UNIT I

DRUG METABOLISM (Part 1)

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DRUG METABOLISM

Drug → Phase 1 → Active drug → Phase 2 → Inactive drug

Drug Metabolism

Liver → Inactive Excretion Products

Toxic Intermediates → Urine → Bile
DRUG METABOLISM

- **Definition**: Process of converting a drug into product or inert substances after or before reaching at the site of action.

- **Metabolism** is an essential pharmacokinetic process, which render lipid soluble and non polar compounds to water soluble and polar compounds so that they are excreted by various process from the body.

- **Biotransformation**: It is a specific term used for the chemical transformation of xenobiotics in the living organisms.

- **Xenobiotics**: These are all chemical substances that are not nutrient for the body (foreign body) and which enter the body through ingestion, inhalation or dermal exposure.
DRUG METABOLISM

- Most organic compounds entering the body are relatively lipid soluble (lipophilic).
- To be absorbed, they must traverse the lipoprotein membranes of the lumen walls of the gastrointestinal (GI) tract.
- Then, once in the bloodstream, these molecules can diffuse passively through other membranes and be distributed effectively to reach various target organs to exert their pharmacological actions.
- Because of reabsorption in the renal tubules, lipophilic compounds are not excreted to any substantial extent in the urine.
DRUG METABOLISM

- Xenobiotics then meet their metabolic fate through various enzyme systems that change the parent compound to render it more water soluble (hydrophilic).
- Once the metabolite is sufficiently water soluble, it may be excreted from the body.
- The previous statements show that a working knowledge of the ADME (absorption, distribution, metabolism, and excretion) principles is vital for successful determination of drug regimens.
DRUG METABOLISM

- If lipophilic drugs, or xenobiotics, were not metabolized to polar, readily excretable water-soluble products, they would remain indefinitely in the body, eliciting their biological effects.

- Thus, the formation of water-soluble metabolites not only enhances drug elimination, but also leads to compounds that are generally pharmacologically inactive and relatively nontoxic.
Consequently, drug metabolism reactions have traditionally been regarded as detoxication (or detoxification) processes.

Unfortunately, it is incorrect to assume that drug metabolism reactions are always detoxifying.

Many drugs are biotransformed to pharmacologically active metabolites. These metabolites may have significant activity that contributes substantially to the pharmacological or toxicological effects ascribed to the parent drug.

Occasionally, the parent compound is inactive when administered and must be metabolically converted to a biologically active drug (metabolite).

These types of compounds are referred to as Prodrugs.
Functions of Biotransformation

- It causes conversion of an active drug to inactive or less active metabolite(s) called as **pharmacological inactivation**.

- It causes conversion of an active to more active metabolite(s) called as **bioactivation** or **toxicological activation**.

- It causes conversion of an inactive to more active toxic metabolite(s) called as **lethal synthesis**.

<table>
<thead>
<tr>
<th>Phenobarbitone</th>
<th>p-Hydroxyphenobarbitone</th>
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<tbody>
<tr>
<td>Phenytoin</td>
<td>p-Hydroxyphenytoin</td>
</tr>
<tr>
<td>Procaine</td>
<td>p-Aminobenzoic acid</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>6-Demethylgriseofulvin</td>
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<table>
<thead>
<tr>
<th>Codeine</th>
<th>Morphine</th>
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<tbody>
<tr>
<td>Paracetamol</td>
<td>Imidoquinone of</td>
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<td>N-hydroxylate</td>
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<tr>
<td>Sulphonamides</td>
<td>Acetyl derivatives</td>
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<tr>
<td>Malathion</td>
<td>Malaoxon</td>
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<tr>
<td>Halothane</td>
<td>Trifluoroacetic acid</td>
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</tbody>
</table>
Functions of Biotransformation....contd

- It causes conversion of an inactive drug (pro-drug) to active metabolite(s) called as **pharmacological activation**

- It causes conversion of an active drug to equally active metabolite(s) (**no change** in pharmacological activity)

- It causes conversion of an active drug to active metabolite(s) having entirely different pharmacological activity (**change** in pharmacological activity)
Sites of Metabolism

- Liver
- GIT
- Lungs
- Kidney
- Plasma
- Skin
- Nasal Mucosa
- Others
Site/Organs of drug metabolism

The **major site** of drug metabolism is the **liver** (microsomal enzyme systems of hepatocytes)

**Secondary organs** of biotransformation

- kidney (proximal tubule)
- lungs (type II cells)
- testes (Sertoli cells)
- skin (epithelial cells); **plasma, nervous tissue (brain); intestines**
Sites of Biotransformation...contd

**Liver**

- The primary site for metabolism of almost all drugs because it is relatively rich in a large variety of metabolising enzymes.

- Metabolism by organs other than liver (called as extra-hepatic metabolism) is of lesser importance because lower level of metabolising enzymes is present in such tissues.

- Within a given cell, most drug metabolising activity is found in the smooth endoplasmic reticulum and the cytosol.

- Drug metabolism can also occur in mitochondria, nuclear envelope and plasma membrane.

- A few drugs are also metabolised by non-enzymatic means called as non-enzymatic metabolism.
Microsomal enzymes: The endoplasmic reticulum (especially smooth endoplasmic reticulum) of liver and other tissues contain a large variety of enzymes, together called microsomal enzymes.

(microsomes are minute spherical vesicles derived from endoplasmic reticulum after disruption of cells by centrifugation, enzymes present in microsomes are called microsomal enzymes).

They catalyse glucuronide conjugation, most oxidative reactions, and some reductive and hydrolytic reactions.

The monooxygenases, glucuronyl transferase, etc are important microsomal enzymes.
Non-microsomal enzymes: Enzymes occurring in organelles/sites other than endoplasmic reticulum (microsomes) are called non-microsomal enzymes.

These are usually present in the cytoplasm, mitochondria, etc. and occur mainly in the liver, GI tract, plasma and other tissues.

They are usually non-specific enzymes that catalyse few oxidative reactions, a number of reductive and hydrolytic reactions, and all conjugative reactions other than glucuronidation.

None of the non-microsomal enzymes involved in drug biotransformation is known to be inducible.
TYPES

BIOTRANSFORMATION REACTIONS - 2 TYPES

- Phase I / Non synthetic / Functionalization
  - A functional group is generated
  - Metabolite – active or inactive

- Phase II / Synthetic / Conjugation
  - An endogenous radical is conjugated
  - Metabolite is usually inactive
TYPES OF BIOTRANSFORMATION

Phase I reaction. (Non synthetic phase).
- a change in drug molecule. generally results in the introduction of a functional group into molecules or the exposure of new functional groups of molecules

- Phase I (non-synthetic or non-conjugative phase) includes reactions which catalyse oxidation, reduction and hydrolysis of drugs.

- In phase I reactions, small polar functional groups like-OH, -NH$_2$, -SH, -COOH, etc. are either added or unmasked (if already present) on the lipid soluble drugs so that the resulting products may undergo phase II reactions.
- result in activation, change or inactivation of drug.

Phase II reaction. (Synthetic phase)
- Last step in detoxification reactions and almost always results in loss of biological activity of a compound.
- May be preceded by one or more of phase one reaction
- Involves conjugation of functional groups of molecules with hydrophilic endogenous substrates- formation of conjugates - is formed with (an endogenous substance such as carbohydrates and amino acids. )with drug or its metabolites formed in phase 1 reaction.
- Involve attachment of small polar endogenous molecules like glucuronic acid, sulphate, methyl, amino acids, etc., to either unchanged drugs or phase I products.
- Products called as 'conjugates' are water-soluble metabolites, which are readily excreted from the body.
• Phase I metabolism is sometimes called a “functionalization reaction.”
• Results in the introduction of new hydrophilic functional groups to compounds.
• **Function:** introduction (or unveiling) of functional group(s) such as −OH, −NH₂, −SH, −COOH into the compounds.
• **Reaction types:** oxidation, reduction, and hydrolysis

• **Enzymes:**
  - **Oxygenases and oxidases:** Cytochrome P450 (P450 or CYP), flavincontaining
  - monoxygenase (FMO), peroxidase, monoamine oxidase (MAO), alcohol dehydrogenase, aldehyde dehydrogenase, and xanthine Oxidase. **Reductase:** Aldo-keto reductase and quinone reductase.
  - **Hydrolitic enzymes:** esterase, amidase, aldehyde oxidase, and alkyldhrazine
  - oxidase.
  - Enzymes that scavenge reduced oxygen: Superoxide dismutases, catalase,
  - glutathione peroxidase, epoxide hydrolase, y-glutamyl transferase,
  - dipeptidase, and cysteine conjugate β-lyase

• **Phase II metabolism includes what are known as conjugation reactions.**
• Generally, the conjugation reaction with endogenous substrates occurs on the metabolite(s) of the parent compound after phase I metabolism; however, in some cases, the parent compound itself can be subject to phase II metabolism.
• **Function:** conjugation (or derivatization) of functional groups of a compound or its metabolite(s) with endogenous substrates.
• **Reaction types:** glucuronidation, sulfation, glutathione-conjugation, Nacetylation, methylation and conjugation with amino acids (e.g., glycine, taurine, glutamic acid).
• **Enzymes:** Uridine diphosphate-Glucuronosyltransferase (UDPGT): sulfotransferase (ST), N-acetyltransferase, glutathione S-transferase (GST), methyl transferase, and amino acid conjugating enzymes.
  - Glucuronidation by uridine diphosphate-glucuronosyltransferase; Sulfation by sulfotransferase

3. Acetylation by N-acetyltransferase; Glutathione conjugation by glutathione S-transferase; Methylation by methyl transferase; Amino acid conjugation
DRUG METABOLISM

Drug → Metabolism → More polar (water soluble) Drug → Excretion
Fig. 3.1: Simultaneous and/or sequential metabolism of a drug by phase I and phase II reactions.
The detailed discussion about Phase I and Phase II reactions will proceed in the next part of slides.
THANK YOU