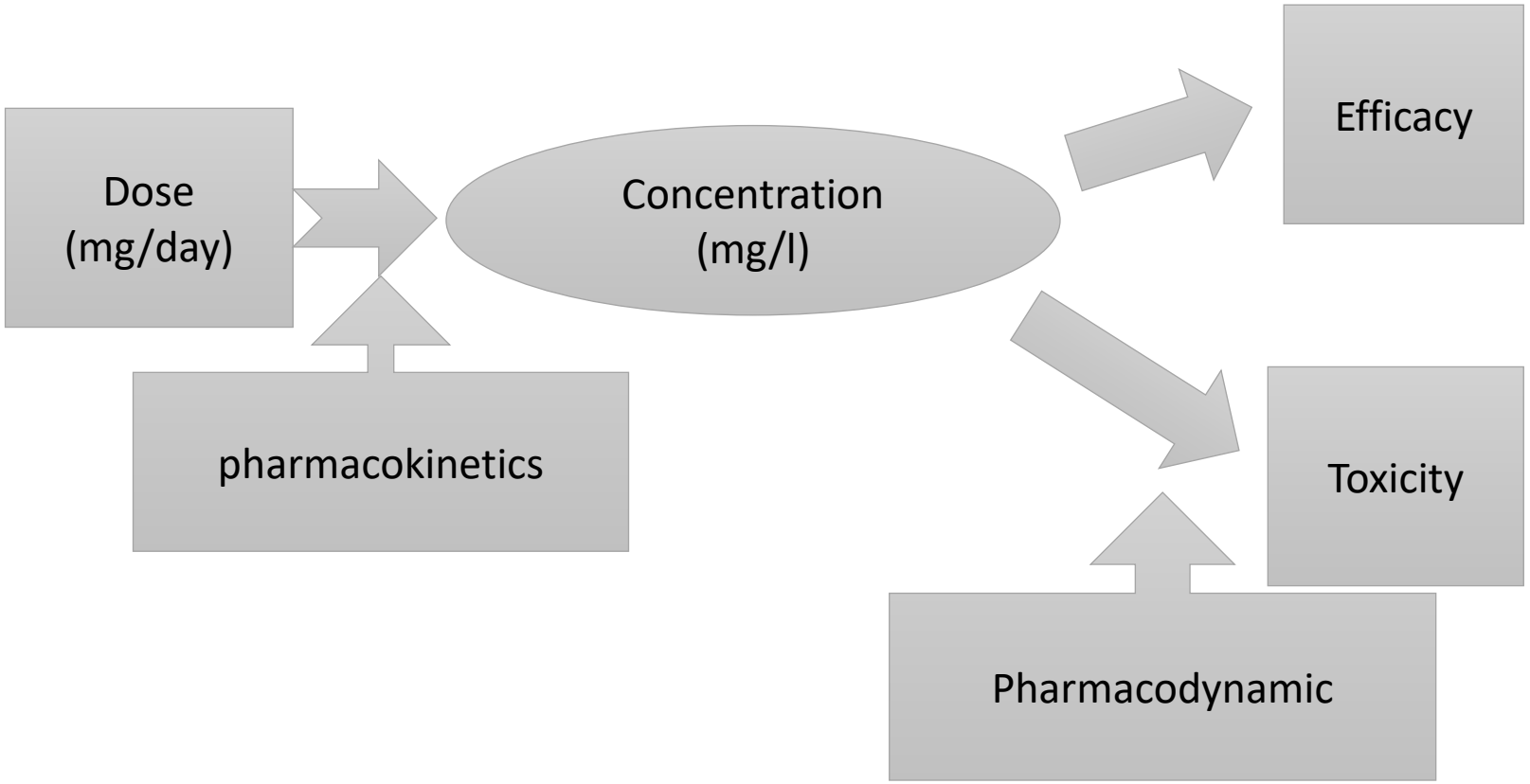
Pharmacokinetics and Pharmacodynamics of Peptide and Protein Drugs

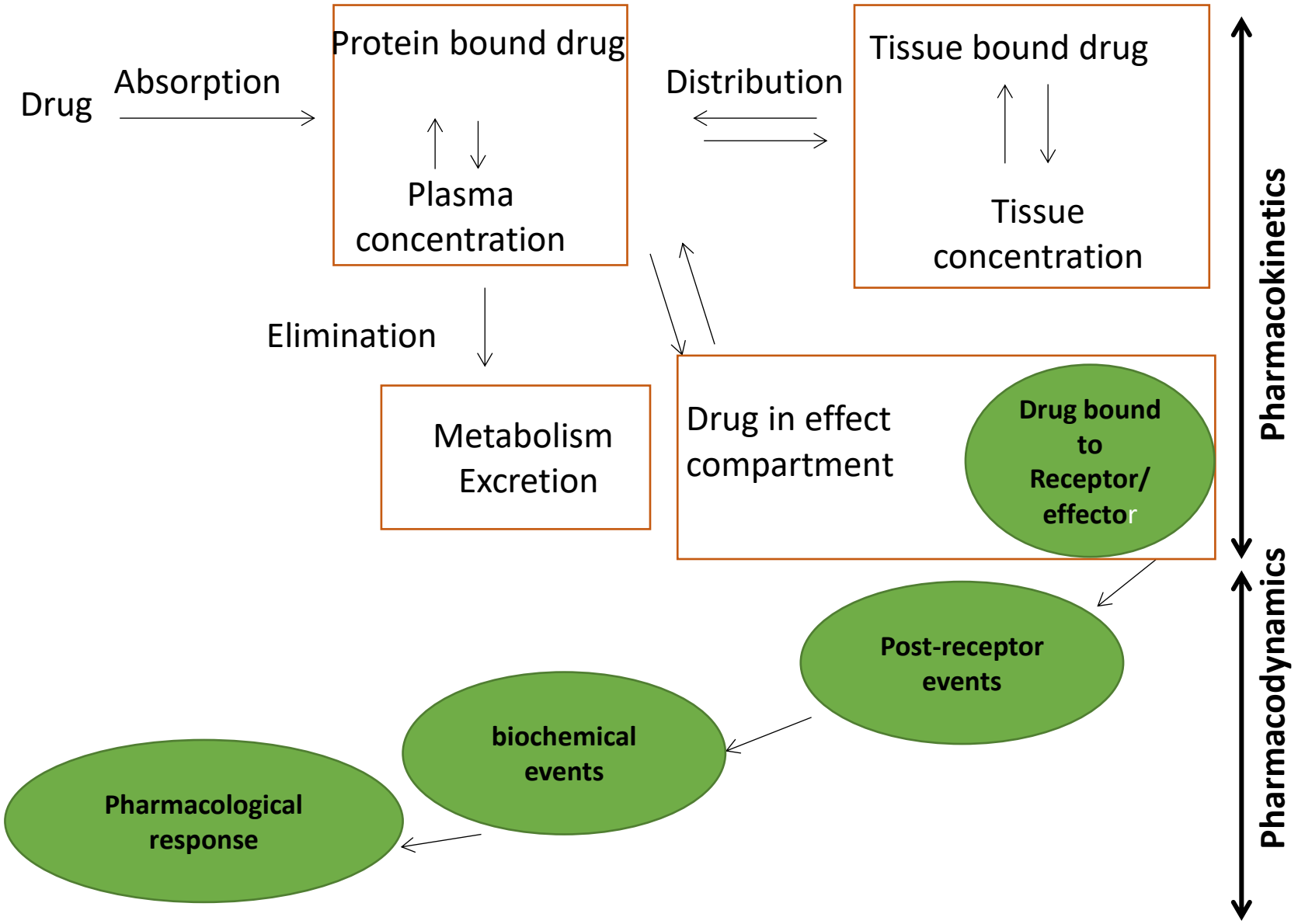
The central paradigm of clinical pharmacology: The dose-concentration-effect relationship



Introduction

- Pharmacokinetics describes **(the time course 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, pharmacodynamic characterizes the intensity of a drug effect or toxicity resulting from certain drug concentration in a body fluid, usually at the assumed site of drug action. It can be simplified to *what the drug does to the body*


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

Importance of pharmacokinetic and pharmacodynamic principles include:

1. **Large extent equally applicable to protein and peptide drugs as they are to traditional small molecule-based therapeutics**.

2. **Deviations from some of these principles** and additional challenges with regard to the characterization of the pharmacokinetics and pharmacodynamics of peptide and protein therapeutics, however, **arise from some of their specific properties:**

A- Their structural similarity to endogenous structural proteins and nutrients.

B- Their intimate involvement in physiologic processes on the molecular level and regulatory feedback mechanisms.

C- The analytical challenges to identify and quantify them in the presence of a myriad of similar molecules.

D- Their large molecular weight and macromolecules character (for proteins).

E- Their definition by the production process in a living organism rather than a chemically defined structure and purity as it is the case for small-molecule drugs

Pharmacokinetics of protein therapeutics

- The in vivo disposition of peptide and protein drugs may often be predicted to a large degree from their physiological function.

❖**For example:** Peptides, have hormone activity, (short elimination half-lives)

- A- desirable for a close regulation of their endogenous levels
- B- thus function.

More details:

- **Insulin,** for example shows **dose-dependent elimination with a relatively short half-life** of 25 and 52 minutes at 0.1 and 0.2 U/kg, respectively.

- **Albumin or long-term immunity functions such as immunoglobulins** are contrary to that **(proteins that have transport tasks) have elimination half-lives of several days**, which enables and ensures the continuous maintenance of physiologically necessary concentrations in the blood stream.

Absorption of protein therapeutics

- *Enteral Administration*

  Peptides and proteins, unlike conventional small molecule drugs, are generally **not therapeutically active upon oral administration.**

- The lack of systemic bioavailability is mainly caused by two factors;

(1) **high gastrointestinal enzyme activity**

(2) **low permeability mucosa.**

- Thus, although various factors such as **permeability, stability and gastrointestinal transit time** can affect **the rate and extent of absorption** of orally administrated proteins, **molecular size** is generally considered the ultimate obstacle.

- **Advantages of Oral administration** is still desired route of delivery for protein drugs due to:

1. **Its convenience**
2. **Cost-effectiveness**
3. **painlessness**

Strategies to overcome the obstacles associated with oral delivery of proteins

Suggested approaches to increase the oral bioavailability of protein drugs include **encapsulation into micro- or nanoparticles** thereby protecting proteins from intestinal degradation.

Other strategies are **chemical modifications s**uch as amino acid backbone modifications and chemical conjugations to improve the resistance to degradation and the permeability of protein drug.

Coadministration of protease inhibitors for the inhibition of enzymatic degradation.

- ***Parenteral Administration***

  Most **peptide and protein drugs** are currently **formulated as parenteral formulations** because of their **poor oral bioavailability**.

- **Major routes of administration** include intravenous (**IV**), subcutaneous (**SC**), and intramuscular (**IM**) administration.

- In addition, **other non-oral administration** pathways are utilized, including **nasal, buccal, rectal, vaginal, transdermal, ocular and pulmonary** drug delivery.

- IV administration of peptides and proteins

↓

avoiding presystemic degradation

↓

achieving the highest concentration in the biologic system.

- **Exception:** IM or SC injections may be more appropriate on achieving biologic activity of the product.

(Since IV administration as either a bolus dose or constant rate infusion, however, may not always provide the desired concentration-time profile).

- For example,

1. **luteinizing hormone-releasing hormone (LH-RH)** in **bursts** stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), whereas a **continuous baseline level** *will suppress the release of these hormones.*

2. **To avoid the high peaks from an IV administration of leuprorelin, an LH-RH agonist, a long acting monthly depot injection of the drug** is approved for the treatment of prostate cancer.

IV versus SC

- A recent study **comparing SC versus IV administration of epoetin-α** in **hemodialysis patients (SC route maintain the homatocrit in a desired target range with a lower average weekly dose of epoetin- α compared to IV).**

- The hematocrit also known as packed cell volume (PCV) or erythrocyte volume fraction (EVF), is the volume percentage (%) of red blood cells in blood.

Limitation of SC and IM

A- One of the potential limitation are the **presystemic degradation process** frequently associated with these administration routes, **resulting in a reduced bioavailability compared to IV administration**.

- The pharmacokinetically derived apparent absorption rate constant k_{app} for protein drugs administrated via these administration routes is thus the combination of absorption into the systemic circulation and presystemic degradation at absorption site, i.e., the sum of a true first-order absorption rate constant k_a and a first-order degradation rate constant.

- The true absorption rate constant k_a can then be calculated as:

$$K_a = F.\ K_{app}$$

Where F is the bioavailability compared to IV administration.

B- **Other potential factors that may limit bioavailability of proteins after SC or IM administration** include:

1. **variable local blood flow**
2. **injection trauma**
3. **limitation of uptake into systemic circulation related to effective capillary pore size and diffusion.**

- Following an SC injection, peptide and protein therapeutics may enter the systemic circulation either via blood capillaries or through lymphatic vessels.

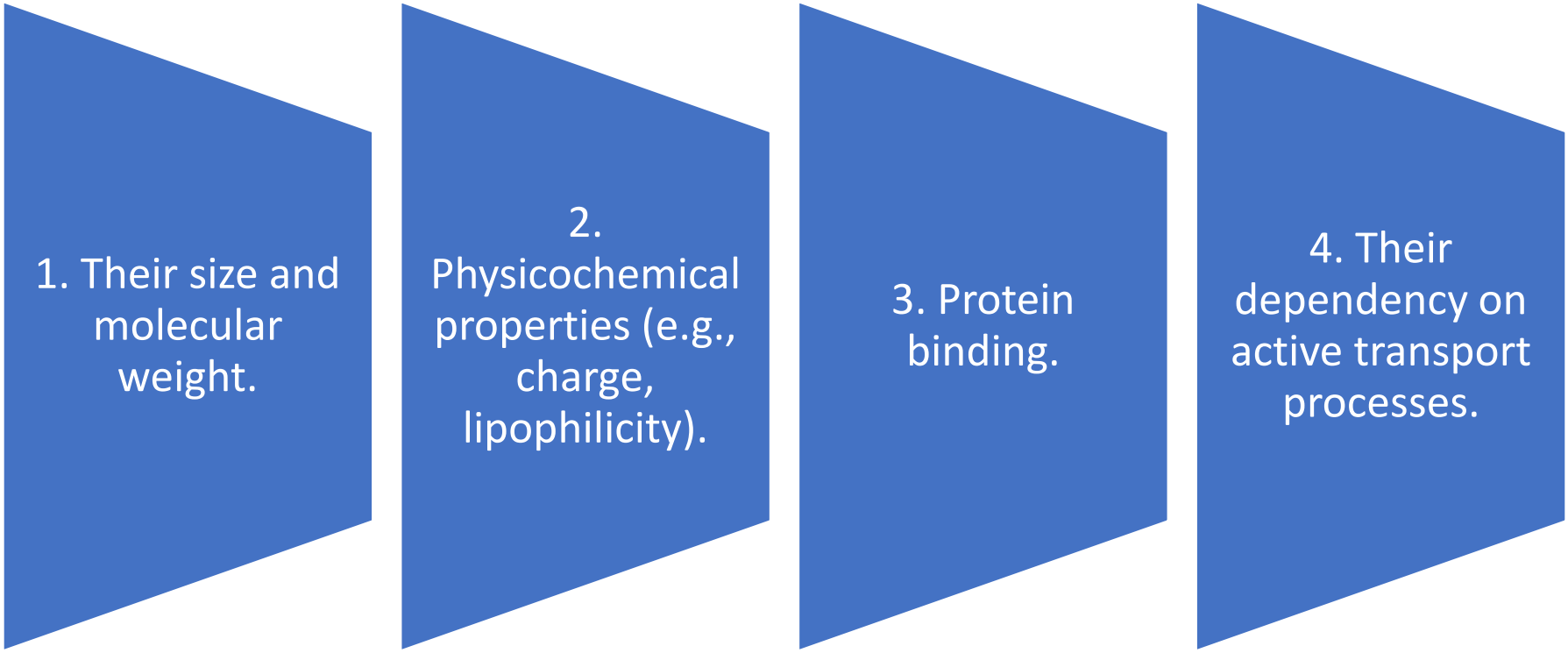
In general

i. macromolecules larger than 16 kDa are predominantly absorbed into the lymphatics

ii. under 1 kDa are mostly absorbed into blood circulation.

Distribution Mechanisms and Volumes

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



1) 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 extracellular space due to:

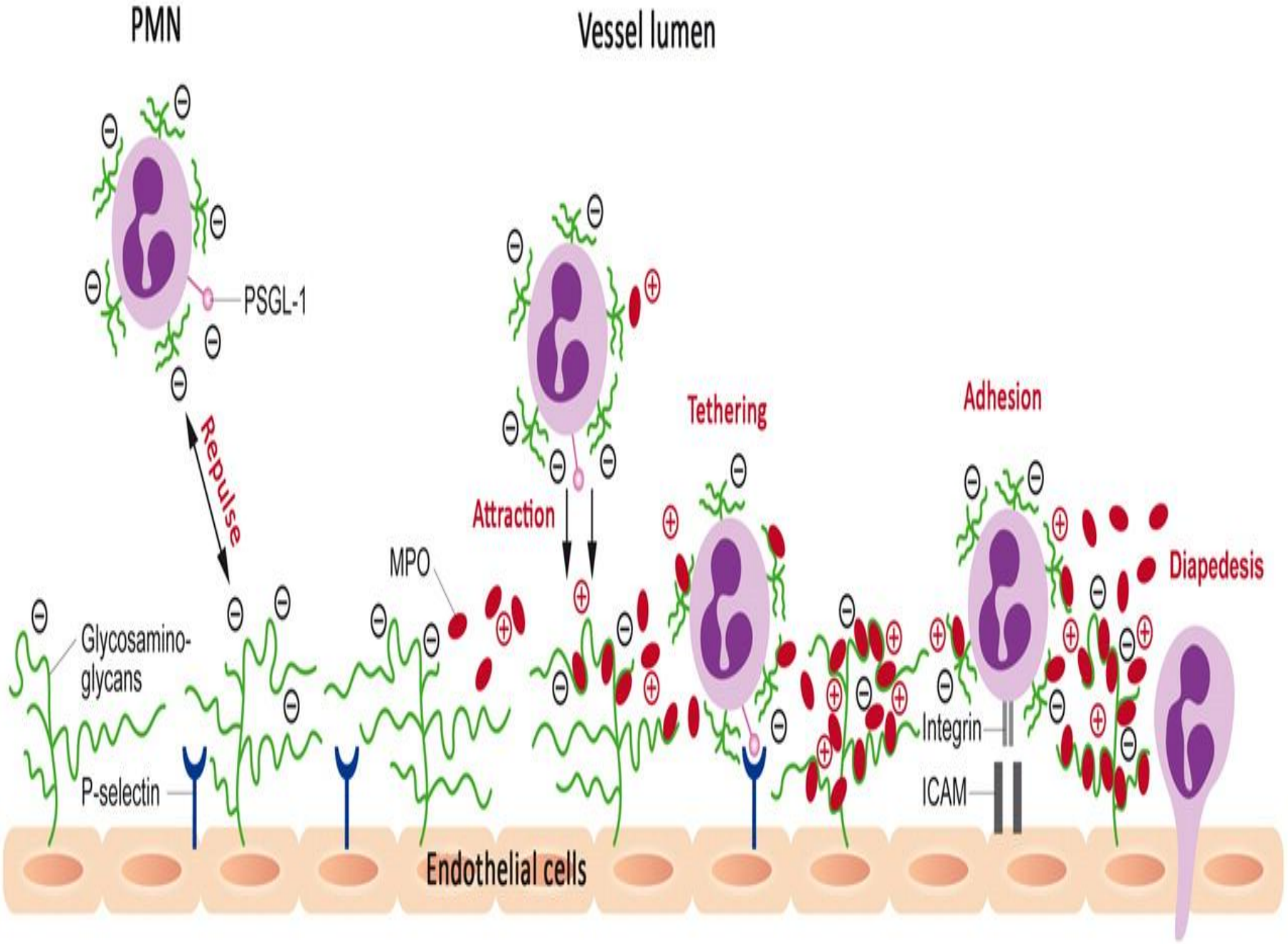
Their limited mobility secondary to impaired passage through biomembranes.

- Thus size-dependent sieving of macromolecules through the capillary walls.

2) Charge may also play an important role in the biodistribution of proteins.

✓It has been suggested that the electrostatic attraction (between positively charged proteins and negatively charged cell membranes) might increase the rate and extent of tissue distribution.

Note: Most cell surfaces are negatively charged because of their abundance of glycoaminoglycans in the extracellular matrix.


PMN
Vessel lumen
PSGL-1
Repulse
Attraction
MPO
Tethering
Adhesion
Diapedesis
Glycosamino-
glycans
P-selectin
Integrin
ICAM
Endothelial cells

3) Active tissue uptake and binding to intra- and extravascular proteins

Increase the apparent volume of distribution of protein drugs.

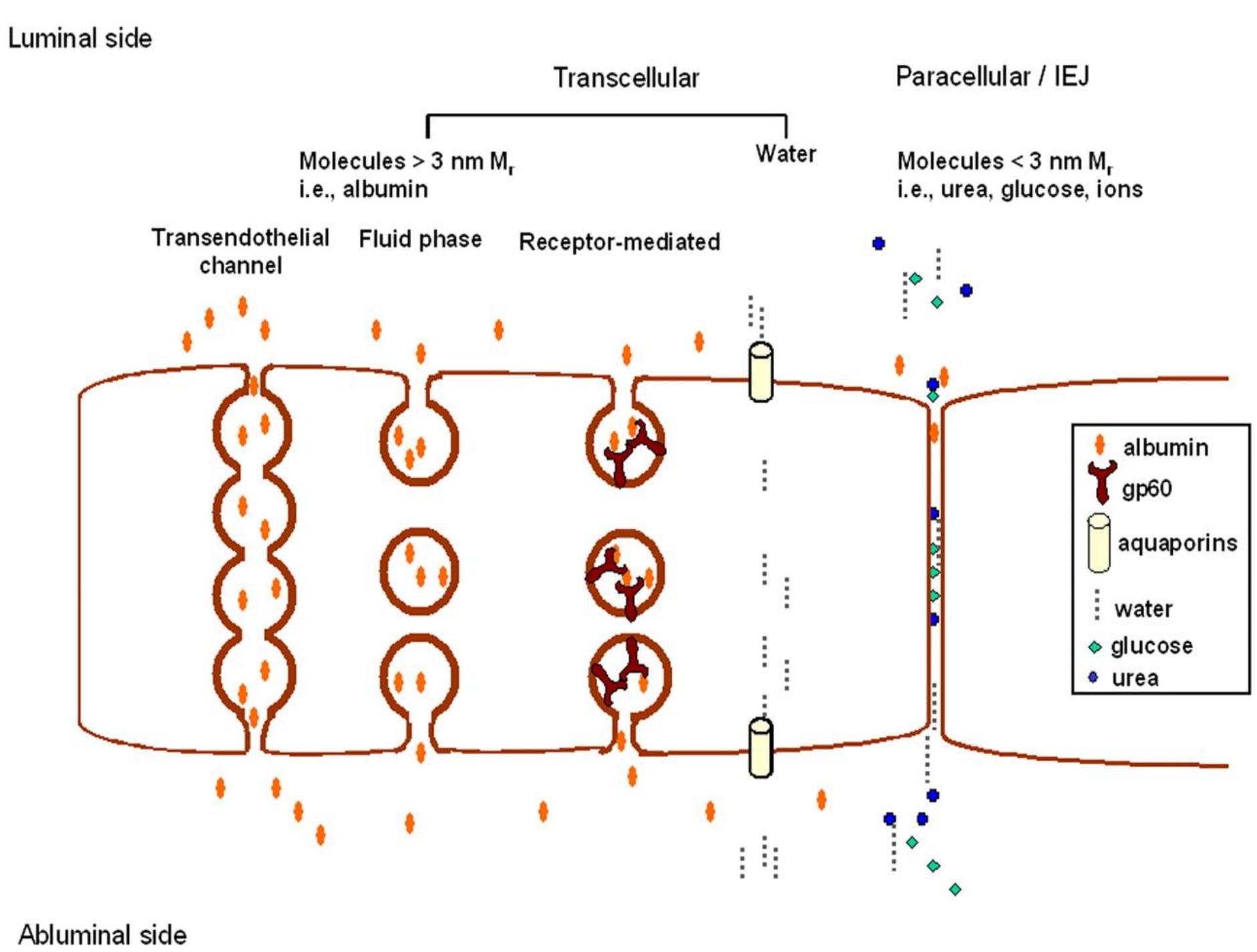
(**For example :** Volume of distribution of interferon β-Ib is 2.8 L/ Kg)

Enter: In contrast to small molecule drugs, **protein transport from vascular space into the interstitial space of tissues** is largely **mediated by convection** *rather than diffusion.*

(unidirectional fluid flux from the vascular space through paracellular pores into the interstitial tissue space).

Exit: The subsequent removal from the tissues is accomplished by **lymph drainage back into the systemic circulation.**

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


Luminal side
Transcellular
Paracellular / IEJ
Molecules > 3 nm M_r
i.e., albumin
Water
Molecules < 3 nm M_r
i.e., urea, glucose, ions
Transendothelial channel
Fluid phase
Receptor-mediated
albumin
gp60
aquaporins
water
glucose
urea
Abluminal side

Pharmacokinetics of proteins

- **After IV administration, peptides and proteins usually follow** a biexponential plasma concentration-time profile that can best be described by **a two-compartment pharmacokinetic model.**

The **central compartment** represents primarily the **vascular space and the interstitial space** of well-perfused organs with permeable capillary walls, including the liver and kidney.

- The **peripheral compartment** is more reflective of concentration-time profile in the interstitial space of slowly equilibrating tissues.

- The central compartment in which proteins initially distribute **after IV** has thus typically a **volume of distribution** equal or slightly larger than the plasma volume, i.e., **3 to 8 L**.

- **The total volume of distribution frequently comprises with 14 to 20 L** not more than 2 to 3 times the initial volume of distribution.

Determination volume of distribution for proteins

- The pharmacokinetic calculations of volume of distribution may be problematic for many protein therapeutics.

- Non-compartmental determination of volume of distribution at steady state (V_{SS}) using statistical moment theory assume first-order disposition processes with elimination occurring from:

1- Rapidly equilibrating or central compartment (liver and kidney).

2.In addition to the proteolysis and receptor-mediated elimination in peripheral tissues may constitute a substantial fraction of the overall elimination process.

- If **protein** therapeutics are **eliminated** from slowly equilibrating tissues at a **rate greater than their distribution process**

Substantial error in the volume of distribution assessment may occur.

Solution:

These challenges in characterizing the distribution of protein therapeutics can only be overcome by **determining actual protein concentrations in the tissue by** :

1- Biopsy or necropsy.

2- Via biodistribution studies with radiolabeled compound and / or imaging techniques.

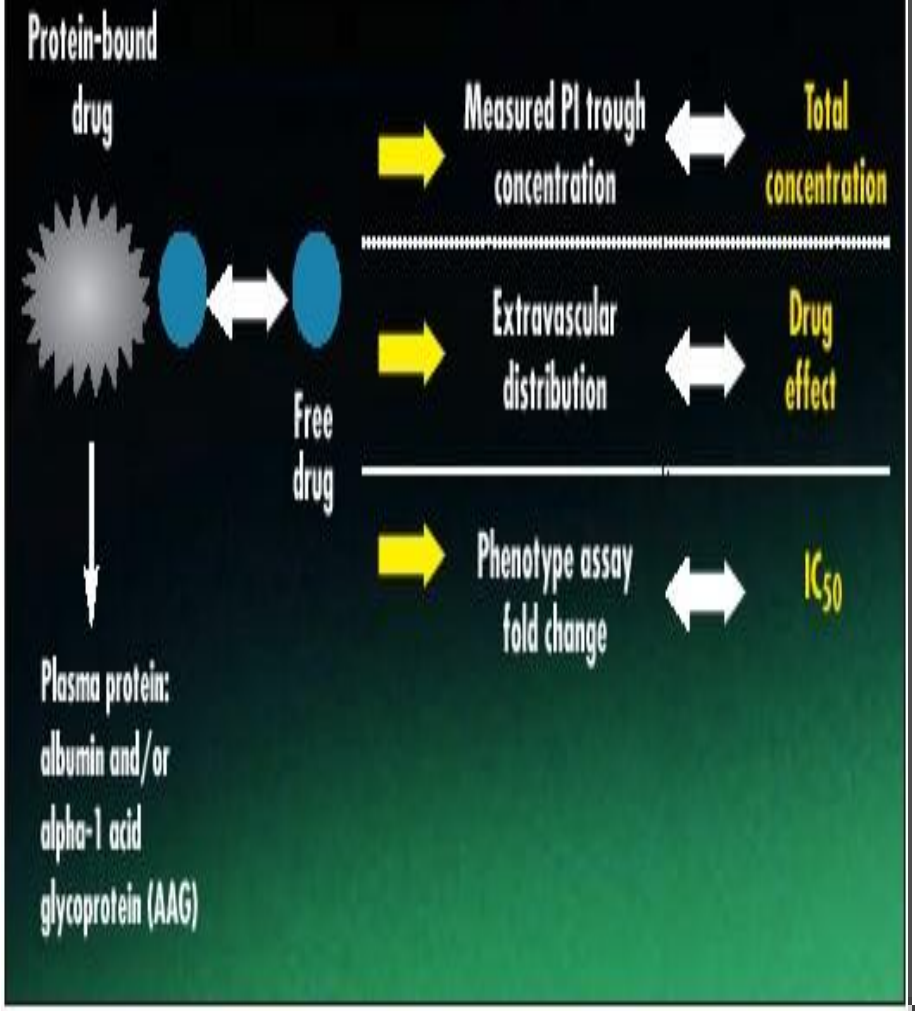
4) Protein Binding of Protein Therapeutics

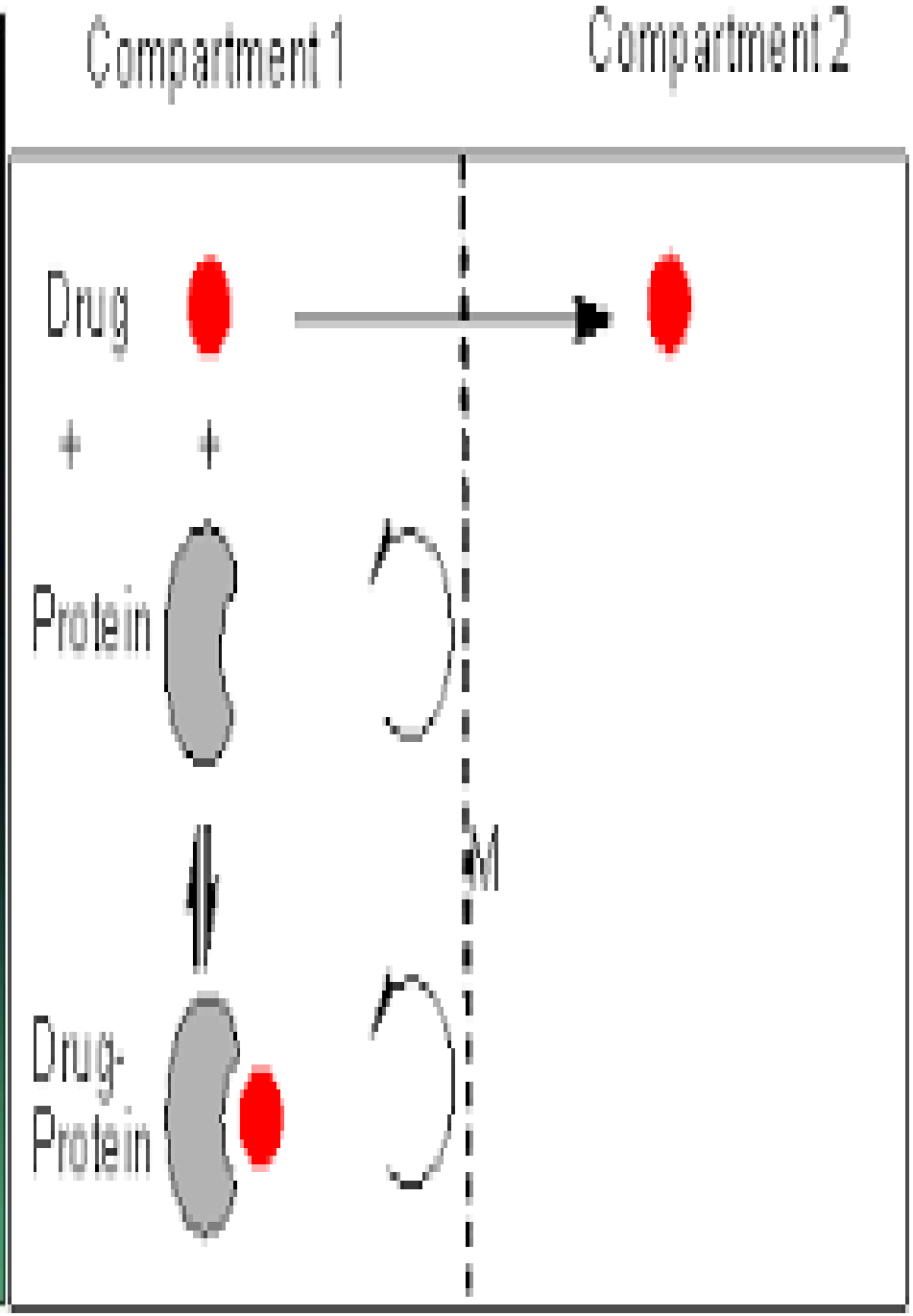
Another factor that can influence the distribution of therapeutic peptides and proteins is:

The binding of active endogenous protein and peptides (therapeutically administered proteins) with specific binding proteins involved in their transport and regulation.

Enable or facilitate cellular uptake processes and thus affect the drug's pharmacodynamics.

Figure 3. **Binding of antiretrovirals to plasma proteins limits the amount of free drug available to inhibit HIV and affects pharmacokinetic values such as the IQ (trough/IC_{50}).**





- It is a **general pharmacokinetic principle**, which is also applicable to proteins (**only the free, unbound fraction of a drug substance is accessible to distribution and elimination processes as well as interaction with its target structures at the site of action**) for example a receptor or ion channel.

Thus **protein binding** may affect the pharmacodynamics, but **also disposition properties of protein therapeutics**.

- **Protein binding affects:**

1. **The unbound fraction of a protein drug and thus the fraction available to exert pharmacological activity.**

2. **Prolongs protein circulation time by acting as a storage depot or it enhances protein clearance.**

Examples

- **Recombinant cytokines**, for example, may after IV administration encounter cytokine-binding proteins including (soluble cytokine receptors and anti-cytokine antibodies).
- In either case, the binding protein may either prolong the cytokine circulation time by acting as a storage depot or it may enhance the cytokine clearance.

Examples

- **Growth hormone,** as another example, **has at least two binding protein in plasma.**

This protein binding substantially:

A- reduce growth hormone elimination with a tenfold smaller clearance of total compared to free growth hormone

B- decreases its activity via reduction of receptor interaction.

Specific protein bindings

- Apart from these specific bindings, **peptides and proteins may also be non-specifically bound to plasma proteins.**

- For example, **metkephamid, a metenkephalin analog**, was described to be **44% to 49% bound to albumin**, and **octreotide, a somatostatin analog**, is up to **65% bound to lipoproteins**.

Distribution via Receptor-Mediated Uptake

- Site-specific receptor-mediated uptake

substantially influence and contribute to the distribution of protein therapeutics, as well as to elimination and pharmacodynamics.

- The generally **low volume of distribution** should **not necessarily** be interpreted as low tissue penetration.

- **Receptor-mediated specific uptake into the target organ**

Therapeutically effective tissue concentrations despite a relatively small volume of distribution.

Example

Nartograstim, a recombinant derivative of the granulocyte-colony-stimulating factor (G-CSF)

characterized by a specific, dose-dependent and saturable tissue uptake into the target organ bone marrow

via receptor-mediated endocytosis.

Questions

1. **What is the role of plasma binding proteins for natural proteins?**

- Plasma proteins may act as circulating reservoirs for the proteins that are their ligand. Consequently, the protein ligands may be protected from elimination and distribution. In some cases, protein binding may protect the organism from undesirable, acute effect; in other cases, receptor binding may be facilitated by the binding protein.

2. **Which pathway of absorption is rather unique for proteins after SC injection?**

- Biodistribution from the injection site into the lymphatic system.

3. **Why are protein therapeutics generally not active upon oral administration?**

- The gastrointestinal mucosa is a major absorption barrier for hydrophilic macromolecule such as proteins. In addition, peptide and protein therapeutics are degraded by the extensive peptidase and protease activity in the gastrointestinal tract. Both processes minimize the oral bioavailability of protein therapeutics.

4. **What is the major driving force for the transport of proteins from the vascular to the extravascular space?**

- Protein extravasation, i.e., transport from the blood or vascular space to the interstitial tissue space, is predominantly mediated by fluid convection. Protein molecules follow the fluid flux from the vascular space through pores between adjacent cells into the interstitial space. Drainage of the interstitial space through the lymphatic system allows protein therapeutics to distribute back into the vascular space.