

Pharmacokinetic processes: metabolism

Metabolism

Metabolism describes the chemical reactions that change drugs into compounds which are easier to eliminate. The products of these chemical reactions are called metabolites.

The reactions are catalysed by enzymes and happen mostly in the liver, though some changes take place in the gut wall, lungs and blood plasma. In these reactions non-polar drug molecules are chemically changed into more polar molecules.

Compounds consisting of

- non-polar molecules tend to be soluble in fats and insoluble in water.
- polar molecules tend to be insoluble in fats and soluble in water.

Producing metabolites which consist of polar molecules means that they can be excreted in body fluids such as urine and bile.

Metabolism is often divided into two phases:

Phase 1 metabolism involves chemical reactions such as oxidation (most common), reduction and hydrolysis. There are three possible results of phase 1 metabolism.

The drug becomes completely inactive. In other words, the metabolites are pharmacologically inactive.

One or more of the metabolites are pharmacologically active, but less so than the original drug.

The original substance is not pharmacologically active, but one of its metabolites is. The original substance is called a prodrug.

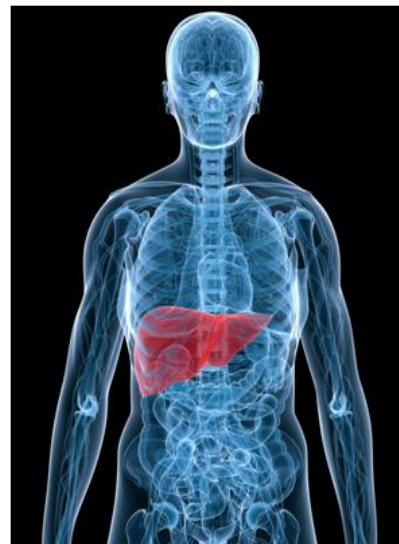


Figure 1 Metabolism happens mainly in the liver, the body's largest internal organ. The portal vein carries blood from the small intestine directly to the liver. Sixty percent of liver tissue is made up of hepatic cells. More chemical processes happen in these than in any other group of cells in the body.

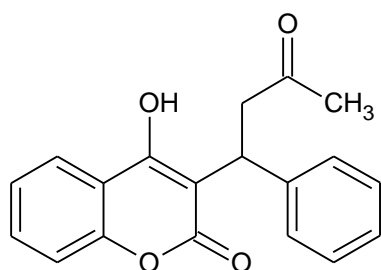


Figure 2 Warfarin is used as an anti-coagulant. None of its metabolites are pharmacologically active and they are excreted by the kidney.

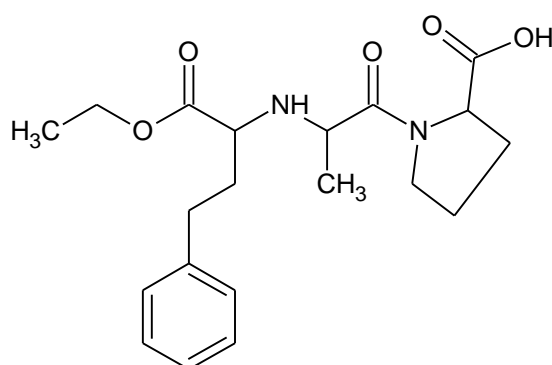


Figure 3 Enalapril is used to treat hypertension and chronic heart failure. However, the compound itself is not a drug – it is a prodrug. Its metabolites are pharmacologically active.

Phase 2 metabolism involves reactions that chemically change the drug or phase 1 metabolites into compounds that are soluble enough to be excreted in urine. In these reactions, the molecule

(drug or metabolite) is attached to an ionisable grouping. This is called conjugation and the product is called a conjugate. Metabolites formed in phase 2 are unlikely to be pharmacologically active.

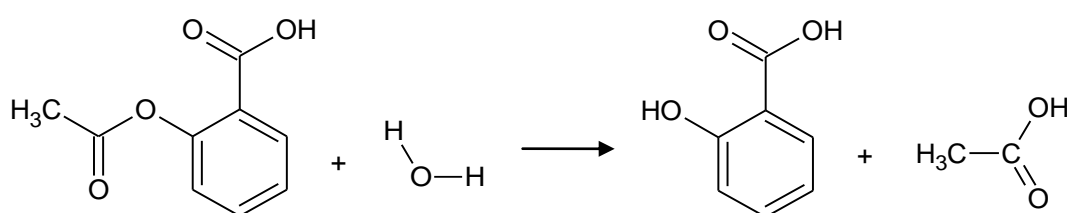
Phase 1 and/or phase 2

Some drugs undergo either phase 1 or phase 2 metabolism, but most undergo phase 1 metabolism followed by phase 2 metabolism.

An example: the metabolism of aspirin

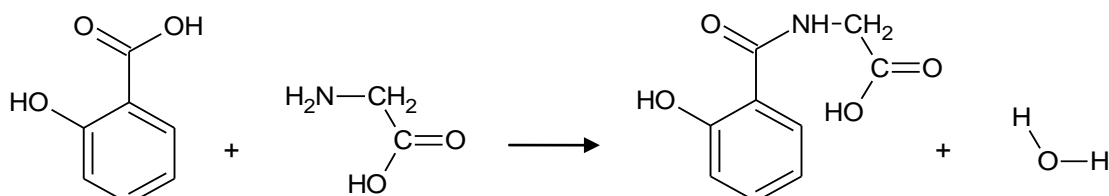
Phase 1

Aspirin (2-ethanoyloxybenzoic acid) hydrolyses to produce 2-hydroxybenzoic acid and ethanoic acid.



Phase 2

Aspirin conjugates glycine or glucuronic acid to make several ionised metabolites that can then be excreted in the urine. For example, glycine conjugates using Coenzyme A (CoA) and energy transferred from chemical reactions involving adenosine triphosphate (ATP):



Finding out

What types of chemical processes happen in the liver's hepatic cells?

Look at the example of a conjugation reaction in the phase 2 metabolism of aspirin. Why is the product of the reaction more soluble in water than aspirin or 2-hydroxybenzoic acid?

Enalapril is an example of a prodrug. Find some other examples.