Biopharmaceutics & Pharmacokinetics
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Biotransformation of drug – Phase II reactions

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PHASE 2 REACTIONS

- Phase II or conjugation (Latin, conjugatus = yoked together) reactions involve combination of the drug or its phase I metabolite with an endogenous substance to form a highly polar product, which can be efficiently excreted from the body.
- In the biotransformation of drugs, such products or metabolites have two parts:

Exocon, the portion derived from exogenous compound or xenobiotic

Endocon, the portion derived from endogenous substance.

- Conjugation reactions have high energy requirement and they often utilise suitable enzymes for the reactions.

- The endogenous substances (endocons) for conjugation reactions are derived mainly from carbohydrates or amino acids and usually possess large molecular size.
- They are strongly polar or ionic in nature in order to render the substrate water-soluble. The molecular weight of the conjugate (metabolite) is important for determining its route of excretion.
- High molecular weight conjugates are excreted predominantly in bile (e.g., glutathione exclusively, glucuronide mainly),while low molecular weight conjugates are excreted mainly in the urine.
- As the availability of endogenous conjugating substance is limited, saturation of this process is possible and the unconjugated drug/metabolite may precipitate toxicity.

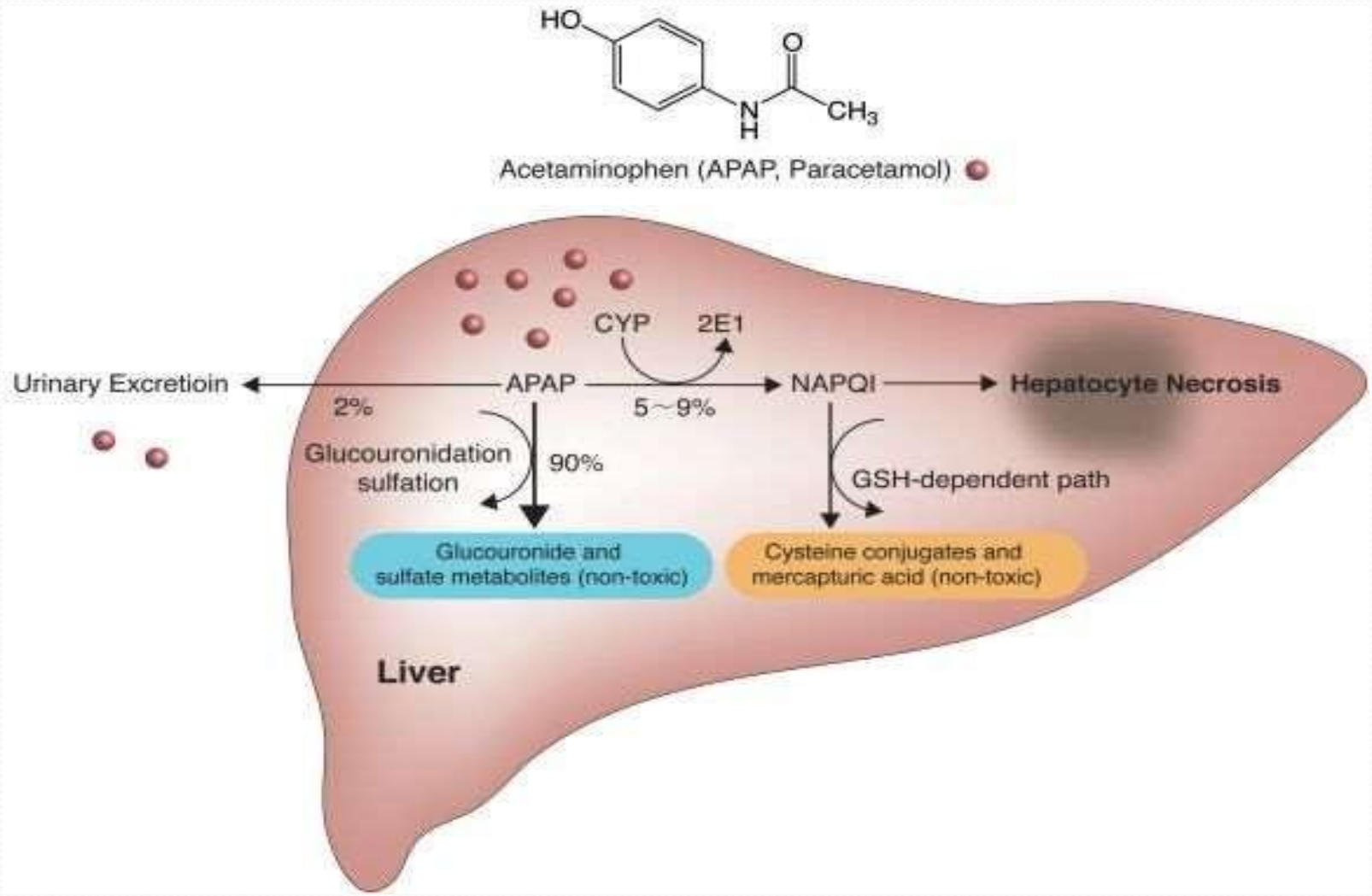
TYPE OF CONJUGATION	ENDOGENOUS REACTANT	TRANSFERASE (LOCATION)	TYPES OF SUBSTRATE	EXAMPLE
Glucuronidation	UDP glucoronic acid	UDP glucoronosyltransferase (microsomes)	Phenols,alcohols, carboxylic acids, hydroxylamines, sulfamides	Nitrophenols, Morphine, acetaminophen, digoxin,digitoxin
Acetylation	Acetyl-CoA	N-acetyltransferase (cytosol)	Amines	Sulfonamides, isoniazid, clonazepam, dapsone, mescaline
Glutathione conjugation	Glutathione (GSH)	GSH-S-transferase (cytosol, microsomes)	Epoxides, arene oxides, nitro groups, hydroxylamines	Acetaminophen, ethacrynic acid, bromobenzene
Glycine conjugation	glycine	Acyl CoA glycinetransferase (mitochondria)	Acyl CoA derivatives of carboxylic acid	Salicylic acid, benzoic acid, nicotinic acid, cinnamic acid,cholic acid

Sulfation	)	Sulfotransferase (cytosol)	Phenols, alcohols, aromatic amines	Estrone,aniline, phenol, 3-hydroxycoumarin, acetaminophen, methyldopa
Methylation	S-adenosyl methionine(SAM)	Transmethylases (cytosol)	Catecholamines, phenols,amines	Dopamine, epinephrine, pyridine, histamine, thiouracil
Water coonjugation	Waterr	Epoxide hydrolase (microsome) (cytosol)	Arene oxides, *cis*- disbstituted & oxiranes Alkene oxides, fatty acid oxides	Bezopyrene 7,8-epoxide, styrene 1,2-oxide, carbamazepine epoxide Leukotriene A

TOXIFICATION

Certain conjugation may lead to the formation of reactive species responsible for the toxicity of the drug

Drug	Toxic metabolite	Toxic effect
Paracetamol	N-acetyl-P-benzoquinonimine	Hepatotoxicity
Isoniazid	Acetylhydrazine	Hepatotoxicity
Halothane	Alkylating metabolites	Hepatotoxicity
Cyclophoshamide	Acrolein	Haemoohagic cytitis
Sodium nitroprusside	Thiocyanate	Acute toxic psychosis


HO
O
N
H
CH3
Acetaminophen (APAP, Paracetamol)
CYP
2E1
Urinary Excretioin
APAP
NAPQI
Hepatocyte Necrosis
2%
5~9%
Glucouronidation
sulfation
90%
GSH-dependent path
Glucouronide and
sulfate metabolites (non-toxic)
Cysteine conjugates and
mercapturic acid (non-toxic)
Liver

ENZYME	DEFECT	USE	CLINICAL CONSEQUENCES
CYP1A2	N-demethylation	Caffeine (CNS stimulant)	Reduced CNS stimulation due to increased gene inducibility and thus increased metabolism/clearance in cigaratte smokers and frequent ingesters of omerazole.
	N-demethylation	Caffeine (CNS stimulant)	Enhanced CNS stimulation.
CYP2A6	Oxidation	Nicotine (cholinoceptor stimulant)	Nicotine toxicity. Lesser craving for frequent cigaratte smoking.
	Oxidation	Nicotine (cholinoceptor stimulant)	Increased nicotine metabolism. Greater craving for frequent cigaratte smoking.
CYP2B6	Oxidation, N-dechloroethylation	Cyclophosphamide, ifosamide (anticancer)	Reduced clearence.Increased risk of ADRs
ALDH	Aldehyde dehydrogenation	Ethanol (recreational drug)	Facial flushing,hypotension, tachycardia,nausea,vomiting

Drugs that enhance drug metabolism

	Drugs whose metabolism is enhanced
Benzo[a]pyrene	Theophylline
Carbazepine	Carbazepine,clonazepam,itraconazole
Chlorcyclizine	Steroid hormones
Ethchlorvynol	Warfarin
Glutethimide	Antipyrine,glutethimide,warfarin
Griseofulvin	Warfarin
Phenylbutazone	Aminopyrine ,cortisol,digitoxin
Phenytoin	Cortisol,dexamethasone,digitoxin,itraconazole, theophylline
Ritonavir	Midazolam
Phenylbutazone	Aminopyrine,cortisol,digitoxin

Drugs that inhibit drug metabolism

	Drug whose metabolism is inhibited
• Allopurinol,chloramphenicol,isoniazid	Antipyrine,dicumarol,probenecid,tolbutamide
• Chlorpromazine	Propanolol
	Chlordiazepoxide,diazepam,warfarin
Cimetidine Dicoumarol	Phenytoin
Diethylpenteamide	Diethylpentenamide
	Antipyrine
Nortriptyline	Digoxin

REFERENCES

- Basics & clinical pharmacology – Bertram G.Katzung &Anthony J.Trevor 13th edition
- Text book of pharmacology – K. D. Tripathi.7th Edition.

Thank You