Metabolism what is it really?

Drug metabolism is the conversion of any drugs or external biochemical substances which are called xenobiotics into less active compounds through enzymes so that it can be easier to eliminate out the body, the resulting products of these biochemical reactions are called metabolites (1). Consequently, chemical substances that are lipophilic are to be modified into chemical by-products that are hydrophilic through metabolism in the liver that is essentially water loving compounds that can well easily be excreted through the human’s kidney and while doing so can detoxify toxic compounds in our body (2).

Phases of drug metabolism in the liver

Metabolism undergoes 2 types of biochemical reaction which are phase 1 and 2. Metabolism Phase 1 reaction involves Catabolic reactions the breakdown of a prodrug or a metabolite through either; oxidation, reduction or hydrolysis that results in exposing or adding a functional or reactive group e.g. -OH, -SH, -NH2, -COOH making it able to undergo phase 2 of metabolism or inactive excreted out of the body via urine or faeces (3, 4).

Table 1. Different catabolic reactions in phase 1 metabolism (2)

<table>
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<tr>
<th>Oxidation</th>
<th>&gt; Involves an added oxygen atom to the drug molecule for it to breakdown. &gt;Involves NADPH and CYP450 monoxygenase too.</th>
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Reduction

Anaerobic conditions, Drug molecules get an addition hydrogen atom. CYP450 reductase purpose is electron transfer. Involves FAD and FMN ENZYME, NADP too. Electron transfer illustrated below NADPH→FAD→FMN→P450→O2

Hydrolysis

Esterases and amidases are the catalysts

Involves addition of h20 to the drug molecule for it to breakdown

On the other hand, Phase 2 of metabolism includes reactions of conjugation with a drug or metabolite. It is done through anabolic reactions which require energy to fuse an existing metabolite/chemical compound to either one or more of these molecules as a functioning group such as; glucuronic acid, sulfuric acid, acetic acid, or glutathione molecules. The usual outcome is the drug is converted into inactive compounds that are less lipid soluble and more hydrophilic thus easier to excrete out of the body (3, 4).

Cytochrome p450 enzymes

Majority of the drugs that humans take get metabolises through the liver cells where cytochrome p450 enzymes are located and are the catalyst for metabolism with many drug and xenobiotics (5). This process of metabolism happens solely in the liver situated in microsomal endoplasmic reticulum and non-microsomal mitochondria (3). Not only that everything we eat/inhale/ touch, the liver would do its job by eliminating any toxic substances inside us to keep us breathing.
Explore why toxic metabolites are more likely to occur in phase 1 metabolism

Type 1 prodrugs usually breakdown by phase 1 metabolic enzymes this could be the reason why phase 1 metabolism is more likely to produce metabolites that are toxic or carcinogenic. Type 2 prodrugs with better permeability and lesser first pass metabolism occurring would bypass other drugs bioavailability problems (6).

Paracetamol

Some drugs depend on phase 2 of metabolism of the drug via conjugation for it metabolites to be safely excreted out of the body system for e.g. paracetamol when metabolised to NAPQI a toxic metabolite when overdosed with it can lead to liver failure, NAC short for N-acetylcysteine is a precursor of glutathione it’s an antidote to paracetamol intoxication it converts NAPQI into a safe metabolite (7, 8).

Valproic acid

Another example is valproic acid used in epilepsy therapy can be toxic and can lead to liver damage including mitochondrial damage and fat accumulation. The culprit is the valproic acid metabolite is VPA short for 2-propyl-4-pentenoic acid (11).

Azathioprine

Azathioprine used in leukaemia treatment is a type 2 prodrug through biotransformation it turns to mercaptopurine. Mercaptopurine when used for treatment our body quickly converts to an inactive metabolite 6-thiouric acid by xanthine oxidase makes the drug non-effective, therefore, higher doses are used to gain bioavailability, so the drug can do its job, although this leads to toxicity. This problem can be overcome by introducing mercaptopurine as its cysteine conjugate which gets rid of the toxicity issue (12, 13).

For further information into this topic please refer to this hyperlink to an education video about drug metabolism

https://www.youtube.com/watch?v=oCPri5JFMdg
Bibliography