Pharmacokinetics I

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DRUG TRANSPORT

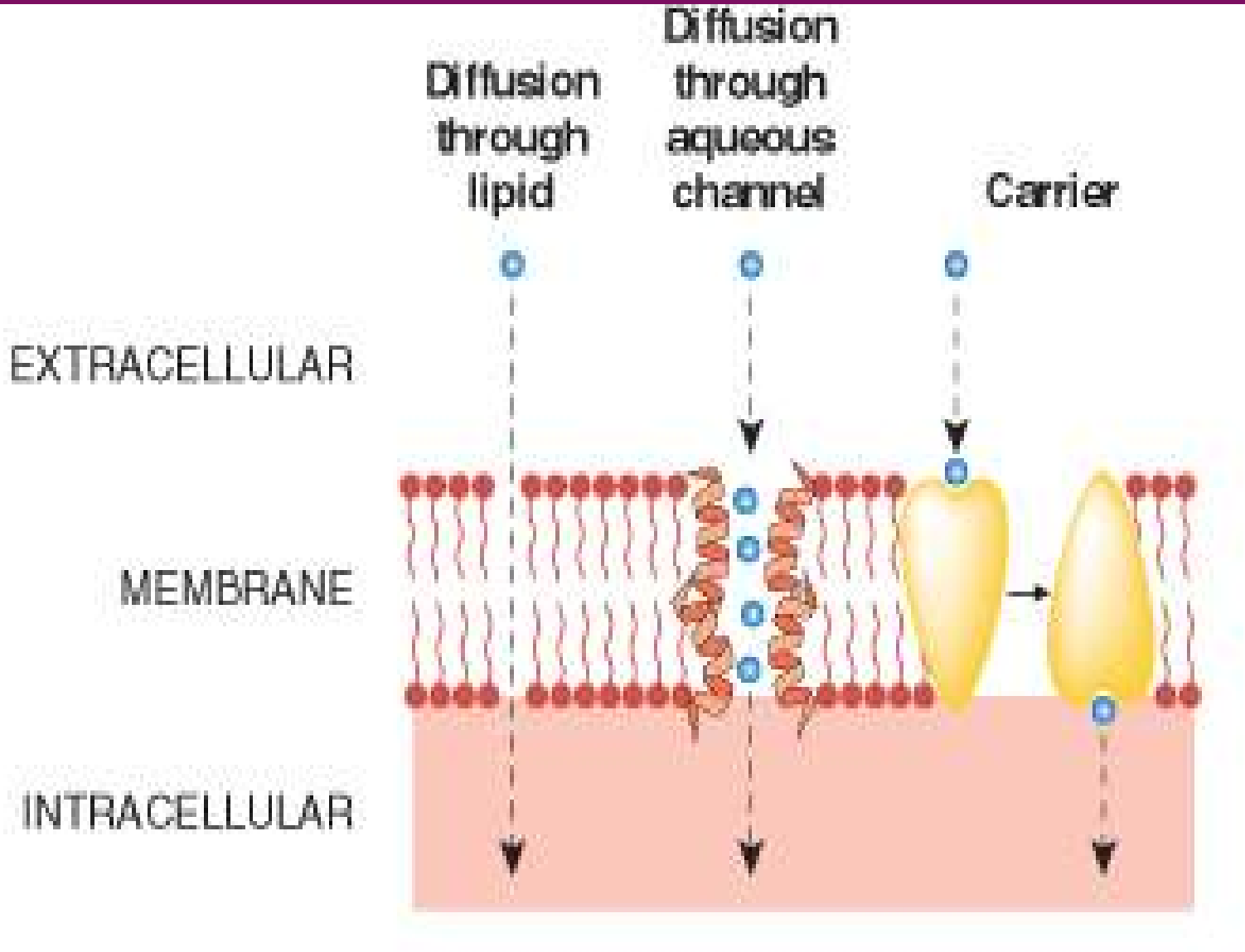
- For a drug to produce a **therapeutic effect**, it must reach to its target and it must accumulate at that site to reach to the **minimum concentration** required to produce the required effect.

- For a drug to reach its site of action in the body, it must cross numerous biological membranes, including the cellular membranes.

These membranes include the gastrointestinal mucosa (if given orally) or lung mucosa (if inhaled), the lymphatic or capillary wall, and the cell wall.

- Drugs in general pass **through** cells rather than **in between** them.

- **Plasma membranes** thus represent the common barrier.
- Most drugs cross membranes by **passive diffusion**.



Diffusion through lipid

- The drug molecule penetrates membranes by passive diffusion along its concentration gradient by virtue of its solubility in the lipid bilayer.

- Such transfer is directly proportional to the magnitude of the concentration gradient and the Lipid: Water partition coefficient of the drug.

The greater the partition coefficient of the drug, the higher is the concentration of the drug in the membrane and the faster is its diffusion.

pH and ionization

- Most drugs are **weak acids** or **weak bases** that are present in solution as both the **ionized** and **non-ionized form**.

- **Non-ionized molecules are usually lipid soluble and can diffuse across cell Membranes**

In contrast, ionized molecules are usually unable to penetrate the lipid membrane because of their low lipid solubility.

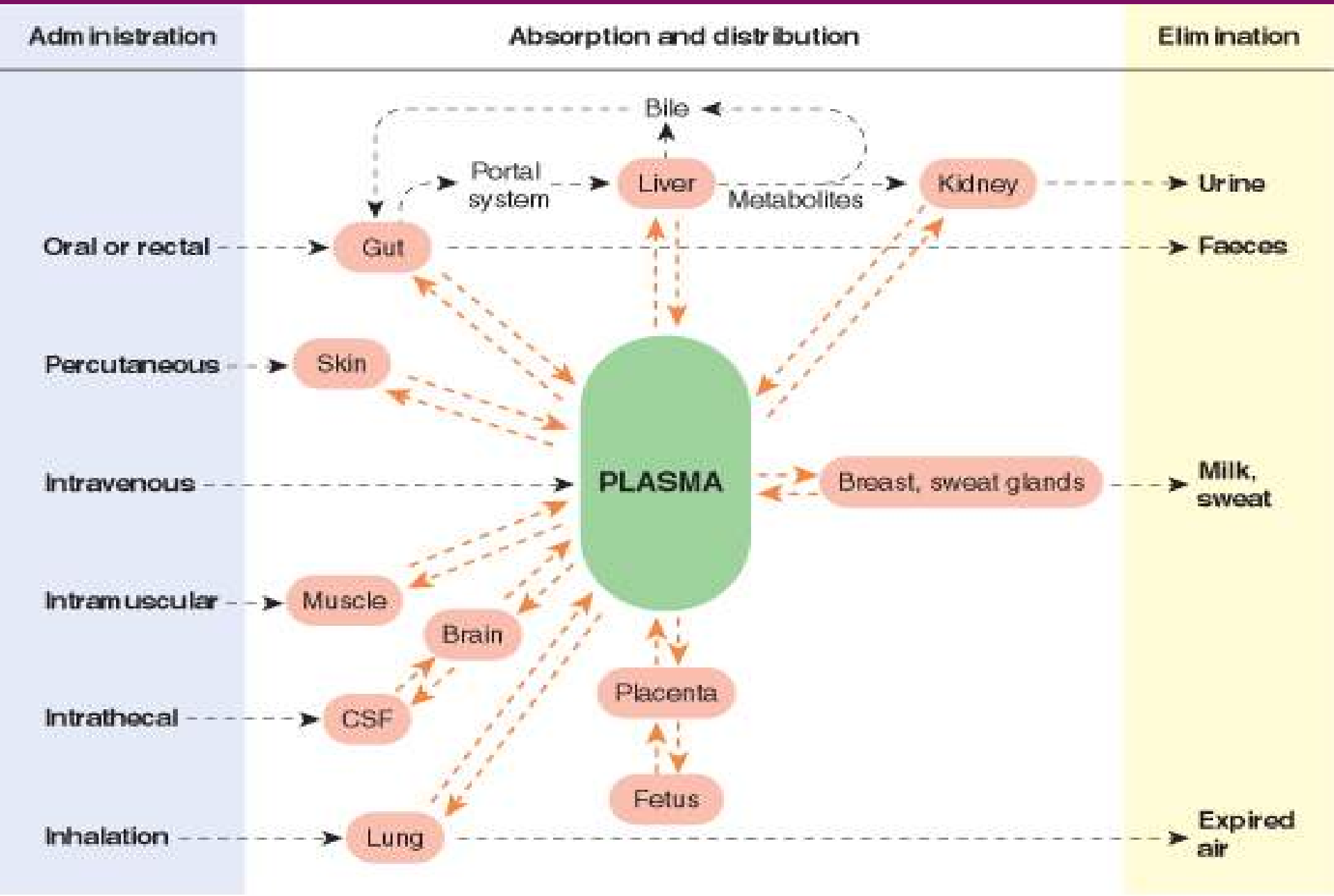
- The ratio of ionized to unionized species depends on the pKa of the drug and the pH of the membrane environment, and can be calculated from the Henderson-Hasselbalch equation.

- The acid (low pH) nature of the stomach generally results in a higher degree of ionization for weak bases than for weak acids.

i.e. Weak acids will be more unionized and thereby absorbed more readily.

- In the small intestine, the pH is about 5.0-8.0 and the reverse situation holds true.

- When there is relative “acidity” of distal tubular urine, there is tendency to increase the ionization of weak bases thereby hastening their renal elimination whereas weak acids passively diffuse (in the unionized form) back into the circulation.



The main routes of drug administration are:

Enteral: oral, sublingual, rectal

Parenteral: intravascular (intravenous), intramuscular, subcutaneous

Other: inhalation, intranasal, intrathecal, topical, transdermal

Oral

1. Easy, practical and reliable way

2. Drug is first dissolved in GI fluids, absorbed through epithelial lining of the GI tract, and enters into blood vessels.

- little absorption in the large intestine

3. Most of the drug is absorbed in the small intestine.

Why?

-- small intestine has a much larger surface area for absorption (~200 m2) as compared to the stomach (~1-3 m2).

-- drug spends more time in the small intestine (~4 hrs) than the stomach (~0.5-1 hrs).

4. Solubility of the drug in the GI tract

5. Time in the GI tract. Any pathological condition that changes that either increase or decrease the passage time of the drug in the GI tract will change the quantity of absorption.

First-Pass Effect

- Since drugs are absorbed from the gastrointestinal tract into the portal circulation, some drugs may be extensively metabolized in the liver or in the intestinal mucosa before reaching the systemic circulation.

Sublingual

- Good absorption through capillary bed under tongue

- Drugs are easily self administered
- Because the stomach is bypassed, acid-lability and gut-permeability is not important

- Drugs are absorbed from the mouth straight into the systemic circulation without entering the portal system and so escape first-pass metabolism by the liver.

Intravenous

- Rapid onset of action because the drug is injected directly into the bloodstream

Useful in emergencies and in patients that are unconscious

The drug avoids the GI tract and first-pass metabolism by the liver

Inhalation

- Inhalation provides the rapid delivery of a drug across the large surface area of the mucous membranes of the respiratory tract and pulmonary epithelium, producing an effect almost as rapidly as by intravenous injection.

- This route of administration is used for drugs that are gasses (for example some anesthetics) or those that can be dispersed in an aerosol (for example some asthma drugs).

- The route is particularly effective and convenient for patients with respiratory complaints (for example asthma or chronic obstructive pulmonary disease) as drug is delivered directly to the site of action and systemic side effects are minimized.

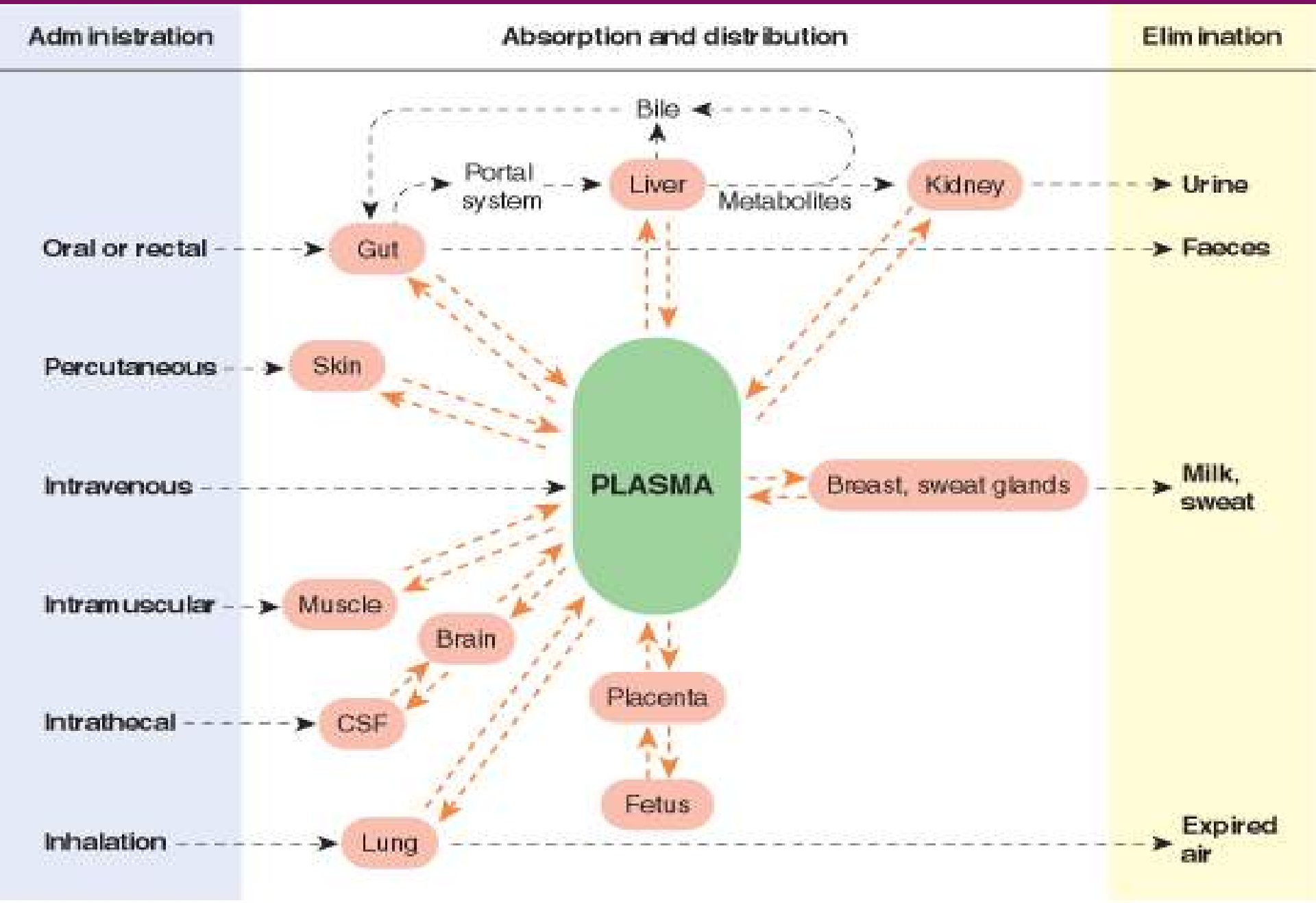
Bioavailability

- **Bioavailability is defined as the fraction of unchanged drug reaching the systemic circulation following administration by any route**

- **Bioavailability would be 100% if a drug is administered intravenously**

- This “first-pass effect” can substantially decrease the amount of active drug reaching the systemic circulation and thus, its bioavailability.

DRUG DISTRIBUTION



Phases of Distribution

(1) An initial phase of distribution may be distinguished that reflects cardiac output and regional blood flow.

Heart, liver, kidney, brain and other well-perfused organs receive most of the drug during the first few minutes after absorption.

(2) Delivery of drug to muscle, most viscera, skin and fat is slower, and these tissues may require several minutes to several hours before steady state is attained.

(3) A third phase of distribution is also possible for some drugs where the drug slowly accumulates in some tissues like fat tissue and other tissues.

Factors influencing drug distribution

1. Membrane permeability of various tissues
2. Blood flow
3. Plasma protein binding
4. Regional differences in pH
5. Capillary permeability