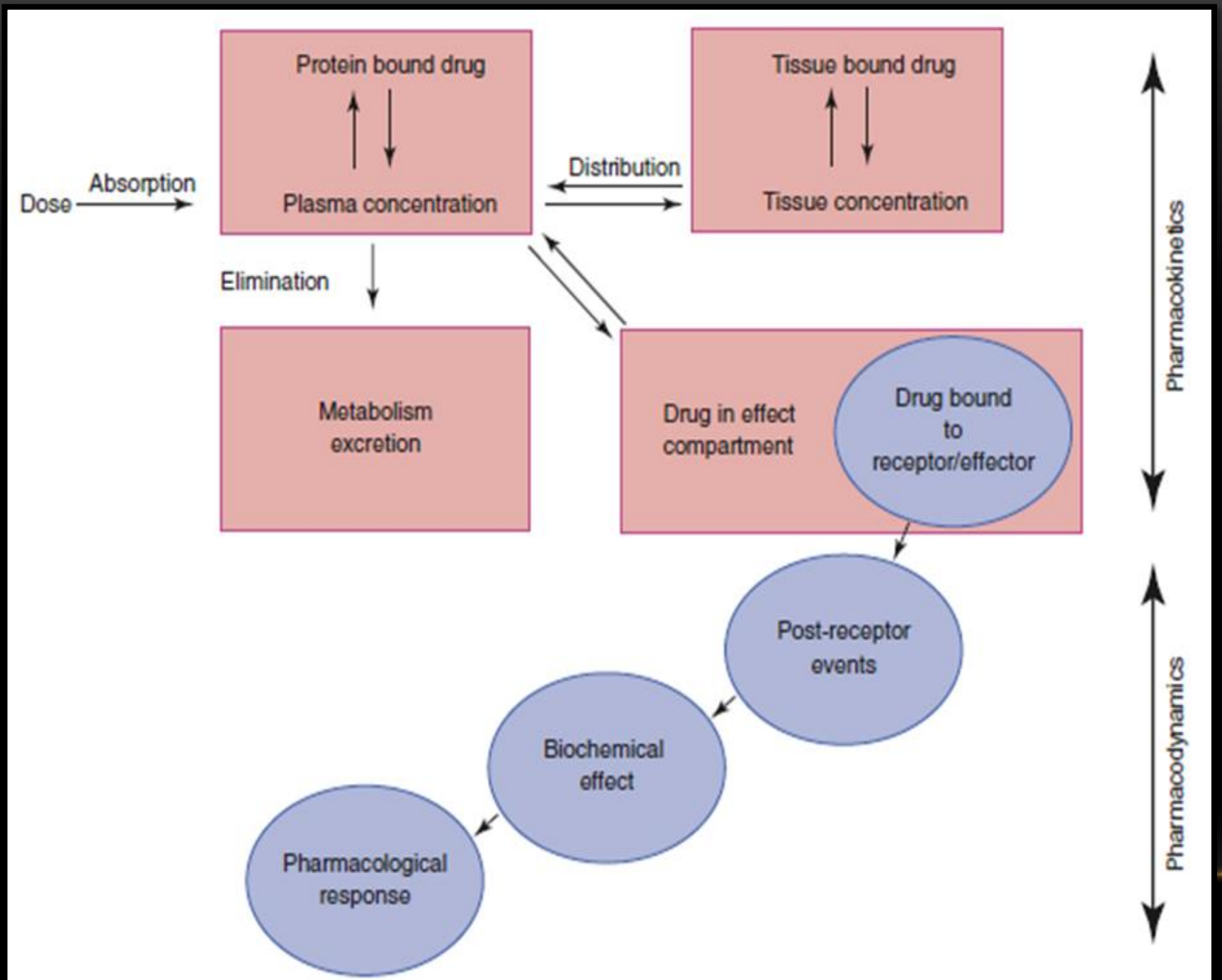
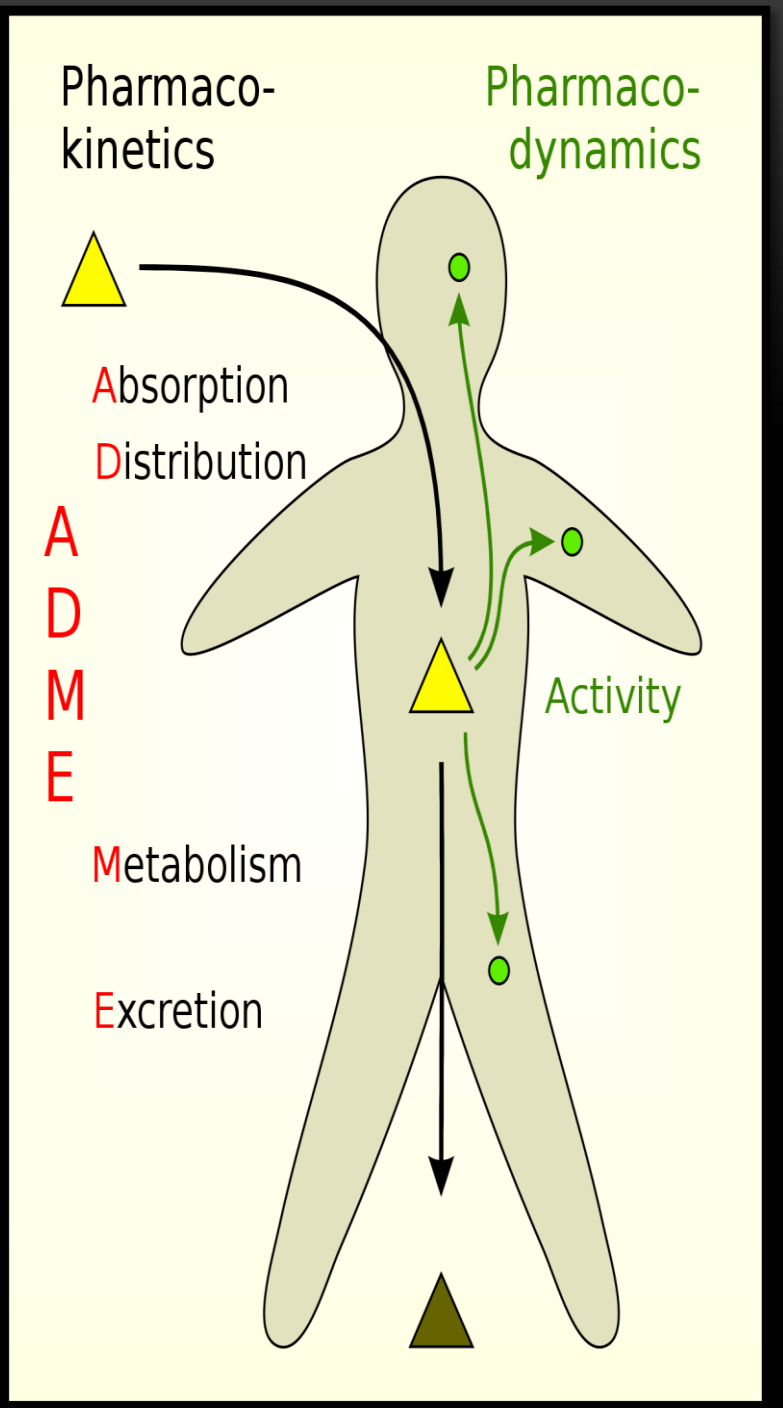


Pharmacokinetics

- **Pharmacokinetics** describes the time course of the concentration of a drug in a body fluid, preferably plasma or blood, that results from the administration of a certain dosage regimen.
- It comprises all processes affecting drug **absorption**, **distribution**, **metabolism**, and **excretion**. Simplified, pharmacokinetics characterizes "**what the body does to the drug** ".
- In contrast, **pharmacodynamics** characterizes **what the drug does to the body**.


Protein bound drug
Plasma concentration
Tissue bound drug
Tissue concentration
Distribution
Dose
Absorption
Elimination
Metabolism
excretion
Drug in effect
compartment
Drug bound
to
receptor/effector
Post-receptor
events
Biochemical
effect
Pharmacological
response
Pharmacokinetics
Pharmacodynamics


Pharmaco-
kinetics
Pharmaco-
dynamics
Absorption
Distribution
A
D
M
E
Metabolism
Excretion
Activity

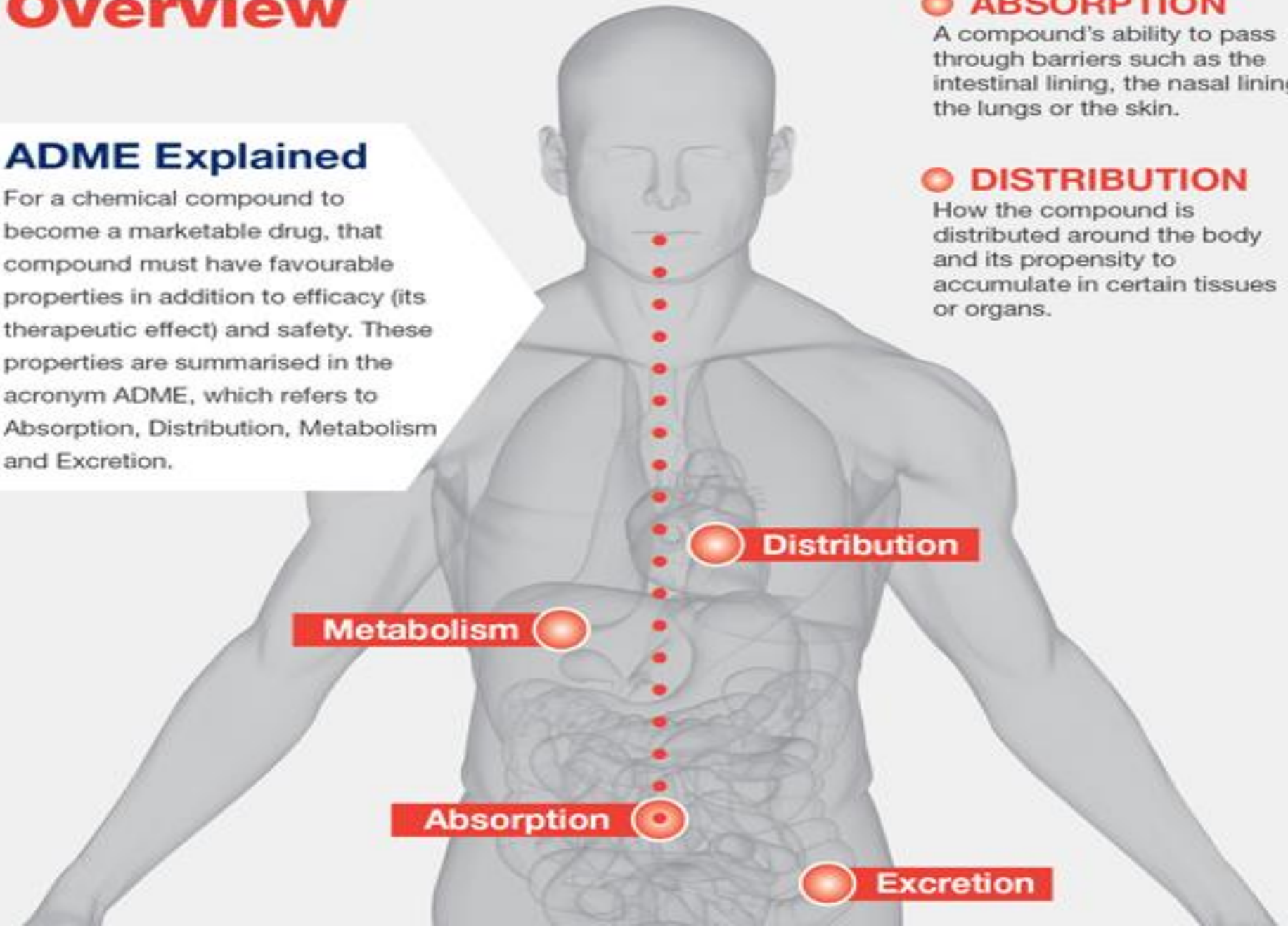
Specific Properties of Peptide and Protein Therapeutics

1. Their definition by the production process in a living organism rather than a chemically exactly defined structure and purity as it is the case for small-molecule drugs.
2. Their structural similarity to endogenous structural or functional proteins and nutrients.
3. Their intimate involvement in physiologic processes on the molecular level, often including regulatory feedback mechanisms.
4. Their large molecular weight and macromolecule character (for proteins).

Overview

ADME Explained

For a chemical compound to become a marketable drug, that compound must have favourable properties in addition to efficacy (its therapeutic effect) and safety. These properties are summarised in the acronym ADME, which refers to Absorption, Distribution, Metabolism and Excretion.



ABSORPTION

A compound's ability to pass through barriers such as the intestinal lining, the nasal lining, the lungs or the skin.

DISTRIBUTION

How the compound is distributed around the body and its propensity to accumulate in certain tissues or organs.

METABOLISM

How the body breaks down the compound, normally by the liver. The key issues are drug-drug interactions, and the effects of the metabolites (the new chemicals created as a result of metabolism).

EXCRETION

The rate and process through which the compound exits the body.

Absorption of Therapeutic Proteins

- **Oral Administration**
- **Peptides** and **proteins**, unlike conventional small molecule drugs, are **generally not** therapeutically active **upon oral administration.**
- **The lack of systemic bioavailability** after oral administration is mainly caused by two factors:

1. High gastrointestinal enzyme activity.
2. Low permeability through the gastrointestinal mucosa.

Absorption of Therapeutic Proteins

- Since oral administration is still a highly desirable route of delivery for protein drugs due to its **convenience, cost-effectiveness, patient acceptance**.
- Suggested approaches to **increase the oral bioavailability** of protein drugs include :

1. **Encapsulation** into micro-or nanoparticles thereby protecting proteins from intestinal degradation.
2. **Chemical conjugations** to improve the resistance to degradation and the permeability of the protein drug.
3. Coadministration of **protease inhibitors** has also been suggested for the inhibition of enzymatic degradation.

Absorption of Therapeutic Proteins

- **Parenteral Administration**
- Major routes of administration include intravenous (IV), subcutaneous (SC), and intramuscular (IM) administration.
- **IV administration** of peptides and proteins offers the advantage of circumventing pre-systemic degradation, thereby **achieving the highest concentration** in the biological system.
- Examples of IV administered proteins: alteplase and recombinant human erythropoietin α.

Absorption of Therapeutic Proteins

One of the potential limitations of SC and IM administration, however, are the **pre-systemic degradation** processes frequently associated with these administration routes, resulting in a **reduced bioavailability** compared to IV administration.

Other potential factors that may limit the rate and/or extent of uptake of proteins after SC or IM administration include:

a) Variable local blood flow

b) Injection trauma

c) Limitations of uptake into the systemic circulation related to effective capillary pore size

- Several peptide and protein therapeutics such as **insulin** are administered as SC injections.

Distribution of Protein Therapeutics

- The rate and extent of protein distribution is determined largely by their:

1. Size and molecular weight
2. Physiochemical properties (e.g., charge, lipophilicity)
3. Binding to transport proteins
4. Their dependency on active transport processes

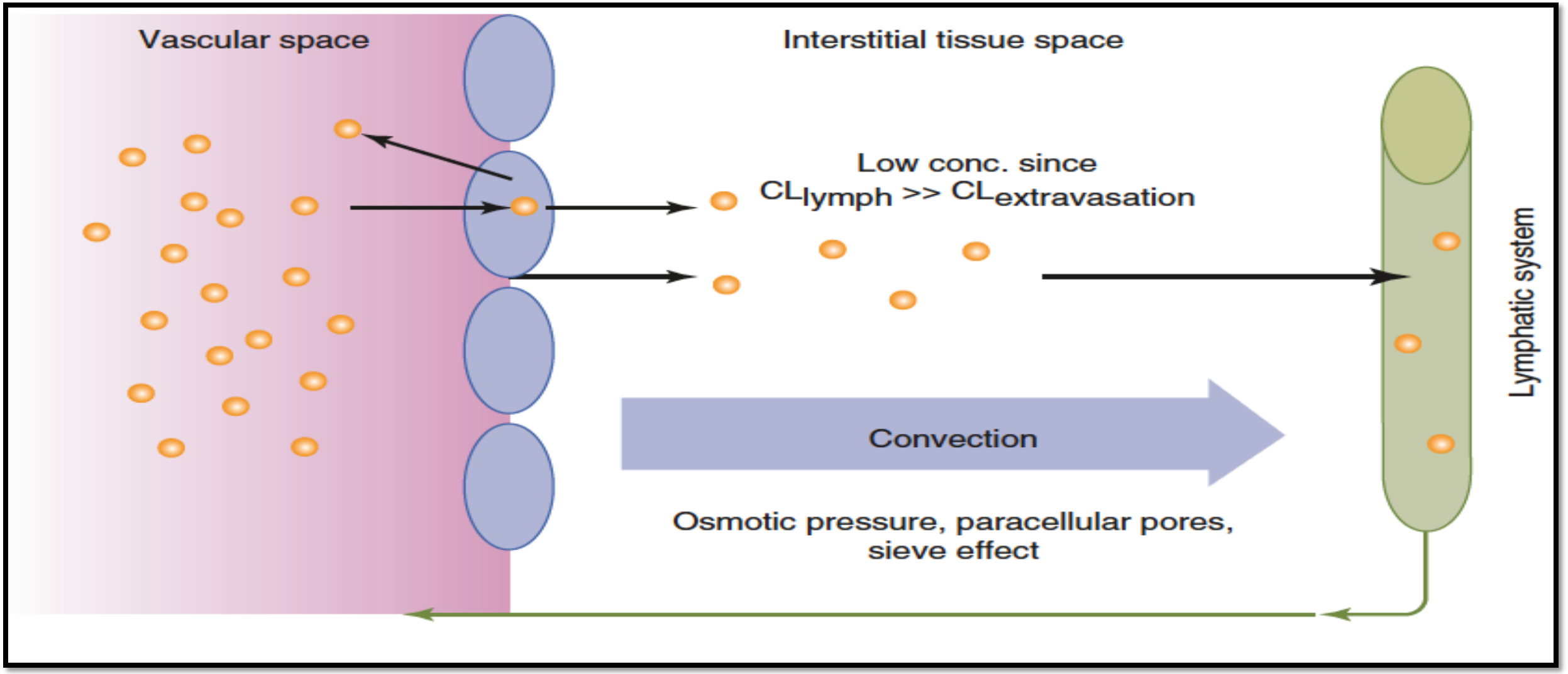
Distribution of Protein Therapeutics

- Since **most therapeutic proteins have high molecular weights** and are thus **large in size.**
- Their apparent **volume of distribution is usually small** and limited **to the volume of the extracellular space** due to their limited mobility secondary to impaired passage through bio-membranes.

Distribution of Protein Therapeutics

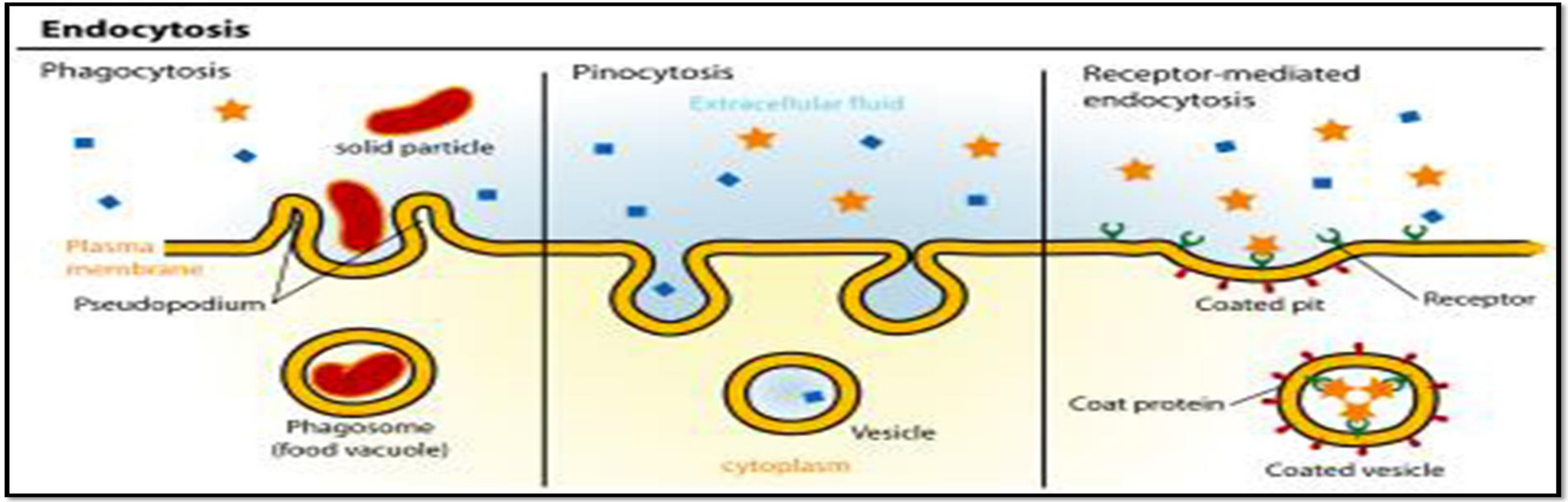
- **In contrast to small molecule drugs, protein transport** from the vascular space into the interstitial space of tissues is largely mediated by **convection rather than diffusion, following the unidirectional fluid flux** from the **vascular space through paracellular pores into the interstitial tissue space.**
- The subsequent removal from the tissues is accomplished by **lymph drainage** back into the **systemic circulation.**

Distribution of Protein Therapeutics



Distribution of Protein Therapeutics

- Another, but much **less prominent** pathway for the movement of protein molecules from the vascular to the interstitial space is transcellular migration **via endocytosis**.



Distribution of Protein Therapeutics

- **Protein Binding of Protein Therapeutics:**
- Another factor that can influence the distribution of therapeutic peptides and proteins is **binding to endogenous protein structures.**
- Physiologically active endogenous peptides and proteins frequently interact with **specific binding proteins** involved in their **transport and regulation**.
- Furthermore, interaction with binding proteins **may enable or facilitate cellular uptake** processes and **thus affect the drug's pharmacodynamics**.
- The binding protein may either **prolong the circulation time** by acting as a storage depot or it may **enhance the clearance**.

Elimination of Protein Therapeutics

- **Protein therapeutics** are generally subject to the **same catabolic pathways** as **endogenous** or **food proteins**.
- The end products of protein metabolism are thus amino acids that are **reutilized** in the endogenous amino acid pool for the new biosynthesis of structural or functional proteins in the human body.
- **Non-metabolic elimination pathways** such as **renal** or **biliary excretion** are **negligible** for most proteins.

Metabolism (Proteolysis)

- In contrast to small-molecule drugs, metabolic degradation of peptides and protein therapeutics by proteolysis can occur non-specifically nearly everywhere in the body.
- The metabolic rate for protein degradation generally increases with decreasing molecular weight from large to small proteins to peptides, but is also dependent on other factors such as size, charge, lipophilicity, functional groups, and glycosylation pattern as well as secondary and tertiary structure.

Proteolysis

- Proteolytic enzymes such as proteases and peptidases are widely spread throughout the body.
- Sites capable of extensive peptide and protein metabolism are not only limited to the liver, kidneys, and gastrointestinal tissue, but also include blood and vascular endothelium as well as other organs.
- The proteases and peptidases are located within cells and out side the cells.
- The peptidases and proteases in the GIT and in lysosomes are relatively unspecific, soluble peptidases in the interstitial space and exopeptidases on the cell surface have a higher selectivity and determine the specific metabolism pattern of an organ.

Gastrointestinal Protein Metabolism

- As pointed out earlier, the GIT is a major site of protein metabolism with high proteolytic enzyme activity due to its primary function to digest dietary proteins.
- Thus, gastrointestinal metabolism is one of the major factors limiting systemic bioavailability of orally administered protein drugs.
- The metabolic activity of the GIT is not limited to orally administered proteins. Parenterally administered peptides and proteins may also be metabolized in the intestinal mucosa following intestinal secretion.
- At least 20% of the degradation of endogenous albumin, for example, has been reported to take place in the gastrointestinal tract.

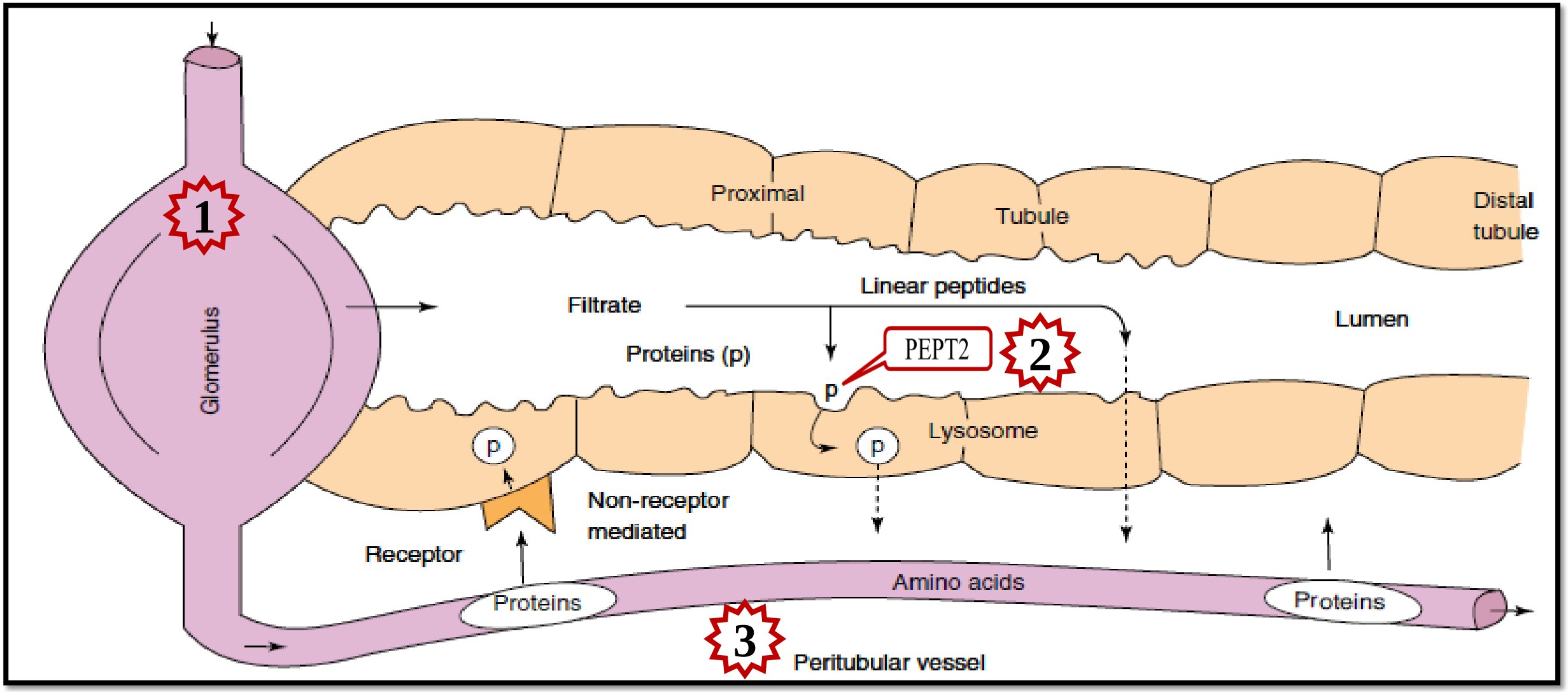
Renal Protein Metabolism

- The kidneys are a major site of protein metabolism for smaller-sized proteins that undergo glomerular filtration.
- The size-selective cutoff for glomerular filtration is approximately 60 kDa although the effective molecule radius based on molecular weight and conformation is probably the limiting factor.
- Glomerular filtration is most efficient, however, for proteins smaller than 30 kDa.
- Peptides and small proteins (< 5 kDa) are filtered very efficiently, and their glomerular filtration clearance approaches the GFR (~120 mL/min in humans).
- For molecular weights exceeding 30 kDa, the filtration rate falls off sharply.

Renal Protein Metabolism

- In addition to size selectivity, charge selectivity has also been observed for glomerular filtration where anionic macro-molecules pass through the capillary wall less readily than neutral macromolecules, which in turn pass through less readily than cationic macromolecules.
- Renal metabolism of peptides and small proteins is mediated through three highly effective processes. As a result, only tiny amounts of intact protein are detectable in urine.

Renal Protein Metabolism



Renal Protein Metabolism

- The first mechanism involves glomerular filtration of larger.
- Complex peptides and proteins followed by reabsorption into endocytic vesicles in the proximal tubule and subsequent hydrolysis into small peptide fragments and amino acids.
- This mechanism of elimination has been described for IL-2, IL-11, growth hormone, and insulin.

Renal Protein Metabolism

- The second mechanism entails glomerular filtration followed by intraluminal metabolism, predominantly by exopeptidases in the luminal brush border membrane of the proximal tubule.
- The resulting peptide fragments and amino acids are reabsorbed into the systemic circulation.
- This route of disposition applies to small linear peptides such as glucagon and LH-RH.

Renal Protein Metabolism

- Recent studies implicate the proton-driven peptide transporters especially proton driven peptide transporters (PEPT2) as the main route of cellular uptake of small peptides and peptide-like drugs from the glomerular filtrates (in the proximal tubule region).
- These high-affinity/ low capacity transport proteins seem to exhibit selective uptake of di and tripeptides.

Renal Protein Metabolism

- For both mechanisms, glomerular filtration is the dominant, rate-limiting step as subsequent degradation processes are not saturable under physiologic conditions.
- Due to this limitation of renal elimination, the renal contribution to the overall elimination of proteins is dependent on the proteolytic activity for these proteins in other body regions.

Renal Protein Metabolism

- The third mechanism of renal metabolism is peritubular extraction of peptides and proteins from post-glomerular capillaries with subsequent intracellular metabolism.

Hepatic Protein Metabolism

- Aside from renal and gastrointestinal metabolism, the liver may also play a major role in the metabolism of protein therapeutics.
- Exogenous as well as endogenous proteins undergo proteolytic degradation to dipeptides and amino acids that are reused for endogenous protein synthesis.
- Proteolysis usually starts with endopeptidases that attack in the middle part of the protein, and the resulting oligopeptides are then further degraded by exopeptidases.


Thank You