

DETOXIFICATION (short note)

BIOTRANSFORMATION OF XENOBIOTICS (short answer)

- Detoxification - series of biochemical reactions occurring in the body to convert foreign (toxic) compounds to non-toxic or less toxic & more easily excretable forms.

Biokinetics

→ μ transforms absorbed nutrients (food, oxygen etc) in to substances required for normal body functions.
eg: phenoxylenzamine.

- Xenobiotics are compounds which may be
 - accidentally ingested
 - taken as drugs
 - compounds produced in the body by bacterial metabolism

→ Human body has a well developed capacity to biotransform most xenobiotics as well as body waste.
eg: bilirubin

→ Liver plays the most important role in biotransformation.

→ The compounds that are detoxified include:

- a) compounds accidentally ingested like preservatives, food additives and adulterants

b) Drugs which are taken for therapeutic purposes.

c) compounds produced in the body which are to be eliminated.
eg: bilirubin, steroids.

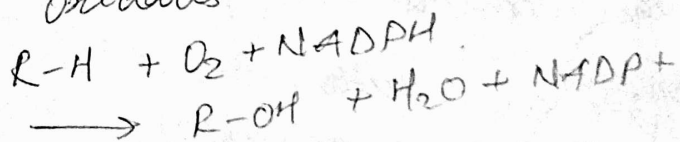
d) compounds produced by bacterial metabolism
eg: amines produced by decarboxylation of amino acids

Enzyme systems.

→ cytochrome P450 enzyme family is involved in biotransformation.

→ There are heme containing membrane proteins, localised in smooth endoplasmic reticulum of liver.

→ Also called mixed function oxidases.



R-H $\equiv$ Represent xenobiotics.

Requires:

P450 flavoprotein - NADPH.

P450 reductase

Molecular O₂

Metabolise ~ 50% of pollutants, drugs, carcinogens & pollutants.

Phases of Detoxification process.

→ Three phases may occur together or separately

• Phase One reactions: Alteration of the toxic substance.

• Phase Two reactions: Involve conjugation of the altered toxic substance.

• Phase Three reactions: Products of phase II further metabolized.

→ Generally detoxification of compound involves phase I and phase II reactions.

Phase One: modify / alter foreign molecule by adding a functional group

→ Results in formation of compounds with decreased toxicity (detoxification) and sometimes increased toxicity (toxification)

eg: methanol $\rightarrow$ formic acid.

Phase one reactions include:

Hydroxylation, oxidation, reduction, hydrolysis, dealkylation etc.

Phase I Reactions (Question).

1. Oxidation reactions:-

→ Aliphatic or aromatic hydroxylation

eg: Toluene $\rightarrow$ benzyl alcohol
mixed function oxidase

→ Oxidation and detoxification of alcohol

Alcohol $\xrightarrow{\text{alcohol dehydrogenase}}$ aldehyde

Aldehyde $\xrightarrow{\text{aldehyde dehydrogenase}}$ acid

2. Reductive Reactions

Nitro compounds.

Nitro benzene $\rightarrow$ aniline.

3. Hydrolysis.

Esters, amines, hydrogins, amides etc.

Aspirin $\rightarrow$ salicylic acid + acetic acid.

Phase II Reactions.

Conjugation:-

A foreign compound combine with a conjugating agent and get converted into soluble non toxic derivatives which are easily excreted.

→ Occurs mainly in liver.

→ Conjugation reaction occurs with a xenobiotic or its metabolite after phase I reaction.

→ May occur either directly or after phase I reaction (oxidation, reduction etc).

→ The effect of conjugation is to make the compound more water soluble (polar).

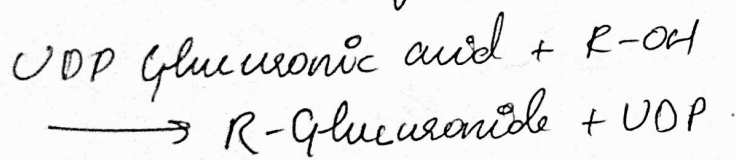
and therefore, more easily excreted in the urine or bile.

Conjugating Agent	Active form.
Sulphate	PAPS
Acetic Acid.	Acetyl CoA.
Methyl group.	SAM.
Glucuronic acid.	UDP Gluc. Acid.
Cysteine	Glutathione.
Glycine.	

→ Most common phase two reactions.

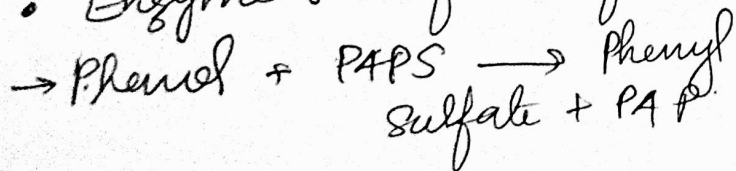
Glucuronic acid.

Enzyme: UDP glucuronyl transferase



Sulphate.

• Enzyme: sulfotransferase.



→ PAPS - 5'phospho adenosine - 3'phospho sulfate.

Glycine.

→ Benzoic acid + glycine
→ Hippuric acid.

Methylation

→ SAM is the methyl donor

and enzyme is methyl transferase.
→ Epinephrine → metanephrine

Glutamine.

phenyl acetic acid + Glutamine
→ phenyl acetyl glutamine

Acylation

→ conjugation with acetic acid
eg: detoxification of drugs like sulfonamide, isoniazide etc.

In some cases phase II reactions may further be metabolized by phase III reactions.

Phase III

→ Not very common.
→ further conjugation with glutathione in certain cases.

Environmental toxins (1 mark)

there are some - causing chemicals and endocrine disruptors.

→ Both naturally occurring and human made.

1 mark Naturally occurring environmental toxins are:
lead, mercury, radon, formaldehyde, benzene and cadmium.

1 mark Human made chemicals: BPA, phthalates and pesticides.

In toxic doses, all of these compounds can negatively affect human health

→ Cancer : radon, formaldehyde, benzene

→ Endocrine disruptors : BPA, phthalates

→ Organ failure or developmental problems :
lead, mercury, cadmium.