Introduction-2

1

Chemical Carcinogens

- Chemical carcinogens defined by their ability to induce tumors.
- Evidence of tumorigenicity are four types of response:

1- Incidence

2- Earlier occurrence

3- Development of types of tumors.

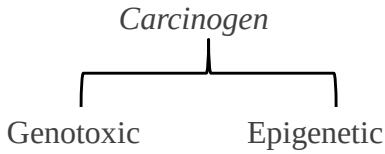
4- Multiplicity of tumors.

2

Chemical Carcinogens (Cont.)

Example of Carcinogens:

- Many organic.
- In organic.
- Sold state material.
- Hormones.
- Immune-suppressor.



3

1-Genotoxic:
Act as electophilic reactant directly on the DNA

Free radical

Produced either forms:

- Their own molecular structure **or**
- altered cellular macromolecules e.g Lipid peroxides

Procarcinogen

Organic chemical that active only after metabolic activation.

(Biotransformation).

4

2- Epigenetic carcinogens

- Carcinogens that do not directly act on DNA.
- They are five types:

1. Solid-state agents: Asbestos, Plastics and Metal.
2. Immuno-supperssor ⟹ Death of immunocytes

e.g. 6-Mercaptopurine (Purine analog).

5

Promoters

- Increase the tumorigenic response to a carcinogen.
- Are not carcinogenic by themselves but potentiate the effect of other carcinogens.
- e.g. (Phenol in tobacco tar)

6

2- Epigenetic carcinogens

3. Hormonal carcinogen

- ✓ Steroid Hormone
- ✓ DDT
- ✓ DES

4. Tumor promoters: e.g. Phenobarbitol
5. Oxidative stress: **Production** of reactive oxygen species (e.g. Superoxide)

7

Co carcinogens

- Administered with the carcinogen
- The overall carcinogenesis process.
- The mechanism can be due to one or more of several possibilities:

  - Interfere in the metabolism of the Genotoxic carcinogen. → ⇑ Conc. Of ultimate carcinogenic metabolites.
  - Sensitize the target tissue of the Genotoxic carcinogen by ⇑ proliferation.

8

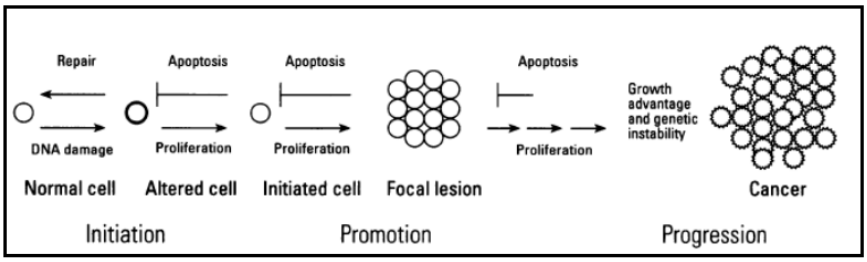
Co carcinogens (cont.)

- Interfere with the repair of DNA damage produced by Genotoxic carcinogen.
- Specifically, or non-specifically the growth of cells with an altered genotype.

⇒ Neoplastic changes

9

Multistage process of cancer (initiation, promotion & progression)



10

Co carcinogens (cont.)

Interfere with :

- the repair of DNA damage produced by Genotoxic carcinogen.
- Specifically or non-specifically the growth of cells with an altered genotype.

→ Neoplastic changes

11

Action of chemical carcinogens Exposure by the body

❖ **Depends on, ADME:**

- **A**bsorption.
- **D**istribution.
- **M**etabolism.
- **E**xcretion

12

Type of Genotoxic activation:

Activation independent

- No metabolism required for activation.

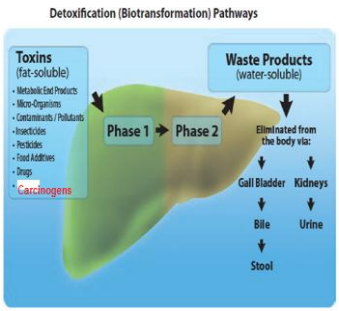
Activation dependent

- Should be metabolically activated (Phase I+II)
- Mainly in the liver

13

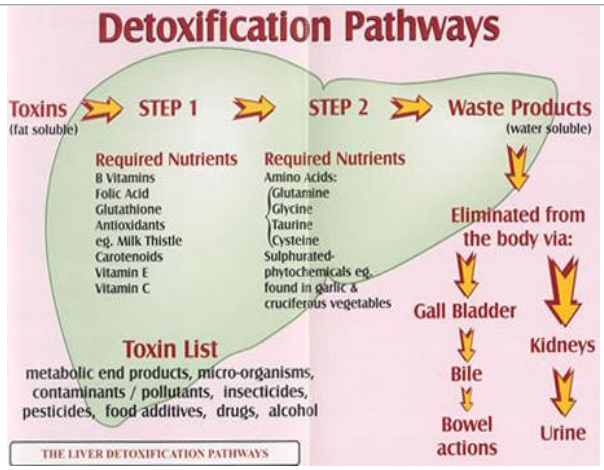
Metabolism of chemical carcinogen

- Xenobiotic any compound that is foreign to the body.
- Metabolism of procarcinogen in the human is done through chemical alteration in the liver, phase I & II.

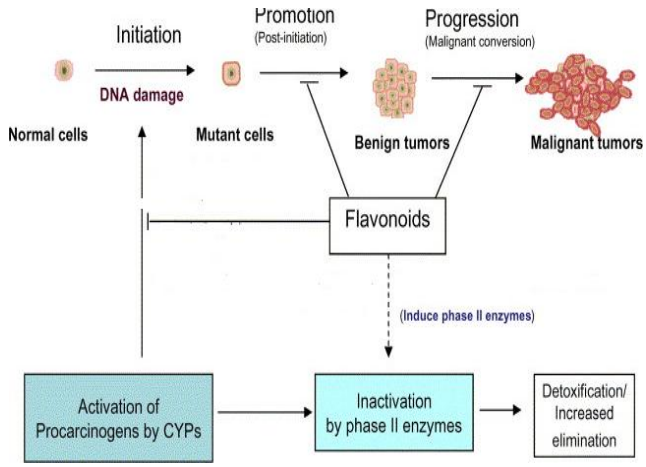


14

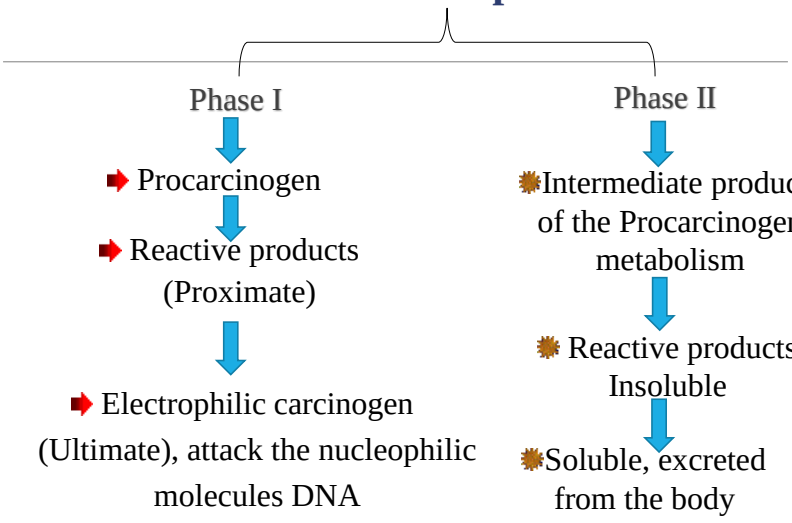
Metabolism of chemical carcinogen(cont.)



Metabolism of chemical carcinogen(Cont.)



Activation dependent



17

Metabolism of chemical carcinogen(cont):

Enzymes that catalyze the biotransformation of drugs, carcinogens and xenobiotics are generally referred to as **drug-metabolizing enzymes (DMEs).**

DMEs can be classified into two main groups: oxidative or conjugative. The NADPH- Cytochrome P450 Reductase (P450R)/ Cytochrome P450 (P450) electron transfer systems are oxidative enzymes that mediate phase I reactions, whereas the UDP Glucuronosyl-Transferases (UGTs) are conjugative enzymes that mediate phase II enzymes.

18

Metabolism of chemical carcinogen(Cont.)

Both enzyme systems are localized to the endoplasmic reticulum (ER) where a number of drugs are sequentially metabolized .

DMEs, including P450s and UGTs, generally have a highly flexible active site that can accommodate a wide variety of substrates.

19

Metabolism of chemical carcinogen(Cont.)

- Phase I:

Is the primary responsibility of the cytochrome P450 family of enzymes.

- Hydroxylation (Monoxygenase, P450).
- Reduction.
- Hydrolysis.

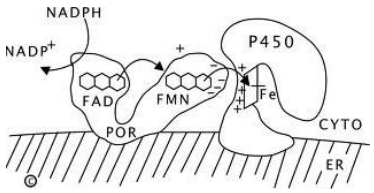
20

Metabolism of chemical carcinogen(cont.) ***

Phase I:

$RH+O_2$ +* NADPH* + H^+ → R-OH + H_2O + $NADP^+$

By mono- oxygenase, e.g., P450:



- Hemoprotein.
- Present in the membrane of ER.
- Has 6 species which act on carcinogen.(P-448 PAHs hydroxylase).

21

Metabolism of chemical carcinogen(cont.)

Phase II:

There are at least 5 types of reaction:

- Glucuronidation
- Sulfation
- Conjugation with GSH.
- Acetylation
- Methylation

22

Metabolism of chemical carcinogen(cont.)

Examples of phase II enzymes:

Superfamily	Function	Substrate examples
Glutathione *S*-transferases (GST)	Catalyse nucleophilic attack by GSH on non-polar compounds	Adriamycin, BCNU, busulfan, carmustine, chlorambucil, cyclophosphamide, DDT, inorganic arsenic, pesticides
Sulphotransferases (SULT)	Sulphation	Steroid hormones, bile acids, isoflavones, paracetamol, minoxidil
N-acetyltransferases (NAT)	*N*-acetylation, *O*-acetylation	Arylamines *N*-hydroxylated heterocyclic amines
UDP-glucuronosyltransferases (UGT)	Glucuronidation	Bilirubin, paracetamol, morphine, zidovudine, NSAIDs

23

Metabolism of chemical carcinogen(cont.)

- Phase II:
  - Glucuronidation:

UDP-glucuronic acid + Carcinogen

↓

Carcinogen Monoglucuronate + UDP

↓

UDP-glucuronic acid

↓

Carcinogen Diglucuronide + UDP

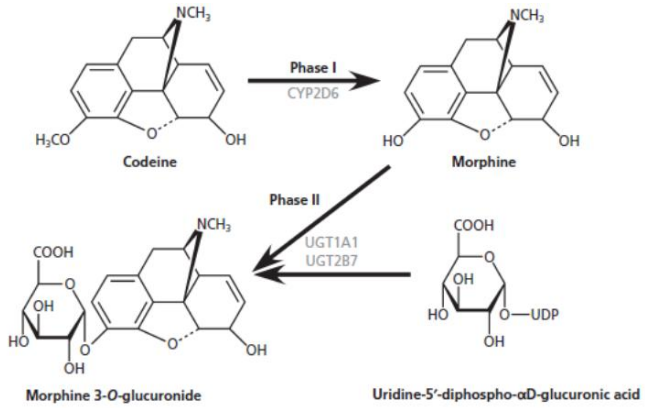
↓

Soluble, can be excreted in urine

24

Metabolism of chemical carcinogen(cont.)

Example of glucuronidation reaction of drug.



Metabolism of chemical carcinogen(cont)

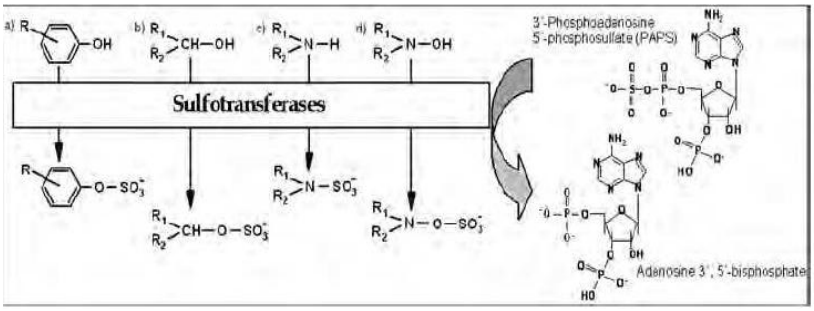
- Sulphation:

The sulf donor is Adenosine-3'-phosphate-5'-phosphosulphate (PAPS).

The `reaction product are sulfates ($R–O–SO^{3-}$) or sulfamates ($R1–NR2–SO^{3-}$).

Metabolism of chemical carcinogen(cont)

- Sulphation (Cont.):

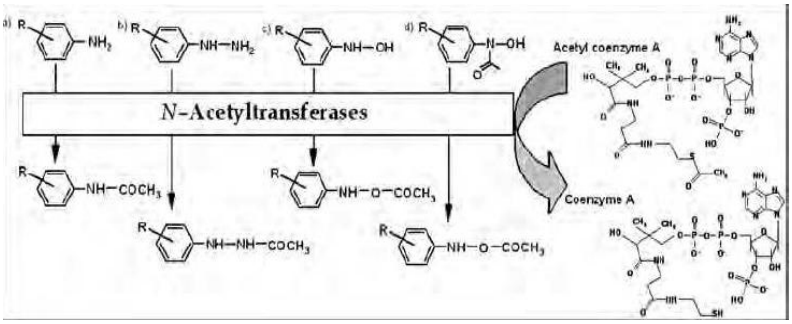


27

Metabolism of chemical carcinogen(cont.)

- Acetylation:

The acetyl donor is Acetyl-CoA and the reaction catalyzed by Acetyl Transferase

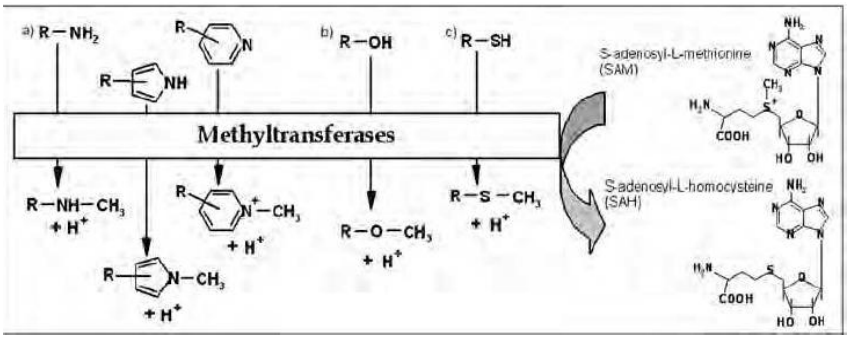


28

Metabolism of chemical carcinogen(cont.)

- Transmethylation:

The methyl donor is S-adenosyl-Methionine. Catalyzed by Methyl transferase.



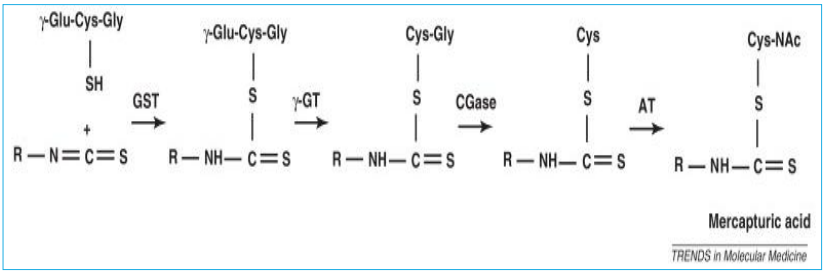
29

Metabolism of chemical carcinogen(cont.)

- Conjugation with Glutathione:

GSH (glycine-cystein-glutamic) bind to some carcinogen.

Catalyzed by Glutathione-s-Transferase.



30

Metabolism of chemical carcinogen(cont.)

- Conjugation with Glutathione (cont.):

Further reaction may occur by removing Gly and Glu from the glutathione then acetyl group is donated to the cysteinyl moiety Mercapturic acid and excreted .

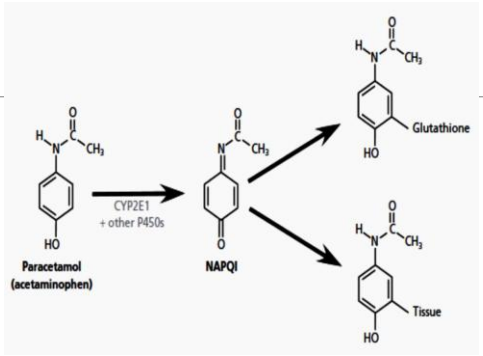
31

Metabolism of chemical carcinogen, Example paracetamol

Metabolic activation of paracetamol (acetaminophen) to a hepatotoxic metabolite. Phase I metabolism, predominantly mediated by CYP2E1, involves *N*-hydroxylation of paracetamol to form the electrophilic intermediate *N*-acetyl-*p*-benzoquinone imine (NAPQI).

32

Metabolism of chemical carcinogen, Example paracetamol (cont.):

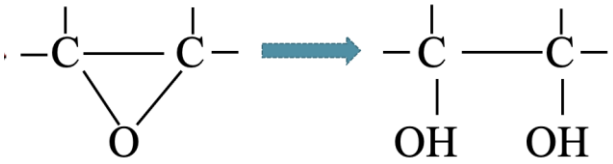


NAPQI is in turn detoxified by a spontaneous reaction with hepatic glutathione. Non-detoxified NAPQI can bind covalently to macromolecules within hepatocytes causing hepatic necrosis, as occurs in paracetamol overdose.

33

Metabolism of chemical carcinogen(cont.)

- When Xenobiotics are metabolized in the body, phase I reactions may produce its active form or may diminish or terminate its action.



Epoxide(active) Dihydrodiol (less active)

34