Our Liver has a big job - Metabolism’s tricky, taxing and toxic

Every time you introduce your body to a substance that’s not normally there, such as a drug, chances are it’ll be the liver’s job to deal with it.

The job description for the liver? Eliminate.

It achieves by making irreversible changes to the chemical structure of the foreign substance in a process that’s commonly termed metabolism [1]. This role of the liver is vital, especially for lipophilic drugs that our kidneys struggle to get rid of through urine [2]. Metabolism in the liver serves to make life easier for the kidneys by converting drugs into molecules that are more easily excreted. Almost all drug metabolism occurs in the liver making the chief drug eliminator [3]. The liver does this in two phases which may or may not occur consecutively.

**Phase 1 Metabolism: Catabolism**

Phase one reactions involve the breakdown of the drug molecule into a simpler form by enzymes. Phase one reactions can be further categorised into different reactions, including reduction, oxidation and hydrolysis [4]. In these processes a more reactive component of the molecule may become exposed such as an alcohol (-OH) group. These processes release energy as catabolic reactions, so the products of phase 1 are usually more chemically reactive than original drug molecule. This decreases the lipophilic properties of foreign substances so that it may now be more easily excreted [1]. More commonly however, phase 1 reactions allow phase 2 reactions to then occur at the reactive site [1].

**Enzymes?**

They’re catalysts of chemical reactions within our body. As such they kickstart many important processes. The most important collection of enzymes in phase 1 reactions are Cytochrome P450 enzymes [5]. These control the oxidation reactions of copious numbers of commonly taken drugs.

**Reactions:**

(1) Reduction = a chemical reaction involving a gain of negatively charged particles (electrons)

(2) Oxidation = opposite of reduction - a chemical reaction involving a loss of electrons

(3) Hydrolysis = the splitting of compound by adding water molecules

*Adapted from UOP [4]*

**What’s Metabolism?**

Metabolism is the alteration of a substance into a more useful or more easily excreted form through a combination of two methods. Our bodies release energy by breaking large molecules down (called catabolism) AND/OR expend energy by building extra components onto existing molecules (called anabolism).

**Lipophilic substances**

Just as oil and water won’t mix, lipophilic substances won’t mix well with our blood or urine which makes them harder to get rid off [2].
Prodrugs + Toxicity of Phase 1
So after Phase 1 reactions we have something more reactive that what we started with, and often times more reactive can mean more toxic [6]. Because the liver is so prolific and persistent with phase 1 reactions there are even some drugs that are inactive when we ingest them, but when broken down become activated. These are called prodrugs, and codeine is one example that is activated to become morphine (shown below). In these cases we trick the liver into controlling the release of a drug so that the effects are more preferable [7].

Phase 2 Metabolism: Anabolism
Phase 2 reactions follow phase 1 reactions at the newly exposed reactive site, where our liver (mostly) [3] will expend energy by joining it to another group. Essentially, the intention is to build a larger molecule which mixes more easily with water and is more easily excreted in urine [2, 4]. This is called conjugation. Conjugation reactions are usually controlled by transferase enzymes, which as the name suggests control the transfer of components between molecules [12].

Conjugation: glucuronidation
Phase 2 reaction in which glucuronic acid, a large polar group, is built onto the existing reactive alcohol group of paracetamol. Research suggests that opiate or excessive alcohol intake can inhibit this process [13].

Liver Metabolism Lego Summary
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The drug molecule enters our body and is not easily removable!
Liver Enzymes (P450)
PHASE 1: The top half is removed to expose a more reactive surface that can be built upon
Occasionally the new reactive surface leads to a bad toxic product
PHASE 2: Usually the liver then builds a structure that can be more easily removed
Bibliography


