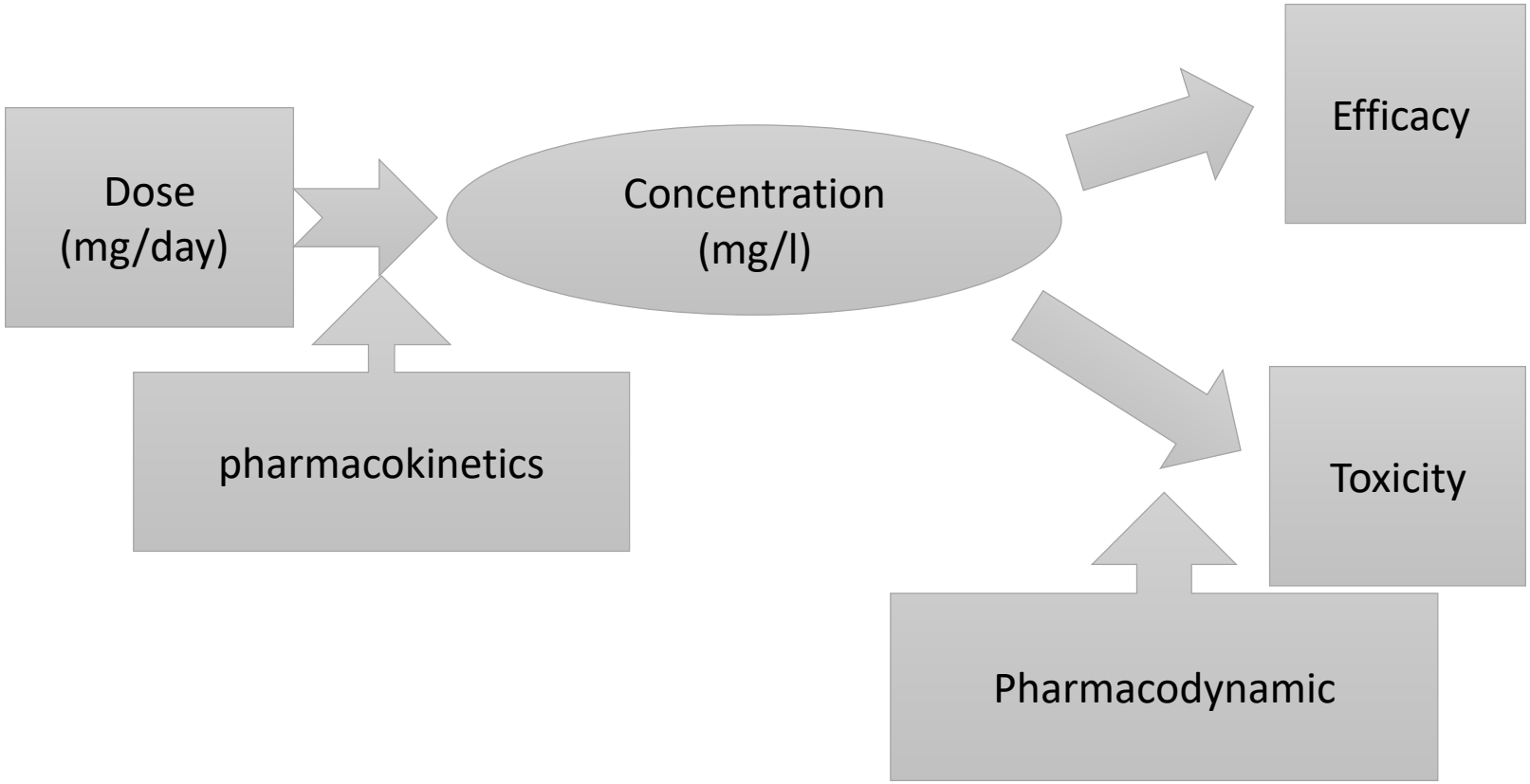
Pharmacokinetics and Pharmacodynamics of Peptide and Protein Drugs

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

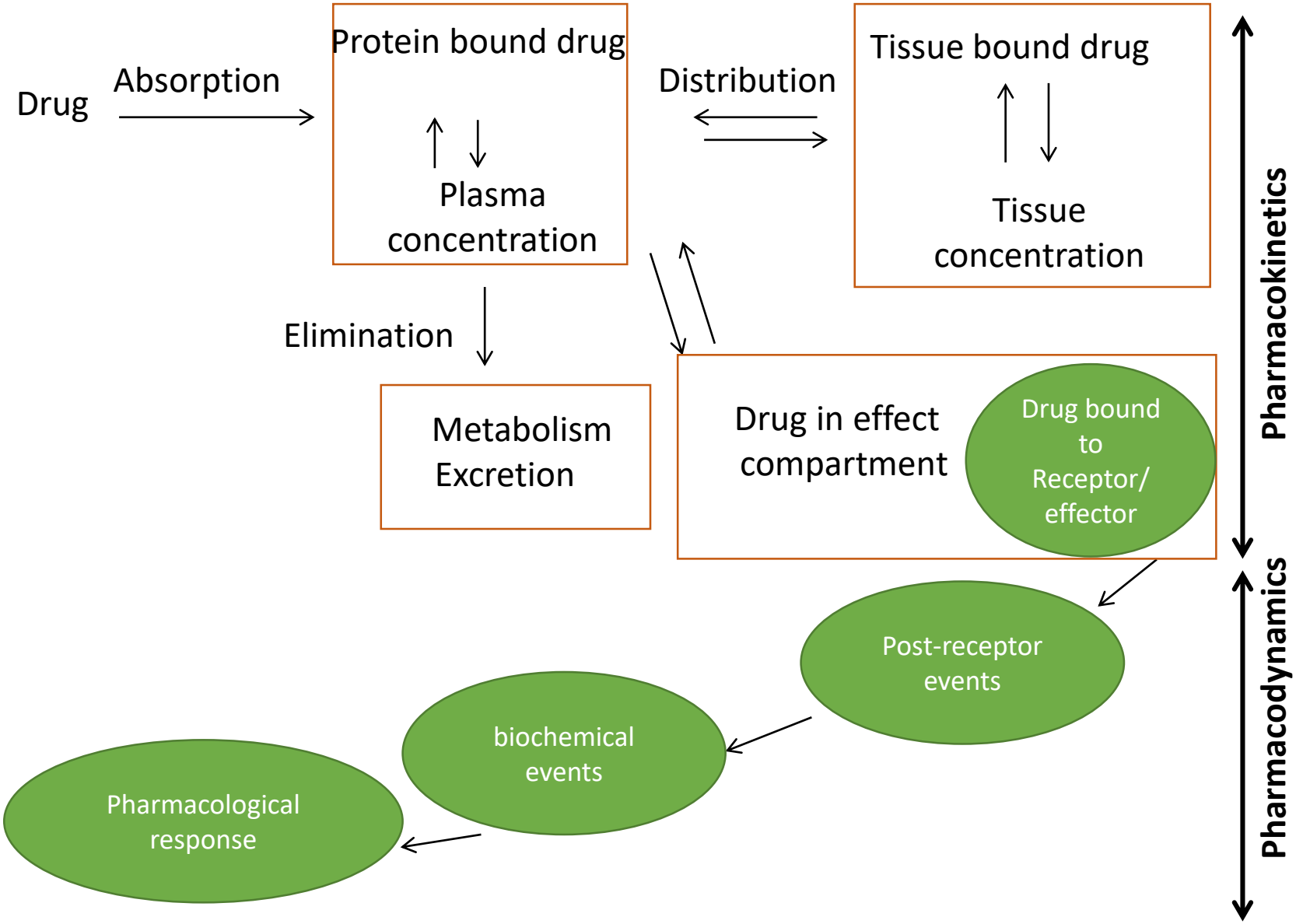


- **Pharmacokinetics** describes (the time course of concentration of a drug in a body fluid, preferably plasma or blood, that results from the administration of a certain dosage regimen).

- It comprises all processes affecting drug absorption, distribution, metabolism, and excretion.

- Simplified, **pharmacokinetics** characterizes *what the body does to the drug.*
- In contrast, 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*

Physiological scheme of pharmacokinetic and pharmacodynamic process



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 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.

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

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 such 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.

- **<u>Exception:</u> 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,

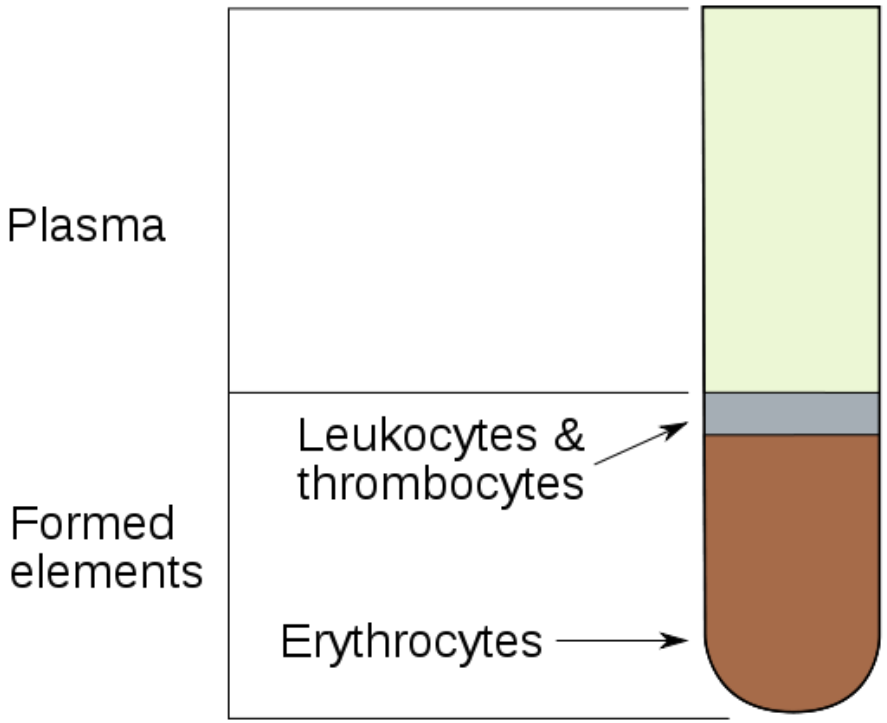
1. luteinizing hormone-releasing hormone (LH-RH) in bursts stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), whereas a continuous baseline level *will suppress the release of these hormones.*

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 epoietin-α in haemodialysis patients to treat uremic anemia (SC route maintain the haematocrit in a desired target range with a lower average weekly dose of epoietin- 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.

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.