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Biotransformation.

- Chemical reaction which occur in body to change drug from nonpolar lipid soluble form to polar water soluble form that can easily excreted by the kidney.

- elimination of xenobiotic often depends on their conversion to water-soluble chemicals through biotransformation, catalyzed by multiple enzymes primarily in the liver with contributions from other tissues.

Importance of Metabolism.

- Inactivation or termination of drug action.
- detoxification Biotransformation is required for protection of body from toxic metabolite).
- activation of prodrug (convert inactive form of drug to active form)

eg: levodopa - carbidopa,
prednisone - prednisolone.

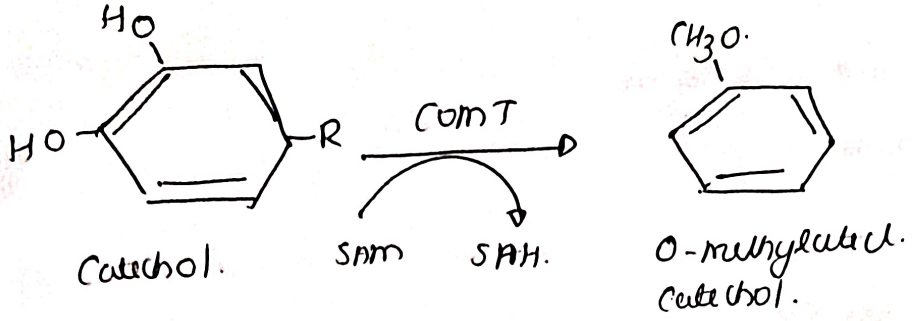
Organ Sites of drug Metabolism

- Liver (major site).
- Intestinal mucosa & lumen.
- plasma
- kidney.
- Skin
- lung.

Plasma

Enzymes	Substrate
Catechol-O-methyl transferase (COMT)	catecholamines (eg: adrenaline)
• Esterases.	Esters. act on drugs. local anesthetics.
Amidases.	Amides. act on drugs local anesthetics.

Catechol - O - Methyl transferase.



Catechol. O-methylated Catechol.

• Cellular sites of drug metabolism.

• cytoplasm
• Mitochondria.
• lysosomes.
• microsomes.

→ Mitochondria
• N-acetyl transferase.
• Introduction of acetyl group.
• monoamine oxidase enzyme.
• oxidation of catecholamines as adrenaline.

• cytoplasm.
• eg. Alcohol dehydrogenase : oxidation of alcohol.
• alcohol → aldehyde acid.
• Ethanol → acetaldehyde → acetic acid.
• $CH_3CH_2OH \rightarrow CH_3CHO \rightarrow CH_3COOH$

microsomes.
• microsomal enzyme system = cytochrome - P-450.
• there are more than 20 families CYP1, CYP2, CYP3.
• subfamilies are identified as A, B, and etc.
• In human, only 3 isoenzyme families are impt CYP1, CYP2 & CYP3.
• cytochrome P450 enzymes. are the most important in biotransformation in terms of the catalytic versatility and number of xenobiotics that it metabolizes : 400 isoenzyme & 36 families.

Oxidation - cytochrome P-450

- CYP 3A4/5 carry out biotransformation of the largest number (30-50%) of drugs.
- Expressed in liver & intestine (responsible for first pass metabolism at this site).

CYP.

- most CYPs are located in the liver ER (microsome)
- CYP's are heme-containing proteins.
- microsomal & mitochondrial CYPs play key roles in biosynthesis or catabolism of steroid hormones, bile acids, fat-soluble vitamins, fatty acids & eicosanoids.
- CYP (gene family) (subfamily) (individual gene).
  - CYP 1A2: metabolizes caffeine.
  - CYP 3A4 → most abundant CYP with broad substrate-specificity

- CYP2E1 – metabolizes acetaminophen and ethanol.
- CYP interaction with CYP reductase

CYP3A4

Organ: Liver, small intestine.

- Substrates – aflatoxin, benzo(a) pyrene, other PAHs.
- Inducers. PCB, DDT, many drugs.
- CYP3A4 is the major CYP in human liver.

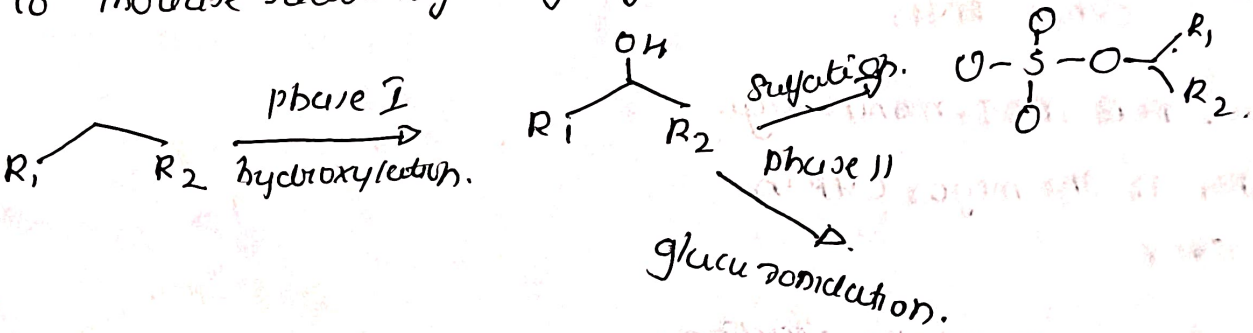
Types of hepatic metabolic reactions.

- two phases of hepatic metabolism
- phase-1 metabolic reactions include.
  - oxidation
  - reduction.

phase I & II Biotransformation

- reactions catalyzed by xenobiotic biotransforming enzymes are generally devided to 2 groups - phase I & II.

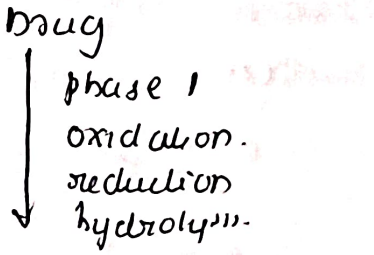
1. phase I reactions involve hydrolysis, reduction & oxidation, exposing or introducing a functional group (-OH, NH_2, SH or COOH) to increase reactivity slightly increases hydrophilicity



2. phase II rxn include glucuronidation, sulfation, acetylation

Types of hepatic metabolic reactions.

- phase I – Metabolites may be active or inactive.
- phase-II – metabolites are inactive.



activation / inactivation.

oxidation reactions

- oxidation
- is addition of oxygen or removal of hydrogen.
- is the most impt drug metabolizing reaction.
- may be microsomal or non-microsomal.

- microsomal oxidation.
- occurs in microsomes.

eg: cytochrome P450 enzymes, NADPH & oxygen.

- Non microsomal oxidation.
- occurs in cytosol or mitochondria.
- these enzymes include. Oxidases & dehydrogenases

Non-microsomal oxidation.

- dehydrogenase.
- required for oxidation of alcohols.
- eg: alcohol dehydrogenase (converts alcohol → aldehyde)

eg. aldehyde dehydrogenase (converts aldehyde → acid)

- Non microsomal oxidation

- oxidases

① Monoamine oxidase (MAO)

is responsible for the metabolism of catecholamines & serotonin

Eg: Moclobemide

- is a monoamine oxidase inhibitor
- for depression treatment.
- used as antidepressant drugs

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② xanthine oxidase

is required for catabolism of xanthine.

- hypoxanthine → xanthine → uric acid

- uric acid accumulation → gout

- allopurinol
- is an inhibitor
- used in treatment of gout

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- required for oxidation of alcohols.
- eg: alcohol dehydrogenase (converts alcohol → aldehyde)

eg. aldehyde dehydrogenase (converts aldehyde → acid)

- Non-microsomal oxidation.

- oxidases.

① Monoamine oxidase (MAO).

is responsible for the metabolism of catecholamines ie adrenaline & serotonin.

eg: moclobemide.

- Is a monoamine oxidase inhibitor
- It increases serotonin in brain.
- used as antidepressant drug.

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② xanthine oxidase.

is required for oxidation of xanthine.

- hypoxanthine → (oxidase) → xanthine → (oxidase) → uric acid.

- uric acid accumulation → GOUT.

- allopurinol.
- Is an inhibitor of xanthine oxidase.
- used in treatment of gout.

Monoamine oxidase

5-hydroxytryptamine (serotonin) $\xrightarrow{MAO}$ 5-hydroxyindole acetic acid.

reduction reaction

- removal of oxygen or addition of hydrogen.
- may be microsomal or non microsomal.

eg: levodopa.

Levodopa $\xrightarrow{\text{DOPA-decarboxylase}}$ dopamine.

hydrolysis

- all are non-microsomal.
- occurs by addition of water molecules in presence of enzymes as. (esterases & amidases)
- esterases – hydrolyze drugs that are esters.
- amidases – hydrolyze drugs that are amides.

Hydrolysis

- esters are acetylcholine. (neurotransmitter)

ester + H_2O → acid + alcohol.

acetylcholine $\xrightarrow{\text{esterase}}$ acetate + choline.

- Amides as lidocaine (used as local anesthetic)

amide + H_2O → acid + amine.

Phase I reactions can result in.

- activation of pro-drug.

eg: levodopa to dopamine.

- inactivation of drug. (termination of action)
- conversion of active drug to active metabolite.
- conversion of non toxic drug to toxic metabolite.
- paracetamol → hepatotoxic metabolite
- product might undergo phase II

phase II Conjugation reaction

- conjugation of metabolite coming from (phase I) with endogenous substances a) methyl group
- acetyl group
- sulphate
- amino acid
- glucuronic acid
- to produce conjugate that is water soluble and easily excreted in urine or bile.

phase-II metabolic rxn.

- all are non microsomal except glucuronidation
- glucuronide conjugation is a microsomal process (most common phase II rxn)
- deficiency of glucuronyl transferase enzyme in neonates may result into toxicity with chloramphenicol (gray baby Syndrome).

Types of Conjugation reactions

C. rxn	Enzyme req.
glucuronide conjugation	glucuronyl transferase
Acetylation CH_3COO^-	N-acetyl transferase
Sulphation (SO_4^{2-})	sulfo transferase
methylation (CH_3)	methyl transferase
amino acid conjugation	glycine conjugation

Characteristics of phase II Metabolites

- phase II metabolites are: usually pharmacologically inactive
- polar
- more water soluble
- easily excreted in urine

Mother of Enzyme Inducers

Factors affecting metabolism of drugs

- age: ↓ rate of metabolism in neonates & elderly
- diseases → ↓ rate of metabolism in liver diseases.
- degree of protein binding ↓ rate of metabolism.
- concurrent use of drugs: Induction & inhibition.
- Nutrition: malnutrition ↓ rate of metabolism.
- Genetic polymorphism.

Factors affecting metabolism

- metabolism may vary from population to another due to existence of different forms of the metabolic enzymes.

eg: metabolism of isoniazid (anti-TB) etc.

- Slow acetylator phenotype → results in decrease in isoniazid metabolism & accumulation of isoniazid with risk of peripheral neuropathy.
- Rapid acetylator phenotype → results into excess metabolites produced with risk of hepatitis.

Enzyme Induction & Inhibition

- Liver microsomal enzymes inducers: drugs that increase activities of liver microsomal enzymes & increase the metabolism of drug itself and other drugs taken with the inducers at same time
- Liver microsomal enzyme inhibitors
- drugs that decrease activities of liver microsomal enzymes and decrease the metabolism of drug itself and other drugs taken concurrently.

Enzyme Inducers

- alcohol
- cigarette smoking
- phenobarbitone hypnotic
- phenytoin (antiepileptic)
- rifampicin (anti TB)
- grape fruits.
- cimetidine.
- erythromycin (antibiotic).
- ketoconazole (antifungal)

Eg.

Enzyme Induction may result in:

- ↑ metabolism and excretion of the inducer drug itself and co-administered drug.
- ↓ action of inducer drug itself & co-administered drug.
- Tolerance may occur: decrease in the pharmacological action of the drug by continuous or repeated administration.
- drug interaction may occur:

decrease in action of one drug by administration of another drug.

- eg oral contraceptive & phenytoin
- failure of oral contraceptive may lead to pregnancy if used with phenytoin.
- ↓ delay the metabolism & excretion of the inhibitor drug & co-administered drug.
- ↑ prolong the action of inhibitor drug & co-administered drug.

eg: warfarin & erythromycin

- Inhibition of warfarin metabolism may lead to increase it's anticoagulant effect (risk of bleeding).