PHARMACOLOGY

Modified no. 5 v2

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Drug metabolism

A change in the chemical structure of the drug, or addition of a hydrophilic groups to an initially lipophilic drug until it becomes sufficiently ionic so as to be easily filtered and excreted by the kidneys

The rate of metabolism (K_m) of a given drug depends upon the chemical characteristics of the drug and has nothing to do with the benefit or harm of the drug

Note:

In general, metabolism of drugs means inactivation of it, and the output of this process is called (metabolites).

Drug metabolism involves 2 major pathways:

1. Pathway I = Oxidation reduction reactions

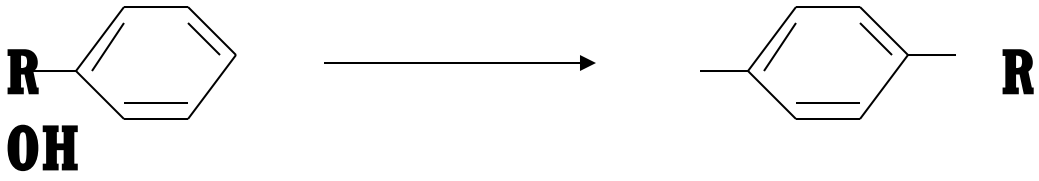
Also known as mixed function oxidase system and cytochrome P_{450} system (CYPs=A;B…)

Examples:

. Aromatic hydroxylation

Note:

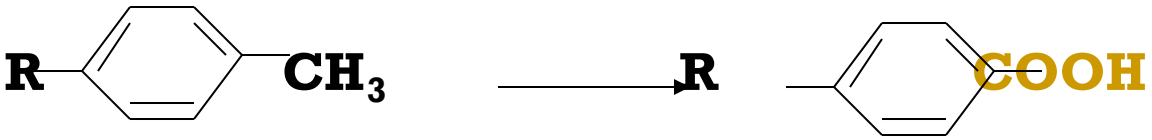
You just need to differentiate between the reactions, as in aromatic hydroxylation we add OH group to aromatic compounds, and this a subtype for pathway 1.



Additional information:

Cytochromes P450 (P450s or CYPs) are a superfamily of enzymes containing heme as a cofactor, that plays a key role in the metabolism of drugs.

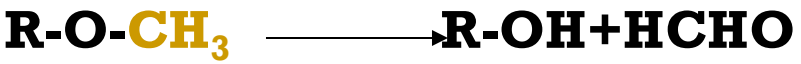
. Aliphatic hydroxylation



Note:

Here we have benzene ring with alkyl group, replacing alkyl with hydroxyl group is aliphatic hydroxylation.

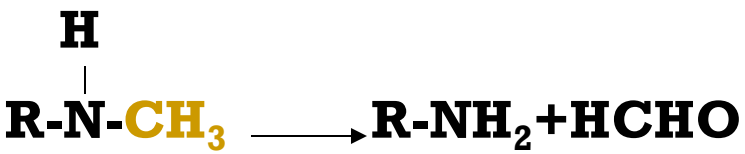
. O-dealkylation



Note:

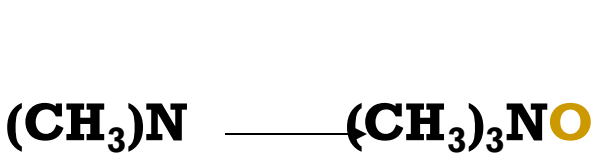
Here we removed alkyl group

. N-dealkylation

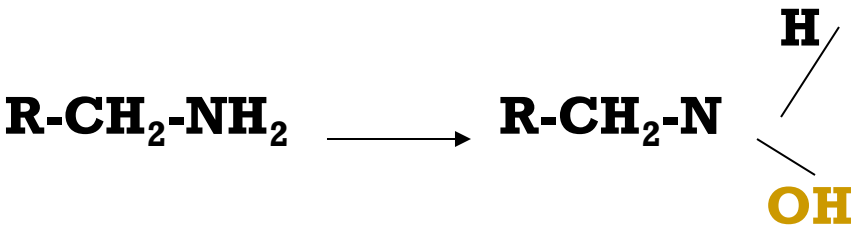


Note:
Removing alkyl group from nitrogen atom.

. N-oxidation; N-hydroxylation

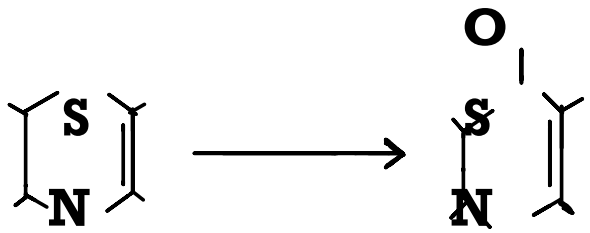


Note:
Adding O to N



Note:
adding hydroxyl group to N

. Sulfoxidation



Note:
Adding oxygen atom to sulfur.

. Hepatic reduction

Azo reduction

R_1-N=N-R_2 R_1-NH_2+H_2N-R_2

Note:
Breaking the double bond between N=N (azo bond), then reduce N with H_2.

Nitroreduction

R-NO_2 R-NH_2

Note:
Replacing the O with H2.

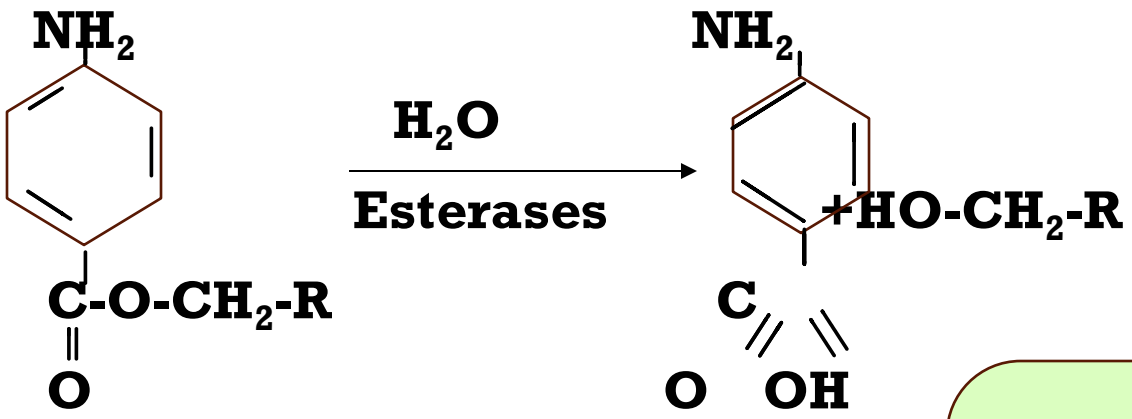
- Nonmicrosomal oxidation and reduction

Alcohol oxidation; chloral hydrate reduction

Note

Nonmicrosomal oxidation in cytosol or mitochondria, that's all what you need to know

- Hydrolysis reactions



Note:

You just have to know that hydrolysis is pathway 1, and you can see we added water in the reaction .

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2. Pathway II = Conjugation reactions

Addition of certain groups to a drug to become more polar and readily excreted

soluble enzymes in cytosol

Acceptor + Donor ——————————— conjugate

(Drug) (activated) of liver (transferases)

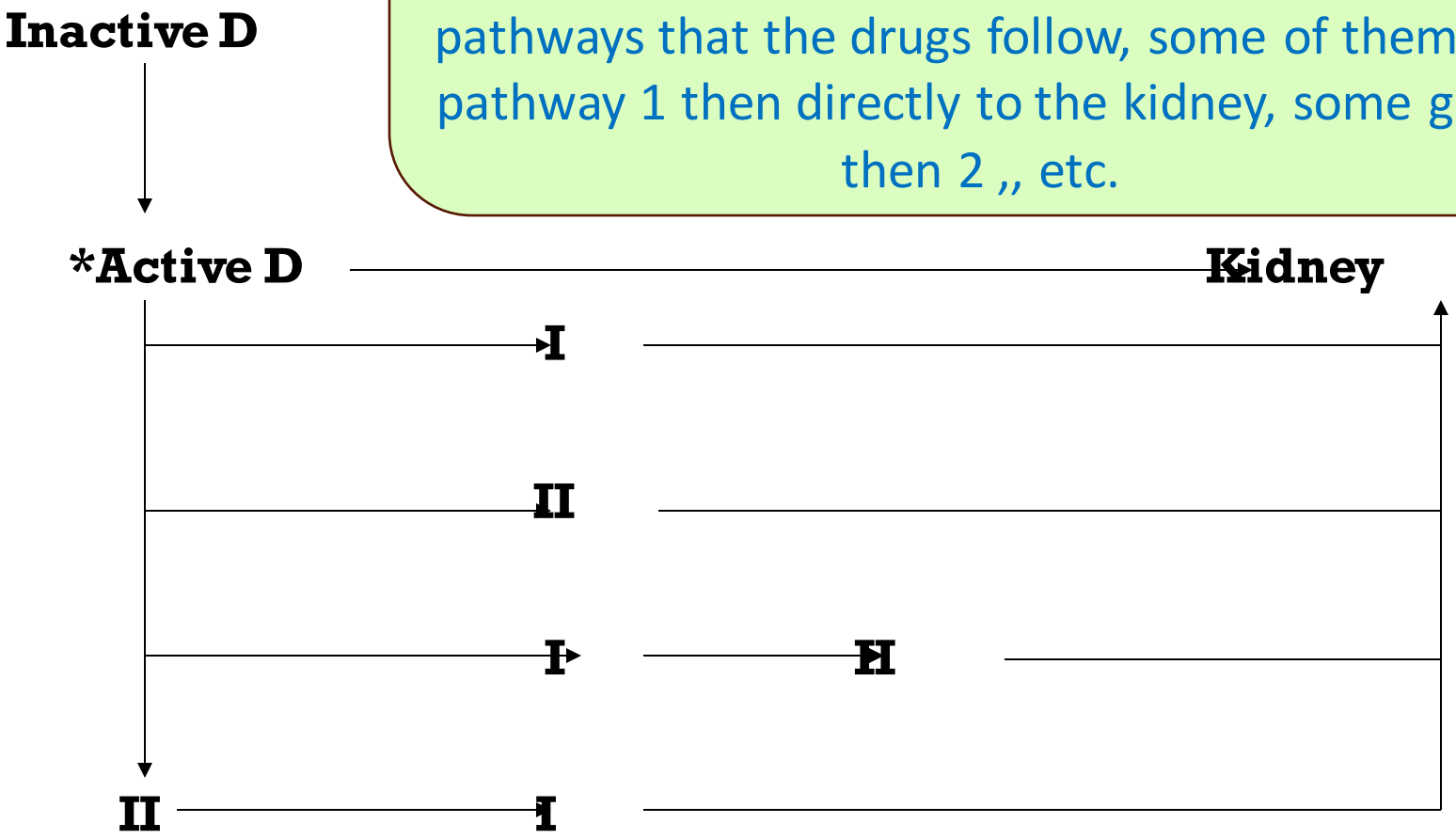
- **Metylation**
- **Acetylation**
- **Glucuronic acid conjugate**
- **Etheneal sulfates**
- **Glycine conjugate (mercaptopuric acid formation)**

Note:

What we need to know in this pathway, we add groups such as methyl (methylation) or acetyl group(acetylation).. Etc. to make it water soluble.

Note:

Metabolism is all about to inactivate the drug by delivering it's metabolites to kidneys, then excrete them outside the body. Here's the pathways that the drugs follow, some of them go pathway 1 then directly to the kidney, some go 1 then 2 ,, etc.



Characteristics of an ideal metabolite:

- **Water soluble**
- **Pharmacologically inactive**
- **Not to be toxic**

Note:

1) In order to be excreted.

Sites of drug metabolism:

- **Liver (major site)**
- **Intestine**
- **Lungs; brain; kidney; plasma, adrenals…etc**

Factors affecting drug metabolism:

- **Genetic factors and species differences (major factor) (slow and rapid metabolizers)**
- **Sex**
- **Drug-drug interactions**
- **Age (paracetamol vs chloramphenicol)**
- **General health of patients and nutritional status**
- **Dose and frequency of administration**

For paracetamol, which is a safe drug, but its metabolites are toxic, and since Children have low metabolism it is considered safe to them compared to adults. The opposite occurs for the other drug.

Note:

1)Since drugs are enzymes (proteins), they are affected by genetic factors, which is the major factor. We can measure how the metabolizers are: slow or rapid by giving the drug to a group of people and measure the metabolites, if it's little then the metabolizers are slow and vice versa.

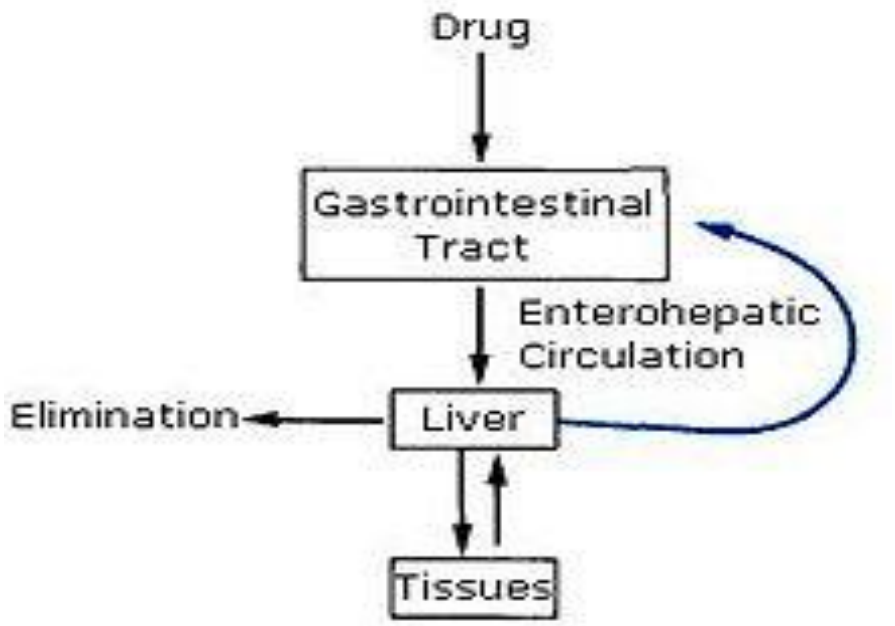
2)Females have lower metabolic rates than males.(not huge difference)

4) Children need less dose than adults because of their slow metabolism.

5) Healthy people have more efficient metabolism.

First-pass effect = rapid metabolism

Enterohepatic circulation



Note:

. Enterohepatic circulation refers to the substances metabolized in the liver, excreted through this bile to get into the intestinal lumen, and then reabsorbed and returned to the liver through the portal circulation.

Note:

First pass effect is the phenomenon which occurs whenever the drug is administered orally, enters the liver, and suffers extensive biotransformation (conjuncation- pathway2) to such an extent that the bioavailability is drastically reduced. It happens when the drug is absorbed through GIT and then via the enterohepatic circulation the drug is absorbed directly into the liver where it undergoes metabolism before being released into the systemic circulation .

INDUCERS

Barbiturates

Theophylline

Phenytoin

Rifampicin

Allopurinol

Smoking

Note:

Inducers means stimulaters, they speed up the metabolism thus reduce the activity of the drug.

In such cases, higher doses are needed.

INHIBITORS

Ketoconazole

Fluconazole

Cimetidine

Erythromycin

Contraceptives

Diltiazem

Grape fruit juice

Note:

Inhibitors lower the speed of metabolism thus increasing the activity of the drug .Here, lower doses are needed.

For example, if (statins) where taken with grape fruit juice, the juice inhibits its metabolism, and statins are known to be toxic because they cause break down of muscles. (Rhabdomyolosis)

Drug excretion = elimination

A process by which a drug or it's metabolites are eliminated from the body

Major sites:

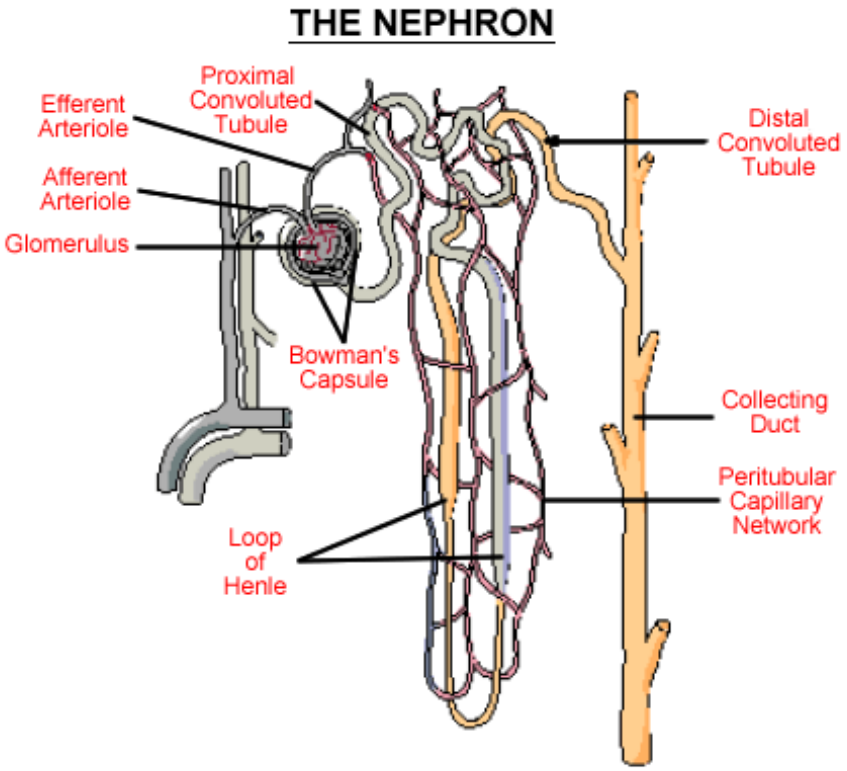
- Kidney (most drugs)

- Liver

Kidney function (old people)!!!!!

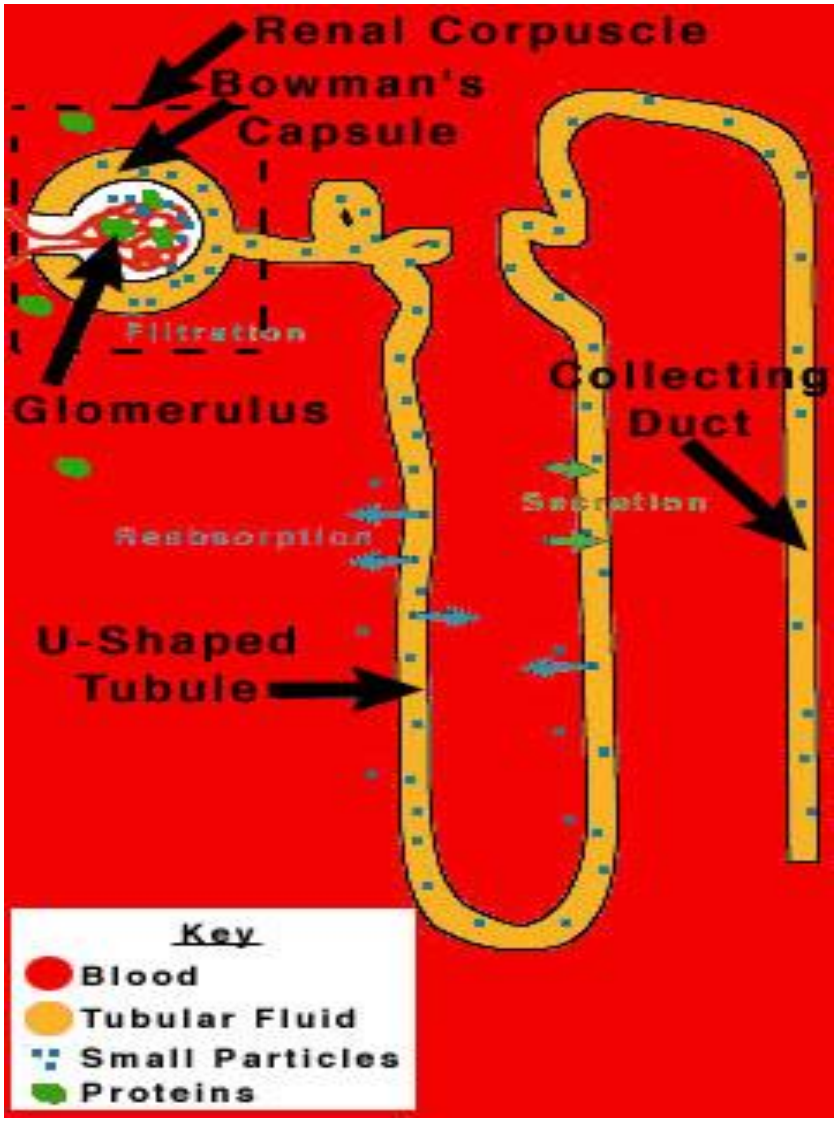
Note:

Some of drugs are secreted through kidney, while others via liver .However, if there's any disfunction in kidney for example, we give the patient a drug that is excreted via liver, and vice versa. And if someone has disfunction with the both, we reduce the dose.



Note:

The nephron is the basic unit of the kidney where most of the drugs are excreted, and there are two mechanisms for excretion that are explained in the next slide


Renal Corpuscle
Bowman's Capsule
Filtration
Glomerulus
Collecting Duct
Secretion
Reabsorption
U-Shaped Tubule
Key
Blood
Tubular Fluid
Small Particles
Proteins

Methods of excretion:

- **Filtration**
- **Tubular secretion**
  - **Specific secretory mechanism for weak acids and another one for weak bases (80% of drugs are excreted by this mechanism)**
  - **Still some drugs remain lipophylic so could be reabsorbed (this could be inhibited by changing pH and provides the use of alkali in enhancing excretion of acidic drugs)**

Probenecid

Penicillin

Note:

Probenecid has the ability to block the transport of organic acids (e.g. penicillins) across epithelial cells (e.g. renal proximal tubule cells) and its use when combined with penicillins resulted in elevated blood levels of the penicillin and a longer duration of antimicrobial action.(longer half life).

The rate of excretion of a given drug is determined by a specific constant known as K_e which depends on AVD and clearance

$$\text{Clearance} = \frac{U_x \text{ (mg/ml)} \times V}{P_x \text{ (mg/ml)}}$$

V_2

(U)x = Urine concentration of the substance(mg/ml)

V =Urine flow rate (ml/min)

(P)x = Plasma conc of the substance(mg/ml)

Renal clearance is the volume of plasma cleared of drugs per unit time

Note:

Clearance can be measured for any substance in our bodies. Urea's clearance indicates the function of the kidney.

$$K_e = \text{Clearance (ml/min)/AVD (ml)}$$

Ke unit: min^{-1} = 1/min

$$K_e = 0.693/t_{1/2}\,(min)$$

$$t_{1/2} = o.693 \times AVD/clearance$$

$$K_T = K_m + K_e$$

Note:

Be careful for the units

And memorize K_e

Additional Information:

Km = (drug conc. at which the rate of elimination is 50% of Vm)

V2
SLIDE 19

(U)x = Urine concentration of the substance(mg/ml)

V =Urine flow rate (ml/min)

(P)x = Plasma conc of the substance(mg/ml)