

Absorption And Metabolism Of Xenobiotics: An Overview

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Abstract

Xenobiotics are chemicals found in organisms, but not expected to be produced or present in them; or they are chemicals found in much higher concentrations than usual. There are five possible processes of intestinal absorption of Xenobiotics, they are active transport, passive diffusions, Pinocytosis, filtration through "pores" and lymphatic absorption. There are number of factors which alter the rate of Xenobiotics absorption which include diet, motility of intestine, interference with gastro intestinal flora, changes in the rate of gastric emptying, age, and the dissolution rate. Xenobiotics are metabolised by biotransformation or detoxification reactions and they are classified into phase one and phase two reactions. Phase one reactions include oxidations reaction, reduction, hydrolysis and phase two reactions include sulfation, acetylation, methylation and conjugation with glucuronic acid, glutathione and glycine. Excretion of Xenobiotics occurs through urine, faeces, breath and sweat.

INTRODUCTION

Xenobiotics are chemicals which may be accidentally ingested or taken as drugs or compounds produced in the body by bacterial metabolism. They are found in organisms but not expected to be produced or present in them, or they are chemicals found in much higher concentration than usual. Drugs such as antibodies are xenobiotics in humans because neither human body produced them nor its a part of the normal diet^{1,2}. Natural products cannot become xenobiotics if they are taken up by another organism such as uptake of natural human hormones, by fish found downstream or sewage treatment plant out falls or the chemical defences produced by some organisms as protection against predators. The term Xenobiotics is derived from the Greek word xenos (stranger) and bios (life). Xenobiotics is often used in the contest of pollutants such as dioxans and poly chlorinated biphenyls and their effect on biota because they are understood as substance foreign to an entire biological system³.

ABSORPTION OF XENOBIOTICS, ,,,

Xenobiotics must cross the intestinal epithelium, basement membrane and capillary endothelium before they reach the blood stream. Mammals do not absorb the Xenobiotics through any special transport processes but share the same transport processes which are used absorption of nutrients. There are five possible processes of Xenobiotics transport across the intestine. They are active transport, pinocytosis, filtration through "pores", lymphatic absorption and passive

diffusion.

ACTIVE TRANSPORT

Active processes require cellular energy, food transfer of substrate across the intestine against higher concentration or electro chemical gradient. The system exists mainly for transport of natural substances (aminoacids, sugar, or bile acids).

PINOCYTOSIS

In this cell membrane forms invagination which finally close to form vesicles which contain fluid from outside the cell. Inside the cell the contents of vesicles are delivered to cytoplasm. In suckling animals this process of transport is used for macromolecules (antigenic peptide, an immunoactive protein).

FILTRATION THROUGH PORES

Both lipophilic and hydrophilic compounds may pass through holes in the cell membrane. Xenobiotics with molecular weight 100 may be absorbed through this process.

LYMPHATIC ABSORPTION

It is well known that dietary short chained fatty acids predominantly absorbed via the lymphatic system in minute droplets known as chylomicrons. These enter the thoracic duct and empty into the systemic venous blood;completely bypassing the liver. Eg: Para amino salicylic acid, tetracycline, DDT, benzpyrene and 3-methyl

cholanthrene_{9,10,11,12,13}.

PASSIVE DIFFUSION

Passive diffusion is a major process for absorption of Xenobiotics. This process is not saturable and transfer is directly proportional to the concentration gradient and to the lipid –water partition coefficient of Xenobiotics. The higher the factors, faster the rate of diffusion, and when concentrations are the same on both sides of membrane, movement of Xenobiotics across the membrane stops. Absorption of structurally related chemicals occurs independently; co absorption does not alter absorption rate of either chemical. The extent of lipid solubility and the ionisation of Xenobiotics influence the rate of chemicals. Many weak acids and bases are readily absorbed while highly ionised acids and bases are less readily transported. Completely ionised compounds are very slowly absorbed. The role of ionisation on absorption of chemicals is further supported by change in the rate of absorption that resulted from a change in the pH of intestinal contents. For instance raising the pH increased the absorption of bases such as quinine and aminopyrene and decreased the absorption of acid such as benzoate and salicylate.

FACTORS AFFECTING INTESTINAL ABSORPTION OF XENOBIOTICS

Factors such as diet, age, species, changes in the motility of the intestinal tract, interference with gastro intestinal content of microorganisms, changes in the rate of gastric emptying in either direction and dissolution rate of Xenobiotics can influence the intestinal absorption of xenobiotics_{14,15,16}.

METABOLISM OF XENOBIOTICS

Xenobiotics are metabolised by biotransformation or detoxification reaction. The compound that are detoxified include

1. Compounds accidentally ingested like preservatives, food additives and adulterants
2. Drugs taken for therapeutic purposes
3. Compounds produced in the body and are to be eliminated. eg: Bilirubin and steroids
4. Compounds produced by bacterial metabolism. eg: Amines produced by decarboxylation of amino acid. Histidine to Histamine, Tyrosine to tyramine_{17,18,19}.

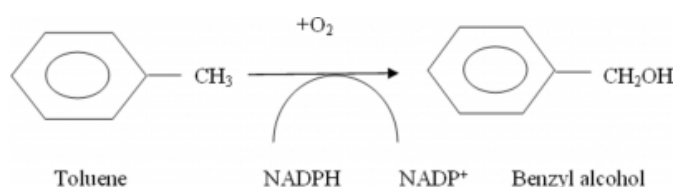
The transformation of specific xenobiotic can be either beneficial or harmful and perhaps both depending on the dose. A good example is biotransformation of acetaminophen₂₀, a commonly used drug to reduce pain and fever. It normally undergoes rapid biotransformation with the metabolite quickly eliminated in urine and faeces. Hence no toxicity is observed. The excess acetaminophen undergoes additional biosynthetic path way, which produces a metabolite that is toxic to the liver. Cytochrome P450 is the main enzyme involved in the biotransformation reaction pathway which produces a metabolite that is toxic to the liver₂₁.

PHASES OF DETOXIFICATION REACTION

Biotransformation reactions are usually classified as phase I and II reaction.

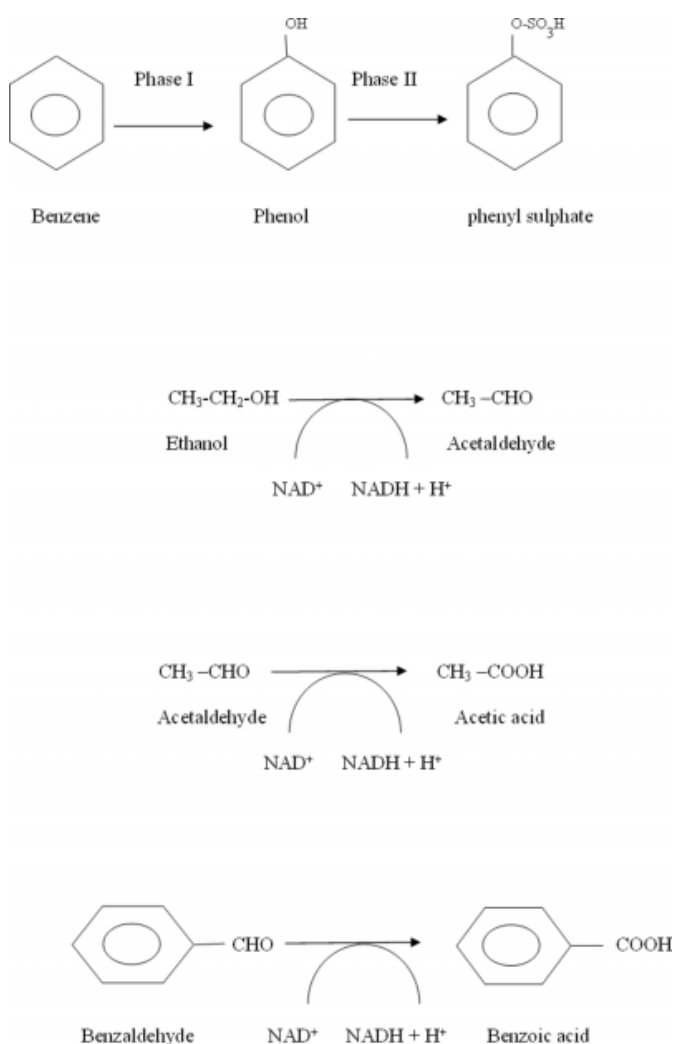
Phase I is an alteration of the foreign molecule, so as to add functional group which can be conjugated in phase II. Phase I reaction result in the formation of compounds with decreased toxicity (detoxification). Sometimes this may result in increased toxicity (entoxification) e.g.: methanol to formic acid. The phase I reactions include hydroxylation, oxidation, reduction, hydrolysis, dealkylation, epoxidation etc ₂₂.

Figure 1



The products of metabolic transformation are either excreted directly or undergo further metabolism by phase II reaction. They involve conjugation with a conjugating agent, thus converting lipophilic drug to water soluble, easily excretable forms. Phase II reactions are sulfation, acetylation, methylation and conjugation with glucuronic acid, glutathione and glycine₂₃. In some instances products of phase II may further be metabolised by phase III reactions. Sometimes both phase I and II reactions are needed to detoxify a compound.

Figure 2



Phase III reactions are not very common. A typical example is further conjugation with glutathione. The Xenobiotics that enter the body are mostly drugs and they are detoxified by the enzymes concerned with drug metabolism. Induction of cytochrome P450 system may even produce unwanted effects in some persons. For example induction of ALA synthase by barbiturates will precipitate attacks in acute intermittent porphyria.

CONCLUSION

This article mainly deals with the xenobiotics, compounds which may be accidentally ingested or taken as drugs or compounds produced in the body by bacterial metabolism. There was an attempt to explicit the absorption, factors affecting absorption, distribution, metabolism and excretion of Xenobiotics.

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