

Phase I reactions

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Keywords: phase I reactions, drug metabolism, chemical reactions

Introduction

Phase I reactions fall under the broad topic of drug metabolism. Metabolism describes the chemical reactions that change drugs into compounds that are easier to eliminate. The reactions are catalysed by enzymes and happen mostly in the liver, though some reactions take place in the gut wall, lungs and blood plasma.¹ Drug metabolism is divided into two phases: Phases I and II. This talk will focus on phase I.

Phase I reactions

There are three possible results of phase I metabolism.²

1. The drug becomes completely inactive, e.g. warfarin.
2. One or more of the metabolites produced become pharmacologically active, e.g. morphine.
3. The original substance is not pharmacologically active, but one of its metabolites is. The original substance is called a prodrug, e.g. enalapril, midazolam.²

Phase I reactions are broadly grouped into three categories - oxidation (most common), reduction and hydrolysis.³

Phase I reactions often make the metabolite more water soluble.

Most drugs undergo phase I metabolism followed by phase II metabolism; however, some drugs undergo either phase I or phase II metabolism, e.g. aspirin.²

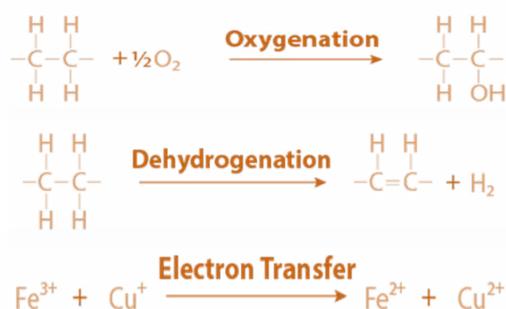


Figure 1: Three types of oxidation reactions³

Oxidation

Oxidation is a chemical reaction in which a drug loses electrons. There are several reactions that can achieve the removal of electrons from the drug.³

The addition of oxygen was the first of these reactions to be discovered and thus the reaction was named oxidation. However, many oxidising reactions do not involve oxygen.³ Figure 1 illustrates some oxidising reactions.

Reduction

Reduction is a chemical reaction in which the metabolite gains electrons.³ There are fewer specific reduction reactions than oxidising reactions.³ Reducing reactions include:

- Azo reduction
- Dehalogenation
- Disulphide reduction
- Nitro reduction
- N-oxide reduction
- Sulfoxide reduction³

Hydrolysis

Hydrolysis is a chemical reaction in which the addition of water splits the metabolite into two fragments or smaller molecules.³ A hydroxyl group (OH^-) is incorporated into one fragment and a hydrogen atom is incorporated into the other.³ Larger chemicals such as esters and amines are generally biotransformed by hydrolysis.³

Cytochrome P-450 enzymes

The most important enzyme system of phase I metabolism is cytochrome P-450 (CYP450), a superfamily of isoenzymes that catalyses the oxidation of many drugs. Although this superfamily has more than 50 enzymes, six of them metabolise 90 per cent of drugs, with the two most significant enzymes being CYP3A4 and CYP2D6.⁴

CYP450 enzymes are membrane-bound proteins, present in the smooth endoplasmic reticulum of liver and other tissues.

Table I: CYP450 inhibitors and inducers⁴

Enzymes	Inhibitors	Inducers
CYP1A2	Amiodarone, cimetidine, ciprofloxacin	Carbamazepine, phenobarbital, rifampin, tobacco
CYP2C9	Amiodarone, fluconazole, fluoxetine, metronidazole, ritonavir, <i>bactrim</i>	Carbamazepine, phenobarbital, phenytoin, rifampin
CYP2C19	Fluvoxamine, isoniazid, ritonavir	Carbamazepine, phenytoin, rifampin
CYP2D6	Amiodarone, cimetidine, fluoxetine, quinidine, ritonavir	No significant inducers
CYP3A4 and CYP3A5	Clarithromycin, erythromycin, ketoconazole, ritonavir, verapamil	Carbamazepine, phenobarbital, phenytoin, rifampin

CYP450 enzymes are so named because they are bound to membranes within a cell (cyto) and contain a heme pigment (chrome and P) that absorbs light at a wavelength of 450 nm when exposed to carbon monoxide.⁴

Drugs interact with the CYP450 system in several ways. Drugs may be metabolised by only one CYP450 enzyme or by multiple enzymes.⁴

CYP450 enzymes can be inhibited or induced by drugs, resulting in clinically significant drug-drug interactions. These can be advantageous or detrimental.⁴

Inhibitors block the metabolic activity of one or more CYP450 enzymes. Inhibitory effects usually occur immediately. Inducers increase CYP450 enzyme activity by increasing enzyme synthesis. Unlike metabolic inhibition, there is usually a delay before enzyme activity increases.⁴

Conclusion

The most common phase I reaction is oxidation. Phase I reactions in general produce a more water-soluble metabolite. The majority of metabolites are generated by the CYP450 system.

Conflict of interest

The author declares no conflict of interest.

Funding source

None.

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