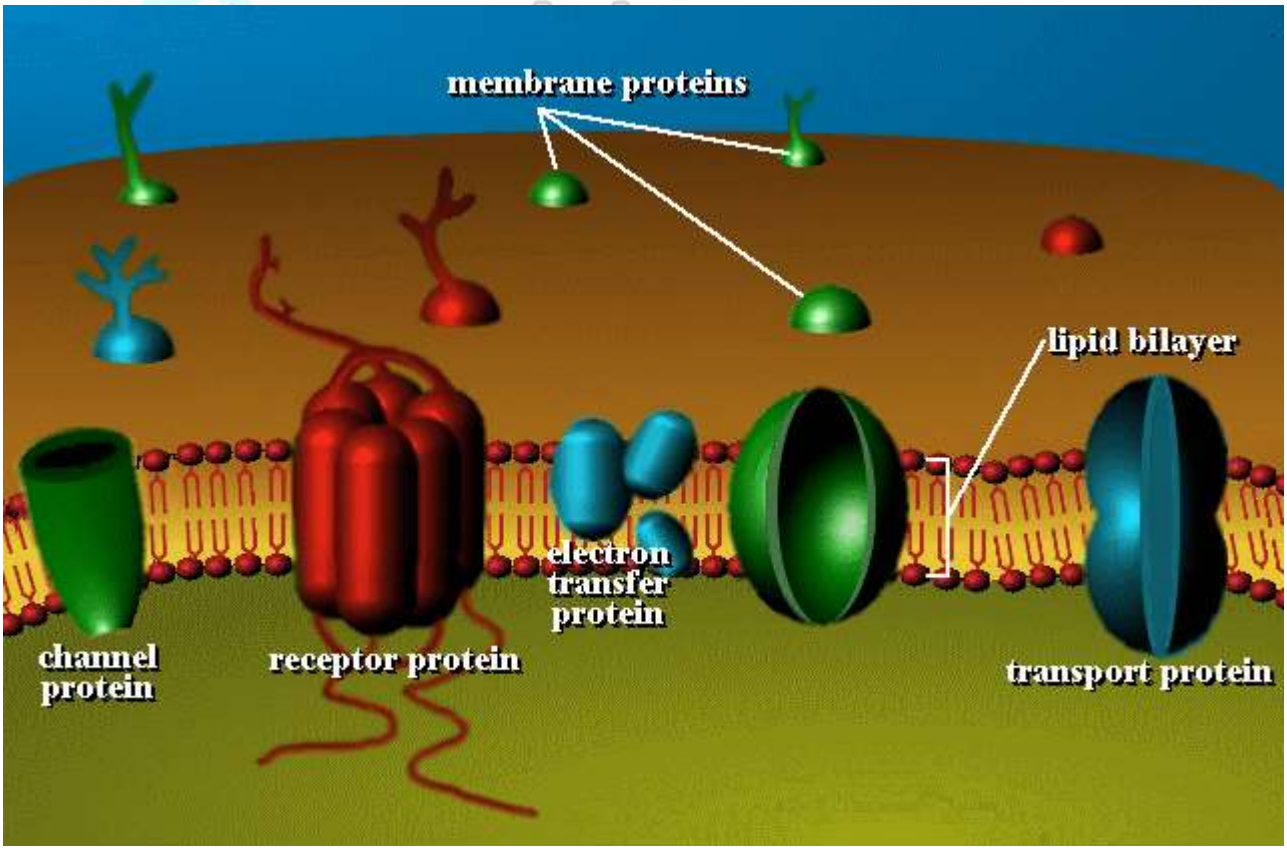
Toxicology Lec 2. Dr.Siham .A.W.

Toxicodynamics:-Determines the number of receptors that can interact with toxicants.(Binding ,Intraction ,and induction of toxic effects).

Toxicokinetics:- refers to the quantitation and determination of the time course of the disposition of toxicant in the organism or (ADME) for a given toxic xenobiotic.

Including :(ADME):-1- Abosoption,2- Distribution and Accumulation, 3-Biotransformation and Detoxication ,4-Excretion (elimination).

Absorption : is the process whereby toxicants gain enterance into the body, for a xenobiotic to exert a toxic effect , it must reach its site of actions.



Sites of absorption:-

There are several sites for the absorption of foreign compounds:-

1- Gastrointestinal tract . the GIT is the most important in toxicology as most foreign compounds are ingested orally ,Chemicals can enter the gastrointestinal tract in either contaminated food or water sources. Absorption of xenobiotics can occur at any part of GIT. However , the degree of absorption is strongly site-dependent may be occur. The important factors can affect on absorption within the various sites of the GIT : 1- Ph of the stomach or intestine contents. 2- period of the time that the substance remains at the site. 3- type of cells at the specific site.

under normal condition , xenobiotics are poorly absorbed within the mouth & oesophagus due to the very short time that a substance residue in these portion of GIT .

The stomach which has high acidity (1-3 pH) is a significant site for absorption of weak acids , which exist in a diffusion , non-ionized & lipid soluble form.

In constant weak bases will be highly ionized & therefore poorly absorbed.

The greatest absorption of chemicals , take place in the intestine , particularly in the small intestine .The intestine has a long surface area consisting of outward projects of thin mucosa into the lumen of intestine, the villi.

The PH of intestine is near neutral (5-8 Ph) both weak acid & weak base are non-ionized so usually readily absorbed by passive diffusion or simple diffusion.

3- Respiration(Inhalation) (Air borne toxicants):-

Most important site for absorption is pulmonary region consists of very small airways (bronchioles) and alveolar sacs of lung.

The alveolar region has a very large surface area (50 times that of skin) In addition , the alveoli consist of a single layer of cells with very thin membrane that separate the inhaled air from the blood stream.

3-Body surface(Dermal) via Skin (Lipid soluble toxicants such as organo -phosphate,and carbon tetra chloride).Is saturable process and is driven by concentration gradients across membranes.

physiochemical properties of the chemical affect on absorption .

Xenobiotics can pass through the body membranes by two types of transport…… 1- Passive transport ……..2- Active transport.

1. Passive transport:- requires no energy expenditure on the body's part to transport the xenobiotic across a cell membrane. According to Fick's law, the diffusion rate is directly proportional to the concentra-ation gradient across a membrane.

Passive transport is characterised by a nonsaturable process and is driven by concentration gradients across membranes.

Passive transport occurs via two distinct mechanisms:…… A- simple diffusion and ……. B-filtration.

A- Simple diffusion:- Most chemicals pass through biological membranes via this mechanism and depends on both the lipid solubility and the size of the molecule.

B-Filtration:- Small molecules may pass through pores in the membrane formed by proteins . this movement will occur down a concentration gradient such as urea

2- Active transport:- mechanisms usually require an energy expenditure on the body's part to transport the xenobiotic across a cell membrane

A:- Active transport: is a saturable process and is not driven by concentration gradients across membranes; rather, active transport moves xenobiotics against concentration gradients

B:- Facilitated transport: expends energy on xenobiotic transport, but it does not occur against a concentration gradient

C:- Pinocytosis: is another type of active transport mechanism that involves the ability of cells to engulf small masses of xenobiotic and carry it through the cell membrane.

DISTRIBUTION :

Distribution is the process whereby an absorbed chemical moves away from the site of absorption to other areas of the body .

A chemical after absorbed it pass through cell linings of the absorbing organ into the interstitial fluid . Blood moves rapidly through the body via the cardiovascular circulation while lymph moves slowly through lymphatic system.

Binding of toxicant to plasma protein. Some toxicant may bind to plasma proteins (especially albumin),affects on distribution of toxicant the unbound toxicant or free toxicant can pass rapidly through the capillary membranes.

Chemical in the blood stream it may be ….1-Excreted or.. 2-Stored… or….. 3-Biotransformed into different chemicals (metabolites) .

The chemical or its metabolites may interact or bind with cellular components.

Storage sites : The primary sites for toxicant storage are…. 1-adipose tissue ,2-… bone ,3-.. liver & 4-… kidney. Lipid soluble toxicants are often stored in adipose tissue.

The liver is a storage site for most toxicants. due to 1-…It has a large blood flow &…2- its hepatocytes (liver cells), contain proteins that bind to some chemicals.

METABOLISM

Metabolism (BIOTRANSFORMATION):- The ideal metabolic system should convert or produce metabolites that are water soluble form (more polar ,and hydrophilic) to allow for efficient excretion in the

urine… or ….bile. In addition, the metabolites should themselves be nontoxic.

The liver, organ the most metabolism capacity. However, other organs such as the kidneys, gastrointestinal tract, skin, heart, and brain also have considerable metabolic capabilities.

The metabolic conversion can be categorized into two steps or phases, classically known as1-… phase I and 2-…. phase II.

Phase I metabolism : converts apolar, lipophilic xenobiotics into more polar and more hydrophilic metabolites via introduction or liberation of functional groups that can be used during phase II.

Cytochrome P450 system :-A hem - containing cytochrome protein located in ER, and is involved in electron transport.

Phase I metabolism uses a wide assortment of reactions that processes the xenobiotic via 1- hydrolysis, 2- oxidation, or3- reduction pathways.

Phase II metabolism :- conjugates either the xenobiotic itself or its metabolite formed during phase I metabolism with a functional group that results in a multifold increase in water solubility.

- Glutathion S-transferases (GST) Conjugation, Glycine Conjugations, Cysteine Conjugation, Acetylation Reactions.

A xenobiotic may undergo phase I only, phase II only, or both phase I and II, depending on the xenobiotic.

for metabolizing xenobiotics; however, not all species have equal capabilities to do so. For example, most species of animals have the ability to glucuronidate of xenobiotics during phase II metabolism, except for felines (e.g., domestic cats, lynxes, and lions). The major pathway for metabolism of acetaminophen is via glucuronidation. Unless acetaminophen is glucuronidated, the cytochrome P-450 system metabolizes this compound into N-acetybenzoquinoneimine, which binds to hepatic proteins and leads to centrilobular necrosis. Therefore, cats that receive a dose of acetaminophen can die of widespread hepatic failure within a few days.

Excretion:-The last step in toxicokinetic is excretion for a xenobiotic and involves removing the xenobiotic out of the body by a number of passages.

Excretion of a xenobiotic is generally performed into two broad categories: renal and nonrenal .

Removing the xenobiotic via the urine (Kidney) is the most common route of excretion; however, other pathways do exist and are important alternates for some chemicals.

Renal excretion may be either1-…. glomerular filtration or2-… active tubular secretion 3 -…… Glomerular filtration .

The glomeruli filter compounds up to the size of plasma albumin (MW. 69000) only free compound (not bound with plasma protein) are filtered by the glomeruli.

One of the alternate pathways is fecal excretion. Not all xenobiotics are completely absorbed, particularly via oral exposure. If absorption is less than 100%, the xenobiotic can continue down the gastrointestinal tract and either be metabolized by gut microbes or be passed unmetabolized out of the body via feces. Even if absorbed, some xenobiotics may be metabolized, excreted via the bile, and removed from the body in the feces.

Enterohepatic circulation, which occurs when a xenobiotic is excreted in the bile and then reabsorbed later in a more distal part of the gastrointestinal tract, can occur with some chemicals and can lead to a prolonged half life and potential toxicity.

The intestinal tract itself can also push xenobiotics into the lumen of the tract and allow them to pass out of the body.

Other nonrenal routes: of excretion include 1-milk (particularly important because of the potential for residues in milk),……..2-cerebrospinal fluid,3-…. sweat, and4-…. saliva. Toxicants that are distributed to the skin can be detected in the5-.. keratin layer several days after exposure, followed by normal sloughing of the skin, which

can rid the body of the xenobiotic.6-.. inhalation is an important route of elimination, particularly when xenobiotics are inhaled or are volatile. For example, dogs administered small amounts of ethanol intravenously have detectable amounts of ethanol exhaled.

First order and zero order kinetics:- are terms used to describe how the body eliminates xenobiotics. most xenobiotics are eliminated via first order kinetics. First order kinetic processes state that the rate of elimination (meaning both biotransformation and excretion) at any time point is proportional to the amount of the chemical in the body at that time. First order kinetics generally consist of nonsaturable .pathways

Zero order kinetics are used to describe the elimination of xenobiotics through pathways that are saturable, meaning that the metabolic pathway can only eliminate a finite amount of chemical per unit of time.

Following are the major ways through which poisons and their metabolites are excreted:-

1. Faecal excretion. Ingestion of a relatively insoluble poison (e.g., lead arsenate) is followed by excretion of the major part in the faeces. Substances may also find their way into faeces via bile; metals stored in the liver are slowly excreted in this way.

2. Pulmonary excretion. Volatile poisons may be mainly excreted in the expired air, e.g., CS2 cyanide. In phosphorus poisoning the breath may smell of garlic odour and glow in the dark. Diagnosis of hemlock poisoning may be made from the characteristic "mouse-like" odour of coniine in the exhaled air (and also in urine). The lesions found in the lungs in paraffin poisoning are probably due to irritant effect caused by pulmonary excretion.

3. Urinary excretion. This is the most important pathway of the excretion of a poison. Irritant poisons cause damage to kidney. Urine is often a convenient material for diagnostic analysis. In veterinary field it

is of great importance in detecting the pasture contamination with fluorides.

4. Milk and dermal excretion. Excretion can also take place through skin, e.g., arsenic, and in lactating animals in milk. Many of the insecticides are fat soluble and it has been shown that DDT, aldrin, and several other chlorinated hydrocarbons can be detected in minute amounts in cow's milk.