

Plasma membrane

To cause an effect, a xenobiotic must reach the target tissue, except certain caustic substances which act locally.

Absorption of foreign compounds from the environment into blood circulation is determined by their capacity to cross a variety of cell membranes (plasma membranes).

Plasma membrane is composed of a mostly phospholipid bi-layer with certain proteins inserted into it, forming aqueous pores, channels, and transporters.

Transport across cell membranes

All routes of xenobiotic administration (except IV) require that the xenobiotic be transported from the site of administration into the systemic circulation.

A xenobiotic is "absorbed" only once it is in the blood or lymph.

1. Passive transport

Mechanism by which many toxicants pass through membranes

Involves movement down their concentration gradient in un-ionized form

Xenobiotic will accumulate in membrane until the ratio of its concentration in the membrane to the extracellular fluid equals its partition coefficient. This establishes a concentration gradient between the membrane and the inside of the cell, and is the passive driving force for this mechanism.

Also depends on the lipophilicity of the compound

Simple diffusion - is not substrate specific and depends on the differences in concentrations on both sides of the membrane and on the lipophilicity of the agent.

Many weak organic acids or bases are readily ionized in solution. The ionized forms have low lipid solubility and thus do not penetrate readily through the lipid domain of the membrane. The non-ionic forms are somewhat lipid soluble and their transport is proportional to their lipid solubility.

Filtration

Route by which many hydrophilic substances enter the cell

Involves aqueous channels located in the cell membrane

Used by compounds with MW less than 100

Filtration is restricted to hydrophilic compounds

Active Transport Systems

Active transport - is substrate specific, occurs against a concentration gradient, and requires the expenditure of energy.

Active transport is a energy-dependent (ATP) process

Often involves transporting substances AGAINST their concentration gradient

Toxicants must sufficiently resemble endogenous substances to qualify for the transport/carrier systems, which are quite specific.

Is unidirectional

Exhibits saturation kinetics

Facilitated diffusion

Is carrier mediated

Does not require the expenditure of energy

Substance is moved down the concentration gradient.

Endocytosis

Cellular uptake of exogenous molecules or complexes inside membrane-derived vesicles.

Adsorptive--uptake of particles that have bound to the outer membrane surface

Phagocytosis— uptake of larger particles
“cell eating”

Pinocytosis— fluid uptake “cell drinking”

Pinocytosis and phagocytosis involve the encirclement of particles by the plasma membrane and subsequent engulfment.

Absorption of xenobiotics

1. Absorption via the GI tract:

The GI tract is one of the most important sites for the absorption of toxicants because many agents enter the food chain and are absorbed with food.

Absorption in the GI tract occurs along the entire tract, but mostly in the small intestine.

Absorption from the Stomach

Primary function of stomach is **NOT** absorption

Stomach does have a rich blood supply which does provide a potential absorption site.

pH of stomach plays a role in driving the degree of toxicant ionization

The stomach may “trap” weak bases—even if administered by IV, leading to an accumulation of toxicants in the stomach. This phenomenon is called ion trapping.

Absorption from the Small Intestine

Small intestine lining consists of a single layer of epithelial cells and has many folds, called villi and microvilli.

Small intestine has a complex and rich supply of blood and lymph vessels.

Has a much higher capacity for toxicant absorption than stomach.

All forms of transport are exhibited here, but predominant process is diffusion.

Most absorption takes place in the first 1-2 m of the small intestine, called the proximal jejunum.

Absorption from the Large Intestine

Large intestine has smaller surface area than small intestine

Large intestine is the last line of absorption for toxicants in the GI tract

The solid nature of intestine contents impedes diffusion of toxicants by acting as a physical barrier to the mucosa.

Factors affecting GI Absorption

Gastric Emptying Time

Less time in stomach, more time in small intestine
Faster absorption

Intestinal Motility

Increased GI motility may facilitate absorption by more thoroughly mixing GI contents and bringing more toxicant in contact with mucosa.

Decreased GI motility — gives toxicant more time to be absorbed.

Intestinal diseases and disorders can be expected to alter toxicant absorption.
Mucosal sloughing
Diarrhea

Food

Generally, the presence of food reduces toxicant absorption.

Certain toxicants can complex with Ca^{2+} ions in food or milk, leading to a reduction in absorption.

The increase in splanchnic blood flow during eating increases the rate of absorption.

Physical Factors

Physical properties of the toxicant

Solubility characteristics of individual toxicants

e.g.
hydrophilic
lipophilic

Ability of toxicant to withstand the harsh pH conditions of the stomach.

Metabolism

Toxicants may be inactivated or activated by GI enzymes or stomach acid before they are absorbed.

Enzymes are present in the gut wall and microflora that may also metabolize toxicants.

Weak acids are absorbed mainly in the stomach because they are present in the non-ionized form; weak bases are absorbed mainly in the intestine because of their non-ionized form.

Most agents are absorbed in the GI tract by simple diffusion and carrier-mediated specialized transport systems. Some chemicals may be absorbed by the same transport system.

Almost all chemicals absorbed in the GI tract are first transported to the liver, because all blood vessels surrounding the GI tract lead to the portal vein and via that to the liver.

Absorption via the Respiratory Tract

Toxicants absorbed via the respiratory tract are gasses, vapors of volatile liquids, and occasionally aerosols.

Aerosols are liquids or solid particles so small that they remain suspended in air for a long time. (i.e.: lead, silica dusts, asbestos)

Lung has a tremendous surface area and vascularity

Lung does not have appreciable sites of metabolic activity

Diffusion through the cell membrane is not rate-limiting in pulmonary absorption of gases because:

- (a) ionized molecules are of very low volatility
- (b) capillaries are in very close contact with the pulmonary pneumocytes
- (c) chemicals absorbed by the lung are rapidly removed by the blood.

Absorption of aerosols and particles by respiratory epithelium depends upon the aerosol size and water solubility of a xenobiotic.

The Main factor determining absorptions of particulate material in the lung is particle size:

Large: > 5 : μ m in diameter
Medium: 2-5 : μ m in diameter
Small: < 1 : μ m in diameter

Large particles are pretty much confined to the nasopharyngeal region. Often transported by cilia to back of esophagus where they are swallowed, coughed out, or blown out. Large particles are never absorbed through

the respiratory tract.

Medium particles are deposited in tracheobronchial region. Transported back up to nasopharyngeal region and again, out.

Small particles are absorbed in the lung. Small particles are deposited all the way down to alveoli:

- 1) alveolar macrophages will scavenge (phagotize) them.
They move into interstitial pulmonary fluid then into the lymphatic system
- 2) If H₂O soluble, they will diffuse into bloodstream. Lipid-solubles also get absorbed.

Removal of particles from the pulmonary tissue may occur by:

- (a) physical processes
- (b) phagocytosis
- (c) endothelial cells lining the lymphatic capillaries.

Absorption Through the Skin

Because skin is not very permeable, it is a relatively good barrier for separating organisms from their environment.

Many chemicals can be absorbed through skin to produce a toxic response.

The rate limiting barrier in the absorption of chemicals through the skin is the stratum corneum, the outer layer of biologically dead cells of the epidermis.

The structure and chemistry of the stratum corneum varies in different regions of the body and between species.

The second phase of percutaneous absorption is through the lower layers of epidermis and dermis and subsequently into venous and lymphatic capillaries of the dermis.

The rate of diffusion of chemicals in the dermis depends on blood flow and interstitial fluid movement.

Other Routes of Absorption

Enteral Routes:

- Swallowing, oral
- Sublingual
- Rectal

Parenteral Routes:

- Subcutaneous
- Intramuscular
- Intradermally
- Transcutaneously
- Intrathecal

Intravascular

IV versus Enteral routes

IV usually by subclavian vein or antecubital veins

Minimal delay--drug/toxicant is in system immediately

Very good control

Slow administration

Fast administration (Bolus)

Stopped instantly

Constant administration for long periods

IV is great for maintaining doses to give constant blood concentrations

IV is the safest way to administer drugs with narrow margin of safety between therapeutic and toxic blood levels. i.e. lidocaine

IV is a good route for those drugs that

1. Are not/cannot be absorbed well from the GI tract
2. Are destroyed by harsh acidic environment of stomach
3. Need to bypass the liver's 1st pass effect

Drawbacks:

Once in the system, it can't be recalled

Distribution

Distribution of chemicals to organs/tissues is determined by the blood flow and rate of diffusion out of the capillaries into the cells of the respective tissues.

Binding of chemicals and dissolution at various storage sites (i.e. fat, liver, and bone) are important factors in determining the distribution of chemicals.

Volume of Distribution

The total volume of fluid compartments to which toxicants may be distributed is approx. 40 liters in a adult.

Factors such as sex, age, edema, body fat, can influence the total volume.

The fluid volume in which a drug seems to distribute is called the apparent volume of distribution. This calculated number gives a idea of the overall distribution of the toxicant.

The rate at which a equilibrium concentration of a toxicant is reached in the extracellular fluid of a particular tissue depends on that tissue's perfusion rate. The greater the perfusion rate, the more rapid the distribution towards equilibrium.

Tissue compartments where a chemical is concentrated can serve as a storage depot

1. **Plasma proteins as a storage depot:**

Protein-ligand interaction occurs mainly as a result of hydrogen bonding and hydrophobic forces, and is competitive

Interaction between plasma proteins and chemicals is reversible.

2. **Other storage depots of chemicals**

- a. Liver
- b. Kidney
- c. Bone

d.

Body fat

3. **Blood-brain barrier:**

Prevents the passage of toxic agents into the central nervous system. Factors responsible for the blood-brain barrier are:

- (a) lack of pores between capillaries
- (b) endothelial cells contain an ATP-dependent transport, a multi-drug/toxicant resistant protein that active transports chemicals into the blood;
- (c) capillaries in the CNS are surrounded by glial cell processes
- (d) low protein concentration in the interstitial fluid.

In general, minor lipophilics can't get in— only highly lipophilic toxicants or actively transported substances get into brain.

Inflammation, such as meningitis or encephalitis may increase the permeability of the BBB

The blood-brain barrier is not fully developed at birth.

Passage of Chemicals Across the Placenta

The placenta provides nutrition to the fetus, exchanges maternal and fetal blood gases, disposes of fetal excretory material, and maintains pregnancy through hormonal regulation.

Many foreign agents including chemicals, viruses and antibodies cross the placenta.

The placental barrier consists of many cell layers interposed between the fetal and maternal circulation; the number of layers varies between species.

Excretion

Toxicants are eliminated from the body by three major routes

- Urine
- Feces, including biliary excretion
- Lungs

Kidney:

Urinary excretion involves elimination of toxicants and their metabolites. *Glomeruli* are the main components of the kidney involved in excretion by three processes: **glomerular filtration, tubular excretion by passive diffusion, and active secretion.**

Compounds up to 60,000 molecular weight are filtered through the glomeruli.

Toxicants present in the glomerular filtrate may be excreted with urine or reabsorbed across the tubular cells back into blood.

Bases are excreted

at lower pH and acids at higher pH.

Protein-bound toxicants may be secreted into urine by active transport driven by Na^+ / K^+ ATPase system located in the basolateral membrane of proximal tubules.

Xenobiotics are eliminated slowly in newborns because their kidney functions are incompletely developed.

Fecal Excretion

Fecal excretion consists of non-absorbed ingesta, biliary excretion and intestinal secretion.

Non-absorbed ingesta - consists of unabsorbed nutrients and xenobiotics.

Biliary Excretion

Toxicants absorbed in the GI tract must be transported to the liver via the portal vein. Metabolites formed are secreted into bile, re-enter the GI tract and are secreted into feces. An increase in biliary secretion can reduce the toxicity of xenobiotics.

Chemicals secreted into the GI tract via bile can be reabsorbed and transported back into the liver, resulting in **enterohepatic circulation**.

Three types of chemicals are excreted into bile depending on the ratio of their concentration in bile versus plasma:

Class A - ratio of about 1 (e.g. sodium, glucose)

Class B - ratio of greater than 1 (e.g. bile acids, bilirubin)

Class C - ratio of less than 1 (e.g. insulin, albumin)

Three active transport systems are responsible for the secretion of organic chemicals into bile: one each for organic acids, organic bases, and metals.

Biliary excretion varies in different species and is compound specific.

Intestinal Excretion:

Some chemicals may be directly transferred from the blood into the GI tract and excreted into feces. Such transfers apparently occur by passive diffusion.

Exhalation

Substances in the gas phase at body temperature are eliminated mainly by the lungs. The amount of liquid eliminated via the lungs is proportional to its vapor pressure.

Other Routes of Elimination of Xenobiotics

- (a) Cerebrospinal fluid
- (b) Milk
- (c) Sweat glands