Shree H. N. Shukla Institute of Pharmaceutical Education and Research, Rajkot

B. Pharm

Semester-IV

Subject Name: Medicinal Chemistry

Subject Code: BP402TP

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Medicinal Chemistry

Drug Metabolism

- Biotransformation: Chemical alteration of the drug in body that converts nonpolar or lipid soluble compounds to polar or lipid insoluble compounds
- Consequences of biotransformation
    - Active drug à Inactive metabolite : Pentobarbitone, Morphine, Chloramphenicol
    - Active drug à Active metabolite: Phenacetin
    - Inactive drug à active metabolite: Levodopa

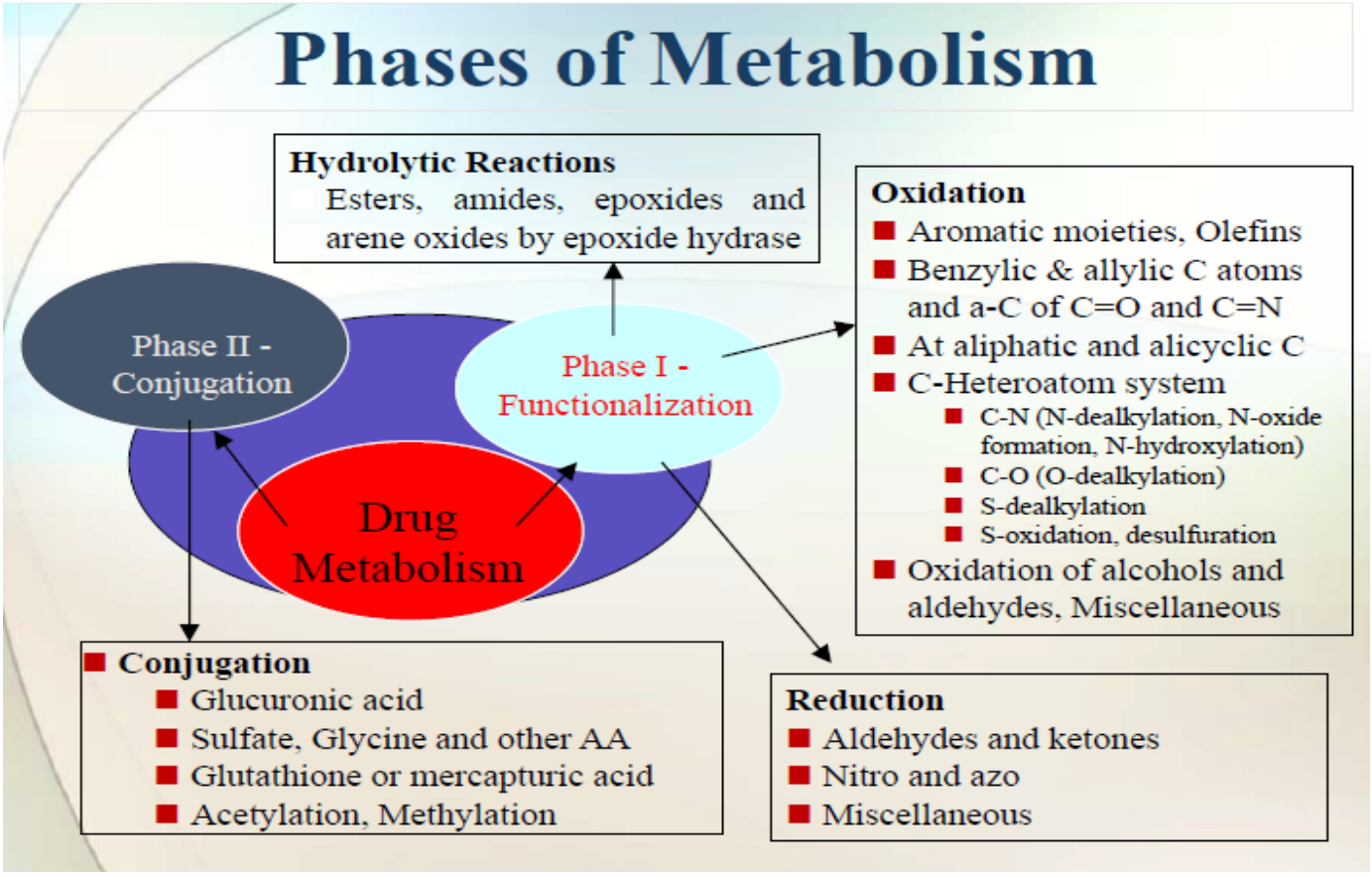
Prodrugs

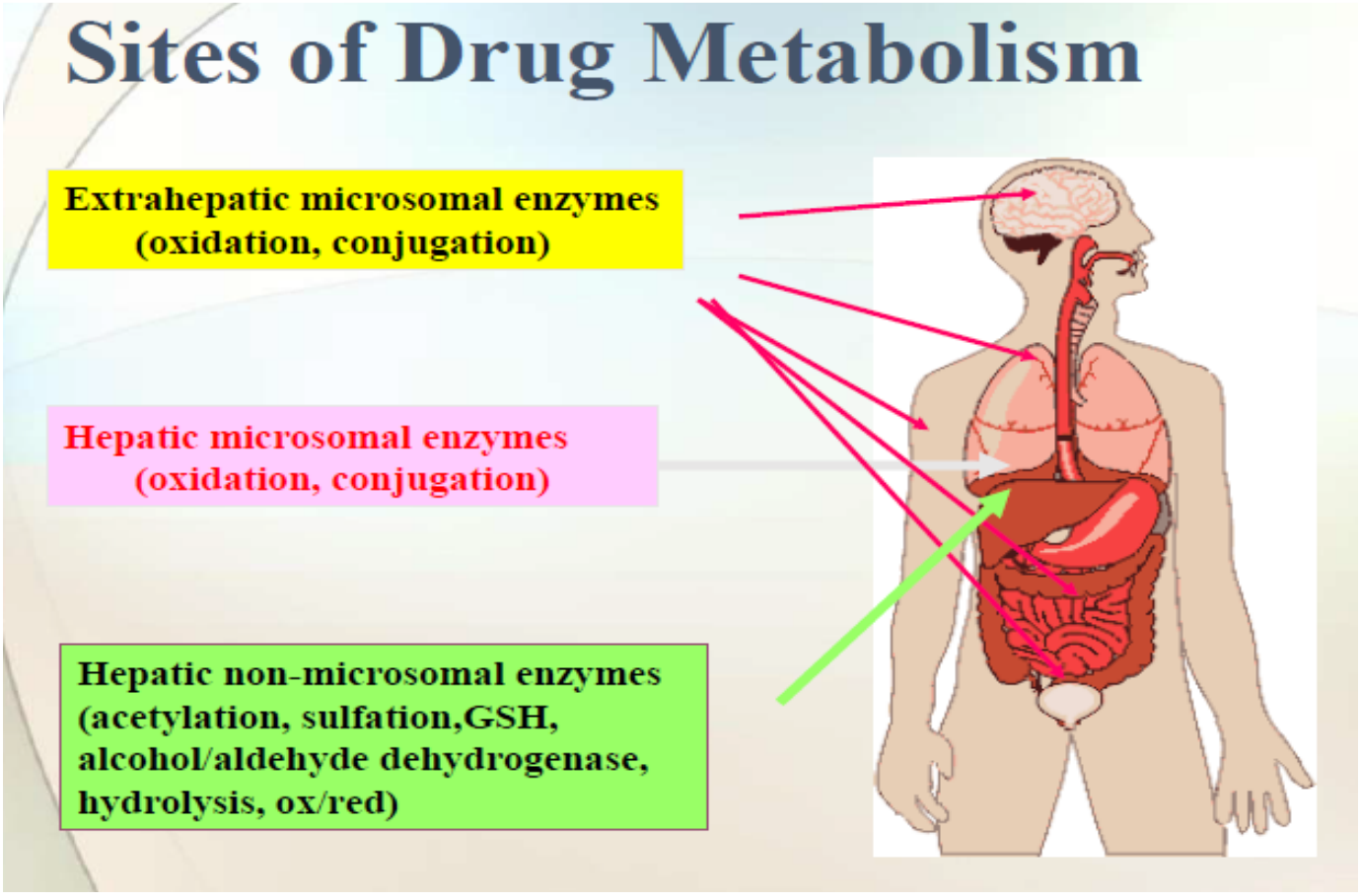
- Inactive drug is converted to active metabolite
- Coined by Albert in 1958
- Advantages:
    - Increased absorption
    - Elimination of an unpleasant taste
    - Decreased toxicity
    - Decreased metabolic inactivation
    - Increased chemical stability
    - Prolonged or shortened action

Phases of Metabolism

- **Phase I**
    - Functionalization reactions
    - Converts the parent drug to a more polar metabolite by introducing or unmasking a functional group (-OH, -NH2, -SH).

- **Phase II**
  - Conjugation reactions
  - Subsequent reaction in which a covalent linkage is formed between a functional group on the parent compound or Phase I metabolite and an endogenous substrate such as glucuronic acid, sulfate, acetate, or an amino acid



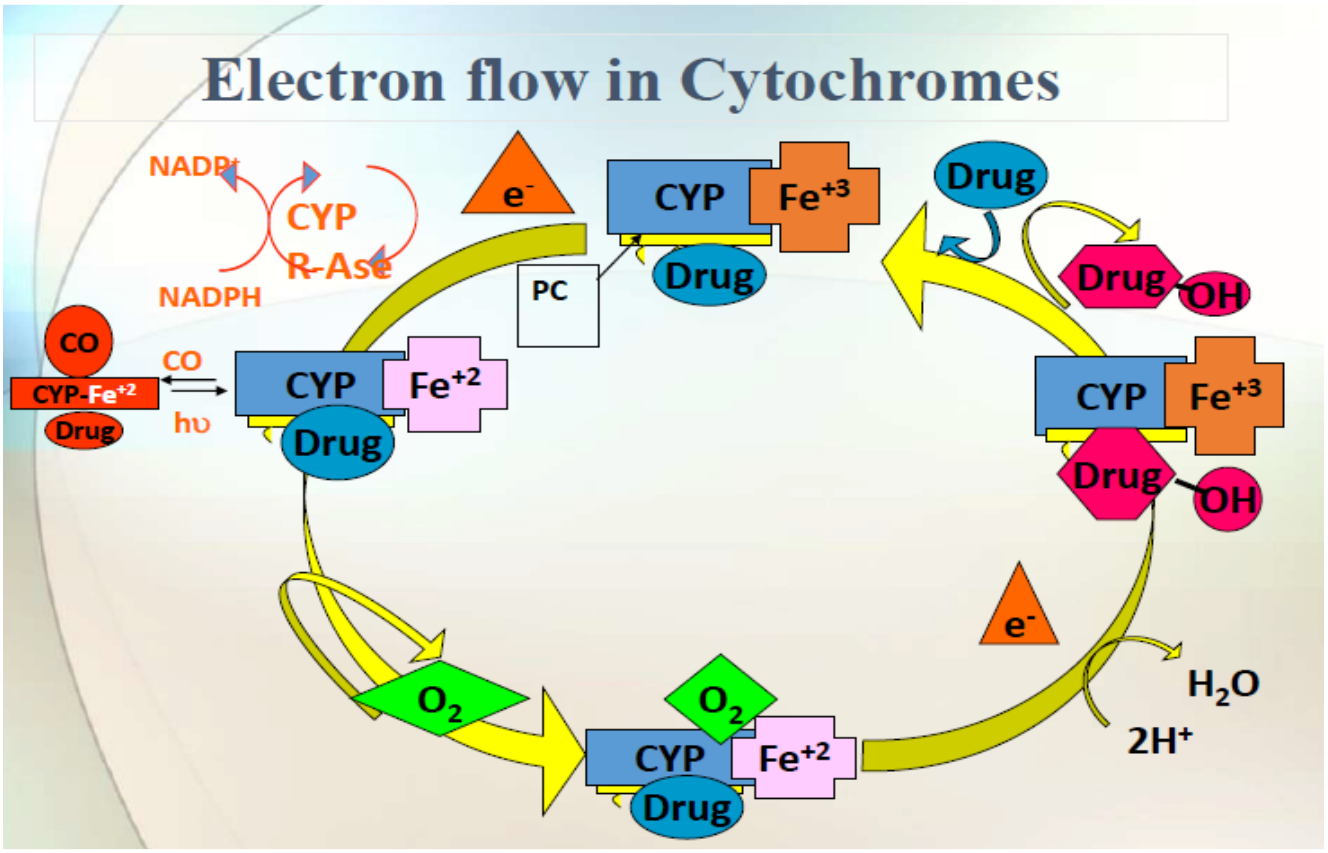


Phase I / Non Synthetic Reactions

Oxidation

- Addition of oxygen/ negatively charged radical or removal of hydrogen/ positvely charged radical.
- Reactions are carried out by group of mono- oxygenases in the liver.
- Fianl step: Involves cytochrome P-450 haemoprotein, NADPH, cytochrome P-450 reductase and O_2
- **Cytochrome P450 enzymes**
- Monooxygenase enzyme family
- Major catalyst: Drug and endogenous
- compound oxidations in liver, kidney, G.I. tract, skin and lungs
- Oxidative reactions require: CYP heme protein,
- the reductase, NADPH, phosphatidylcholine and molecular oxygen

- Location: smooth endoplasmic reticulum in
- close association with NADPH-CYP reductase in 10/1 ratio
- The reductase serves as the electron source for the oxidative reaction cycle



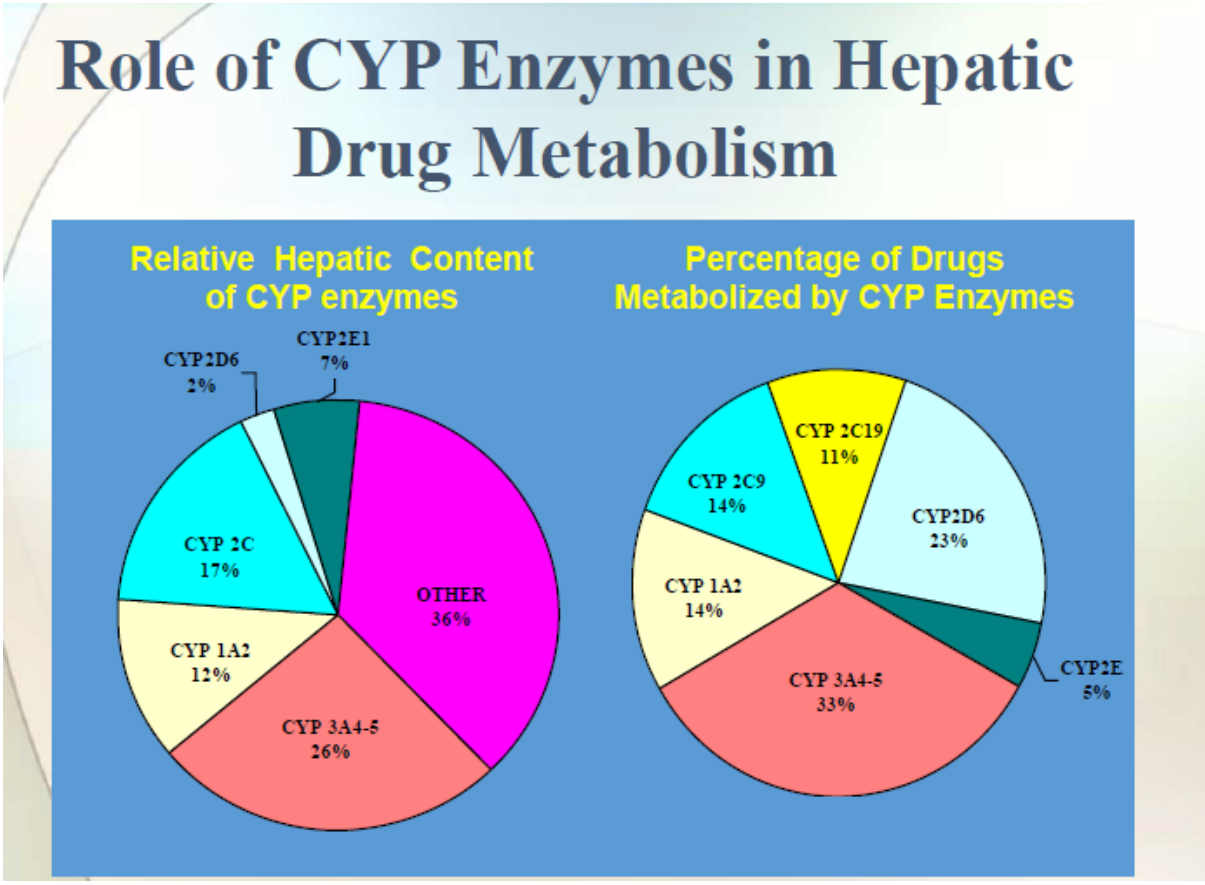
Cytochrome P family

- Multiple CYP gene families have been identified in humans, and the categoriezed based on protein sequence homology
- Most of the drug metabolizing enzymes are in CYP 1, 2, & 3 families .
- Frequently, two or more enzymes can catalyze the same type of oxidation, indicating redundant and broad substrate specificity.
- CYP3A4 is very common to the metabolism of many drugs; its presence in the GI tract is responsible for poor oral availabilty of many drugs

Cytochrome families Continued….

- Families: CYP plus arabic numeral (>40% homology of amino acid sequence, eg. CYP1)

- Subfamily: 40-55% homology of amino acid sequence; eg. CYP1A
- Subfamily: Additional arabic numeral when more than 1 subfamily has been identified; eg. CYP1A2
- Italics: Indicate gene (*CYP1A2*); regular font for enzyme



Non-CYP Drug Oxidations

- Monoamine Oxidase (MAO), Diamine Oxidase (DAO)
  - MAO (mitochondrial) oxidatively deaminates endogenous substrates including neurotransmitters
  - Dopamine, serotonin, norepinephrine, epinephrine
- Alcohol & Aldehyde Dehydrogenase
  - Non-specific enzymes found in soluble fraction of liver
  - Ethanol metabolism
- Flavin Monooxygenases

- Require molecular oxygen, NADPH, flavin adenosine dinucleotide (FAD)

Reduction

- Converse of oxidation
- Drugs primarily reduced are chloralhydrate, chloramphenicol, halothane.

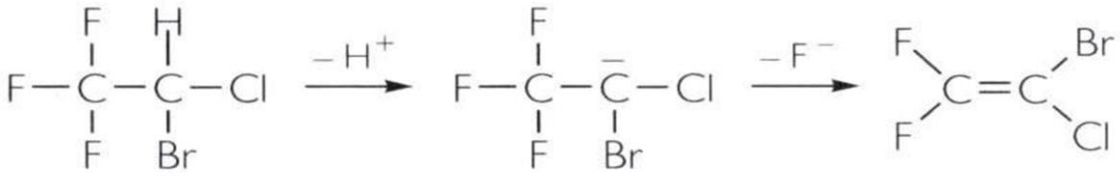


Figure 1.25 Reductive defluorination of halothane.

Hydrolysis

- Cleavage of drug molecule by taking up a molecule of water.

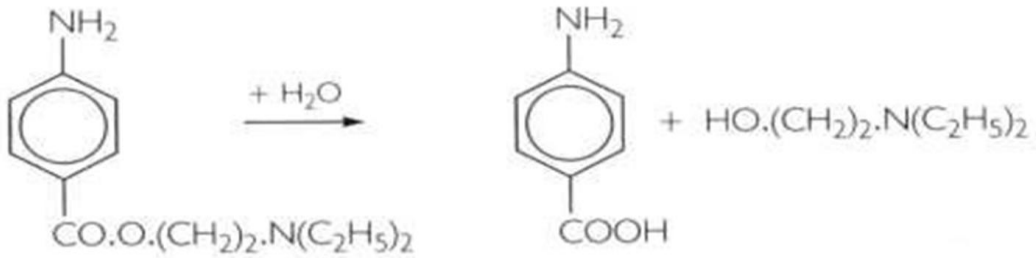


Figure 1.26 Hydrolysis of procaine.

- Sites: Liver, intestines, plasma and other tissues
- Examples: Choline esters, Procaine, Isoniazid, pethidine, oxytocin.

Cyclization and Decyclization

Cyclization

- Formation of ring structure from a straight chain compound
- E.g. Proguanil

Decyclization

- Opening up of ring structure of the cyclic drug molecule

- E.g. Barbiturates, Phenytoin.

Phase II/ Synthetic reactions

- Conjugation of the drug or its phase I metabolite with an endogenous substrate to form a polar highly ionized organic acid
- Types of phase II reactions
    a. Glcuronide conjugation
    b. Acetylation, Methylation
    c. Sulfate conjugation, Glycine conjugation
    d. Glutathione conjugation
    e. Ribonucleoside/ nucleotide synthesis

Glucuronide Conjugation

- Conjugation to α-d-glucuronic acid
- Quantitatively the most important phase II pathway for drugs and endogenous compounds
- Products are often excreted in the bile
- Requires enzyme UDP-glucuronosyltransferase (UGT)
- Compounds with a hydroxyl or carboxylic acid group are easily conjugated with glucuronic acid which is derived from glucose
- Enterohepatic recycling may occur due to gut glucuronidases
- Drug glucuronides excreted in bile can be hydrolysed by bacteria in gut and reabsorbed and undergoes same fate.
- This recycling of the drug prolongs its action e.g.Phenolpthalein, Oral contraceptives
    - Examples: Chloramphenicol, aspirin, phenacetin, morphine, metronidazole

Acetylation

- Common reaction for aromatic amines and sulfonamides
- Requires co-factor acetyl-CoA
- Responsible enzyme is N-acetyltransferase
- Important in sulfonamide metabolism because acetyl-sulfonamides are less soluble than the parent compound and may cause renal toxicity due to precipitation in the kidney
- E.g. Sulfonamides, isoniazid, Hydralazine.

Sulfate Conjugation

- Major pathway for phenols but also occurs for alcohols, amines and thiols
- Sulfate conjugates can be hydrolyzed back to the parent compound by various sulfatases
- Sulfoconjugation plays an important role in the hepatotoxicity and carcinogenecity of N- hydroxyarylamides
- Infants and young children have predominating O-sulfate conjugation
- Examples include: a-methyldopa, albuterol, terbutaline, acetaminophen, phenacetin

Amino Acid Conjugation:

- ATP-dependent acid: CoA ligase forms active CoA- amino acid conjugates which then react with drugs by N-Acetylation:
  - Usual amino acids involved are:
    - Glycine. Glutamine, Ornithine, Arginine

Glutathione Conjugation:

- Glutathione is a protective factor for removal of potentially toxic compounds

- Conjugated compounds can subsequently be attacked by g-glutamyltranspeptidase and a peptidase to yield the cysteine conjugate => product can be further acetylated to N-acetylcysteine conjugate

  E.g. Paracetamol

  Hofmann elimination

  Inactivation of the drug in the body fluids by spontaneous molecular re arrangement without the agency of any enzyme

  e.g. Atracurium.

Factors affecting Drug Metabolism

❖ **Enzyme induction**

- ✓ Many drugs, and environmental chemicals enhances the metabolism of themselves or other co-ingested compounds ……this will alter their pharmacologic and toxicologic effects.
- ✓ It is a dose-dependent phenomenon.
- ✓ This mainly occur by inducing transcription of CYP450 mRNA which leads to overproduction of these enzymes in the liver and other extra-hepatic tissues.
- ✓ **Enzyme induction: is the process by which the rate of synthesis of an enzyme is increased relative to the un-induced organism**
- ✓ **Enzyme inducers:**
- ✓ Many drugs (table attached) have the ability to stimulate the activity of CYP450 isoforms.
- ✓ Many environmental chemicals also alter the activity of CYP450 isoforms:
- ✓ Cigarette smoking.
- ✓ Polycyclic aromatic hydrocarbons.
- ✓ Xanthines and flavones in food.
- ✓ Halogenated hydrocarbons in insecticides.
- ✓ Food additives.
- ✓ These chemicals do not have something in common except they are all metabolized by one or more CYP450 isoforms.

  The importance of studying enzyme induction:
- ✓ Evaluating the pharmacologic, toxicologic and explaining certain unexpected drug interaction in patients.

- ✓ Studying the drug-drug interactions

As a result of induction:

- ✓ The drug may be metabolized more rapidly to more potent or more toxic metabolite.
- ✓ Or enhance the activation of procarcinogens
- ✓ Or metabolized to less active metabolite.
- ✓ Many drugs are CYP450 inducers of CYP450 subfamilies, at the same time may be also substrates for the same isoforms:
- ✓ Examples:
    - o Phenobarbital
    - o Phenytoin
    - o Rifampicin
    - o Cigarette smoking

Enzyme induction and drug-drug interactions

- Examples of drug-drug interactions result from enzyme induction:
    - Rifamipicn induce metabolism of contraceptives by CYP3A4..... Reducing their serum levels..... Increases the risk for pregnancy.
    - Phenobarbital, cigarette smoking and dexamethasone induce the metabolism of estrogens, vitamin D and bilirubin in women …….decrease their biological activity……. So cigarette smoking in premenopausal women increases the risk of osteoporosis and early menopause.
    - Cigarette smoking lowers the serum levels of theophylline, imipramine, estradiol, decreases the urinary excretion of nicotine and decreases the drowsiness from diazepam, chlordiazepoxide
    - Administration of some drugs for a long time may stimulate their own metabolism….. Apparent tolerance:

The sedative action of Phenobarbital becomes shorter with repeated doses due to the increase in self metabolism.

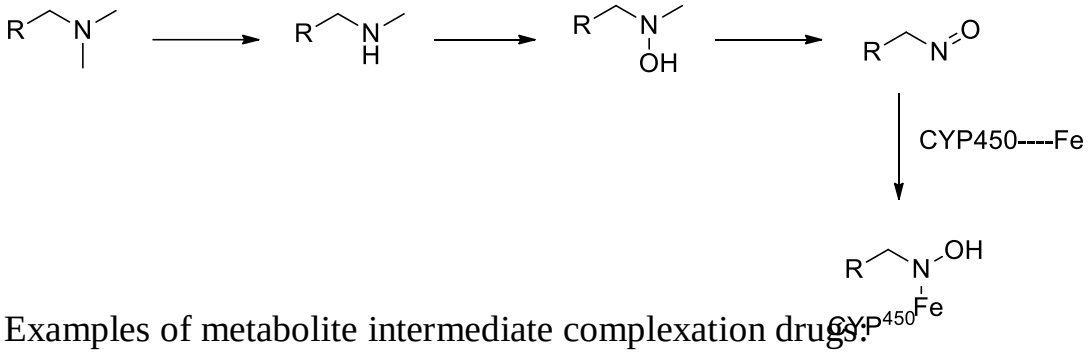
- Enzyme induction and food-drug interactions
    - o Cabbage and cauliflower stimulate monooxygenase activity in rat intestine.
    - o Flavones, safrole, eucalyptol, xanthines and volatile oils present in food and plants also have enzyme induction properties.

Enzyme inhibition

- Can be divided into three major categories:

- Reversible inhibition.
- Metabolite intermediate complexation of CYP450.
- Mechanism-based inactivation of CYP450.
- Reversible inhibition:
    - Is a result of reversible interaction at the heme-iron active centre of CYP450, the lipophilic site or both.
    - This action will be abolished once the enzyme inhibitor is discontinued.
    - Examples: fluoroquinolones, cimetidine, azoles antifungal agents.

- Metabolite-intermediate complexation of CYP450:
    - Happens when the metabolite of certain drugs forms stable covalent bond with the reduced ferrous heme intermediate.
    - Alkylamines are examples of such drugs due to the formation of the nitroso metabolite:



- Examples of metabolite intermediate complexation drugs:
    - Macrolide antibiotics.
        - Eryhthromycin.
        - Clarithromycin.
    - Orphinadrine (anti-Parkinson agent).
    - The clinical significance of this inhibition is the impairment of metabolism of many coadministerd drugs as well as the associated changes in pharmacokinetics for these drugs

- Mechanism-based inhibition (suicide inhibition):
    - Some drugs contain functional groups that when oxidized by CYP450 generate metabolites that bind irreversibly to the same enzyme.

- Examples:
    - Alkane and alkenes containing drugs can form radical intermediate after oxidation with CYP450…. This will alkylates the heme moiety…. Abnormal porphyrins….. 17-α-acetylenic progestin, norethindrone are examples of such drugs
    - Cyclophosphamide…forms acrolein and phosphoramide.
    - Chloramphenicol….(what is the reactive intermediate?).

Factors affecting drug metabolism

- Species may differ in details of the reaction and enzyme control.
- Factors influencing drug metabolism:
    - Genetic factors: results in differences in the expression of metabolizing enzymes and genetic polymorphism).
    - Physiologic factors: including age, hormonal changes, sex differences, pregnancy and nutritional status.
    - Pharmacodynamic factors: including dose, frequency, route of administration and protein binding.
    - Environmental factors: this depends on the competition with other drugs for the metabolizing enzymes by toxic chemicals such as CO and pesticides.

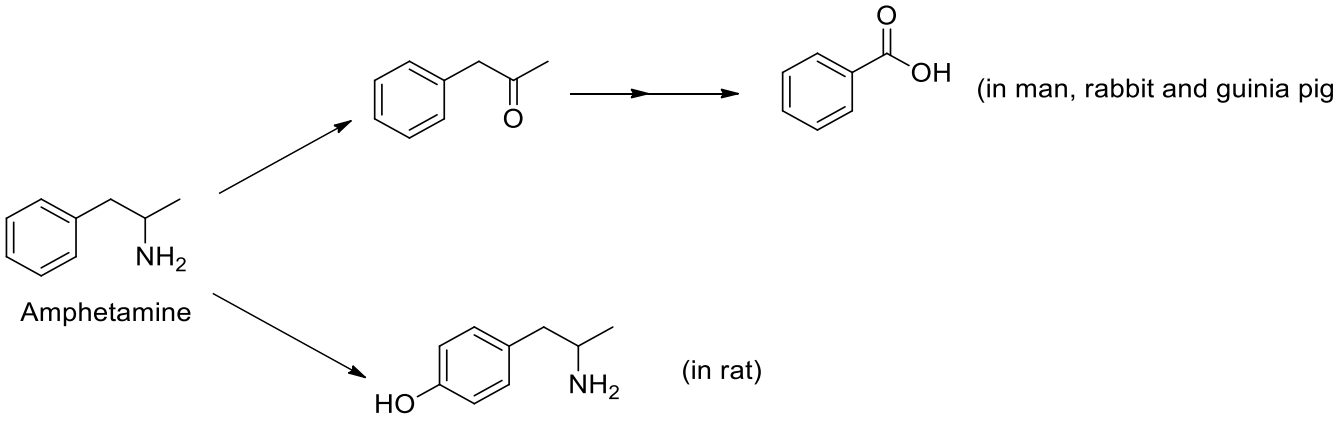
Drug metabolism and age

- It is well documented that the metabolism of many drugs and their elimination is impaired in the elderly.
- In elderly there are many physiologic changes that affect the plasma concentration and renal clearance….these will decrease the hepatic blood flow, glomerular filtration, hepatic enzymes activity and plasma protein binding.
- First pass metabolism of many drugs is reduced in elderly patients: such drugs are diazepam, theophylline, morphine, propranolol and amitriptyline.

- All of the common phase-II enzymes are affected by aging
- The human fetus has only the cytochrome P450 monooxygenase 3A (CYP 3A)which is capable of metabolizing xenobiotics during the first part of gestation.
- Placenta of tobacco smokers has shown increase of CYP1A activity that will form toxic metabolites which will covalently bind to fetus macromolecules….. Teratogenic and hepatotoxic effect.
- Phase-II enzymes are found in low to negligible concentration in the fetus….. High risk of toxicity by pregnants metabolites

Species and strain differeneces

- There are metabolic differences between species, such as between human and dogs, rabbit, pigs, cats and birds.



- The conjugation with amino acids differs between species as well:
  - Glycine conjugation is common in most animals.
  - Birds normally use ornithine amino acid for conjugation.
  - Strain differences in mice and rabbit have been noted: mainly due to genetic variations that affect the amount of metabolizing enzymes

Hereditary or genetic factors

- Genetic factors in human is the main cause for the differences in the rate o drug metabolism.
- the difference in the rate of acetylation is one example:
    - Rapid acetylators have more hepatic acetyl *N*-transferase than the slow acetylators.
    - 90% of Asians and Eskimos are rapid acetylator.
    - Egyptians and Mediterranean are slow acetylators.
    - The rate of acetlations is clinically important in terms of therapeutic response and toxicity.
- Also, genetic factors affect the arte of oxidation.

Sex differences

- The rate of metabolism also varies according to sex in some animal species.
- Generally it is species dependant:
    - Rabbit and mice do not show a significant sex differences in drug metabolism.
    - In humans, few repots of sex differences have been observed:
        - Nicotine and aspirin seem to be metabolized more rapidly in male compared to female.

Genetic Polymorphism

- Can be defined as the genetic differences in the natural expression of enzyme isoforms.
- Resulted in inter-individual variation in the metabolism of drugs.
- Three families of CYP450 exist(CYP1-3).
- Two phenotypes:
    - Extensive metabolizer (EM).
    - Poor metabolizer (PM).

- Poor metabolizer s(PM) are normally associated with higher risk of serious side effects due to the accumulation of drugs in the body.
- Poor metabolizer (PM) also experience loss of activity in some drugs (codeine is an example)
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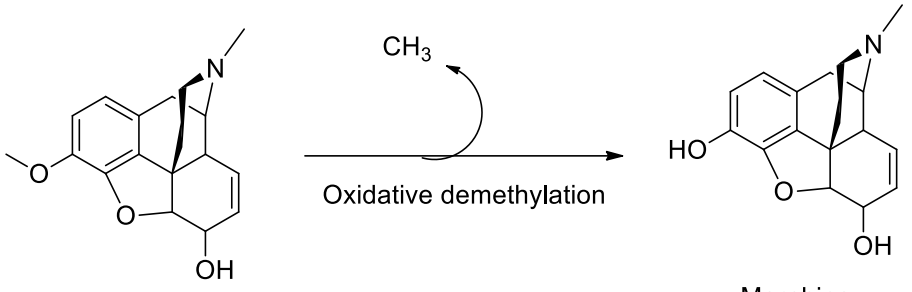

Codeine Morphine