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# Drug Metabolism

MBChB 221B

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## Why is Drug Metabolism important?

In changing the molecular structure, drug metabolism can directly influence the concentration-time profile in the body

- time to peak concentration, peak concentration, time to be eliminated etc

*This is important because* ***concentration relates to drug effect***

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## Learning objectives

To understand

- what drug metabolism involves
- how drug metabolism can influence concentration, duration of action and perhaps influence route of administration
- The potential role in drug-drug interactions and toxicity

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## Drug metabolism

Metabolism is the biotransformation of drugs
- Enzyme-catalysed chemical change to the drug molecule; either building molecule up or breaking down

- Plays a vital role in drug *elimination*
  - Elimination = metabolism + excretion
  - Altering the chemical structure of the molecule often means its ability to move around the body is altered (easier to excrete)

- Metabolism often terminates drug activity by changing the structure of the drug, it changes how that drug can interact with targets (e.g. receptors)
  - Generally decreases activity (drug structure has been optimised for interaction with target)
  - Increased drug activity
    - Activation of prodrug (e.g. codeine → morphine)
  - No change in activity
    - Metabolite is also biologically active (e.g. diazepam → nordiazepam)
  - Production of toxic metabolites
    - e.g. paracetamol → NAPQI

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## Possible sites of drug metabolism

- Liver
  - Major site of drug metabolism
- Intestinal wall
  - CYP450 enzymes
- GI tract
  - Gut bacteria and proteases
- Plasma
  - Esterases (prodrug activation)
- Lungs
  - Metabolism of aerosol sprays

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## First-Pass Metabolism

- Drugs taken orally may be metabolised as they pass through the gut wall or when they first reach the liver **before** they reach the target site
- May limit the usefulness of oral route of administration
  - Morphine
  - Nitroglycerine (TGN)
- May necessitate an alternative route of administration (e.g. sub-lingual for TGN) or the need to develop a prodrug

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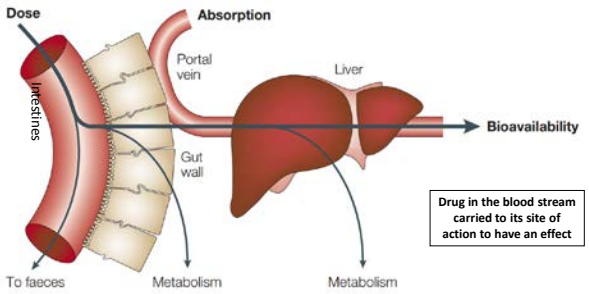
## Influence of first pass metabolism on the amount of oral drug that gets into the bloodstream




Van de Waterbeemd and Griffin. Nat Rev Drug Discov. 2: 192–204, 2003

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## Metabolic reactions

- **Oxygenation**
  - Increase proportion of oxygen on the molecule
- Reduction
- Hydrolysis
  - Water molecule is added to compound, usually resulting in bond cleavage
- Conjugation
  - Addition of endogenous substrate
  - usually increase molecular mass, polarity, water solubility
  - Glucuronidation, sulfation, acetylation, glutathionylation

*Enzymatic metabolism processes may occur in sequentially, may compete, or may not occur at all; opportunistic!*

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## Oxidation

- CYP450 family most important oxidative enzymes (cytochrome P450 dependent mixed function oxidases, located on the smooth endplasmic reticulum)
- Oxidation can occur by other enzymes:
  - Alcohol dehydrogenase
  - Aldehyde dehydrogenase
  - Aromatase
  - Amine oxidases
  - …and others! ANY enzyme can be a 'drug metabolising enzyme' if a drug has a close structural resemblance to its endogenous substrate

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# CYP450 family

- Superfamily of more than 20 gene families in humans, just 4 isoforms responsible for majority of phase I oxidative reactions (CYP3A4, CYP2D6, CYP2C9 and CYP2C19)
- Requires $O_2$, NADPH and cytochrome P450 reductase
- Five features of CYP oxidation:

1. Substrate binding
2. Oxygen binding
3. Oxygen splitting
4. Inserting oxygen into substrate
5. Release of the metabolite

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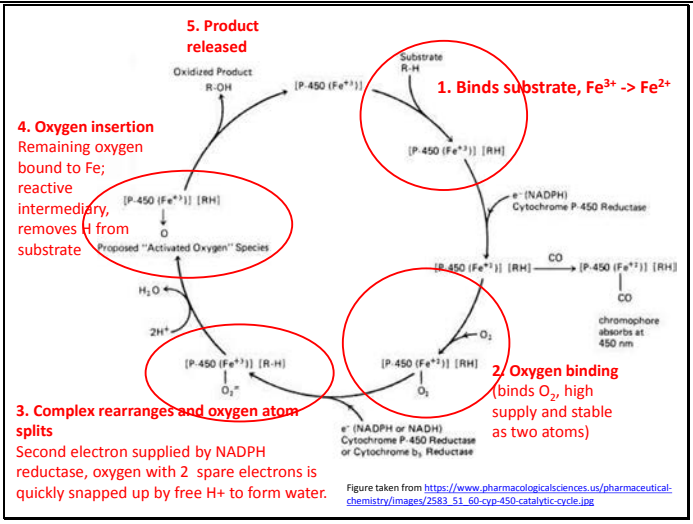


Figure taken from https://www.pharmacologicalsciences.us/pharmaceutical-chemistry/images/2583_51_60-cyp-450-catalytic-cycle.jpg

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# Nomenclature of CYPs

**CYP 3 A 4**

**cytochrome**

**p450**

**Family**
Genes contain at least 40% sequence homology

At least 74 families identified, 17 found in humans

**Subfamily**
>60% aminoacid homology

**Isoform**
Specific gene variations may account for differences in activity

*Drugs that are metabolized by the same CYP enzyme may show drug-drug interactions*

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## Localisation of CYPs

| CYP | % in liver | Other significant sites of expression |
|---|---|---|
| **CYP3A4** | **>35** | ~70% of intestinal CYP, also in kidney, lung, placenta & uterus |
| **CYP2D6** | **<5** | Low expression & activity in intestine; less than 5% of hepatic CYP but activity is high (~20% of CYP drug metabolism) |
| **CYP2C9** | **>15** | ~15% of total intestinal CYP |
| CYP2E1 | ~15 | Not responsible for much drug metabolism in liver. Also in lung & placenta |
| **CYP2C19** | **<5** | |

Table adapted from Basic pharmacokinetics and pharmacodynamics: An integrated textbook and computer simulations. S E Rosenbaum. John Wiley & Sons, Inc. 2011

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## CYP1A2

- Marker drug: Theophylline
- Clinically-relevant drugs:
  - Theophylline
  - Clozapine
- Drug interactions:
  - Cimetidine
  - Tobacco (smoking); diet

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## CYP2E1

- Marker drug: Ethanol
- Clinically-relevant drugs:
  - Paracetamol
- Drug interactions:
  - Ethanol: chronic ethanol consumption increases CYP2E1 expression so may increase the formation of the toxic metabolite of papracetamol

| | | |
|---|---|---|
| Slide 16 | **CYP2C9**<br>• Marker drug: *S*-Warfarin<br>• Clinically-relevant drugs:<br>– Warfarin<br>• Drug interactions:<br>– Inhibitors such as cimetidine increase activity<br>– Inducers such as rifampicin decrease activity | |
| Slide 17 | **CYP2C19**<br>• Marker drug: *Omeprazole; proguanil*<br>• Clinically-relevant drugs:<br>– Omeprazole<br>– Cyclophosphamide<br>– Clopidogrel<br>• Genetic polymorphisms may play important role<br>– See Nuala Helsby lecture | |
| Slide 18 | **CYP2D6**<br>• Marker drug: *Debrisoquine*<br>• Clinically-relevant drugs:<br>– Tricyclic antidepressants (amitriptyline)<br>– Beta blockers (metoprolol)<br>– Codeine<br>• Genetic polymorphisms may play important role<br>– See Nuala Helsby lecture | |

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## CYP3A4

- Marker drug: *Erythromycin*
- Clinically-relevant drugs:
  - Major enzyme for ~ 30% of drugs currently on the market
  - Calcium channel blocker (felodipine)
  - HMG-CoA reductase inhibitor (simvastatin)
  - Immunosuppressant (ciclosporine)
- Drug-drug interactions rather than genetic polymorphism are the major concern
  - Grapefruit juice an inhibitor
  - St John's wort an inducer
  - See Nuala Helsby lecture

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## Conjugation reactions

- Glucuronidation is major pathway
- Often follows on from CYP-catalysed reaction but not all drugs require prior metabolism
  - concept of phase I & phase II reactions
- Because large change in the physicochemical properties of the drug molecule, nearly always leads to loss of pharmacological activity
  - Notable exception is morphine, where morphine-6-glucurionide is more active
- Large capacity, so not so readily prone to drug-drug interactions
- Overlapping substrate selectivity means less prone to the effects of genetic polymorphisms

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## Factors influencing drug metabolism