Drug Metabolism

1. What **is** drug metabolism?
   1. And what is it **not**?
2. Describe the general model for metabolism
   1. What steps are there?
   2. Where do they occur?
   3. What catalyses them?
3. In what ways can metabolism vary from individual to individual and with time?
   1. Give some examples

Drug Metabolism

Drug metabolism includes any process within the body that changes the drug but does not eliminate it. Some key points:

|  |
| --- |
| It is not **detoxification** *Many metabolic products are less toxic, but not all* |

|  |
| --- |
| It is not **deactivation**  *Many metabolic products are less active, but not all* |

# Some History

Richard Tecwyn Williams, a Welsh biochemist, is responsible for the current language describing metabolism.

He realised that a relatively small number of reactions were responsible for most transformations of drugs:

* Non-synthetic reactions
  1. Oxidation
  2. Reduction
  3. Hydrolysis
* Conjugation/Synthetic reactions
  1. Glucuronidation
  2. Sulfation
  3. Acetylation
  4. Methylation

He also realised that there was often a well-defined order in which these things happened:

1. **Phase 1:** non-synthetic reactions
2. **Phase 2:** synthetic reactions

And thus, the terminology was borne. As time has gone on many exceptions to this have been discovered but the language remains.

# General effects of metabolism

Although the only defining feature of metabolism is change, various other properties are commonly observed too:

1. Increased water solubility
2. Decreased toxicity (*but look out for many important exceptions*)
3. Decreased activity (*but remember pro-drugs and drugs with active metabolites*)

# Sites of metabolism

## Organ-specific metabolism

Metabolism of drugs occurs in many organs:

1. Liver (*probably the most generally important*)
2. Lungs
3. Kidneys
4. Gut
5. Brain
6. Plasma

The key idea is that, whilst the liver is very important, it cannot be assumed to be the only site of significant metabolism. The most important site is agent-specific.

## Non-organ-specific metabolism

Some substances break down spontaneously in plasma without the help of enzymes or specific process.

An example of this the Hofmann elimination of atracurium. (Note: the phrase Hofmann elimination is sometimes used incorrectly as a general term for this spontaneous breakdown)

# Common metabolic reactions

It is common to describe metabolic processes as have a **phase 1** (non-synthetic) component, and a **phase 2** (synthetic) component, and to describe them as happening sequentially.

This is not universally true but many descriptions use this as a base for understanding and then describe the exceptions.

## Phase 1 reactions

The P450 system is a mixed-function oxidase system responsible for many observed phase 1 reactions.

It is found in the endoplasmic reticulum in the liver. It is also distributed in various other tissues including the lungs and kidneys.

Enzymes in this group are further subdivided into families (CYP1, CYP2, CYP3 etc.) and subfamilies (CYP3A, CYP3B etc.), and isoforms (CYP1A1) based on shared amino acid sequences.

There is considerable genetic and functional variation.

## Phase 2 reactions

These mostly occur in the liver (but also the lungs amongst others) and are catalysed by a variety of non-specific enzymes.

# Variation in Metabolism

## Acquired variation

Metabolic enzymes are susceptible to induction or inhibition by some drugs leading to unpredictable handling of otherwise unrelated substances:

* **Inhibitors:** cimetidine, most antibiotics
* **Inducers:** rifamycins, alcohol, smoking, many anticonvulsants

## Inherited variation

### Phase 1: ultrafast metabolisers of codeine

Inherited ultrafast P450 enzymes responsible for the metabolism of codeine result in rapid conversion to morphine which appears to lead to:

1. Lots of side effects
2. Poor analgesic properties

### Phase 2: fast acetylators

Acetylation seems to have a particularly wide variation in speeds amongst large portions of the world’s population:

* Roughly 50:50 split in Caucasians and African Americans

In some drugs, the higher levels resulting from slow acetylation can be problematic:

* Isoniazid efficacy is unaffected
* Higher rates of peripheral neuropathy amongst slow acetylators