تفريغ ميديسينال

Phase II

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الصيدلاني\ة:

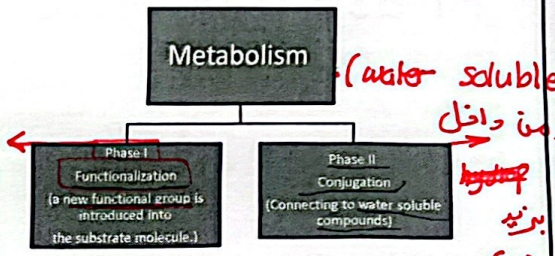
لجان الدُفعات

Soul Academy

PHASE II METABOLISM

Drug metabolism

- The aim of all drug metabolism processes is to **detoxify** the drugs, Very often these metabolites lose the activity of the original drug, but in some cases, they may retain a certain level of activity.

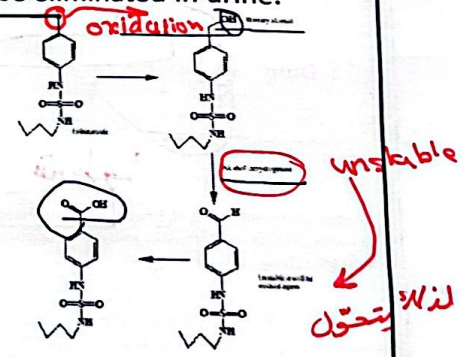


Drug metabolism

- Major organ in drug metabolism is the liver
- Why we study metabolism?
- **Detoxifications** : Drugs, plant toxins, food additives, environmental chemicals, insecticides, and other chemicals foreign to the body undergo enzymatic transformations that usually result in the loss of pharmacological activity
- **Bioactivation:** enzyme-catalyzed reactions may lead to the formation of a metabolite having therapeutic or toxic effects (as in prodrugs)

Example on benzylic oxidation (Tolbutamide)

- So Tolbutamide will be eliminated in urine:
- 1. Alcohol
- 2. Carboxylic acid
- 3. Conjugated



Phase II reactions

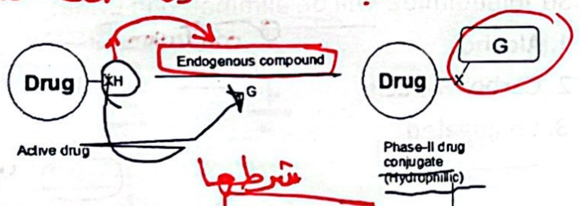
Phase II reactions

- Reactions which conjugate the drug or its phase-I metabolite with a hydrophilic, endogenous species (conjugation reactions).
- These endogenous compounds are:
- Glucuronic acid
- Sulfate group
- Amino acid (Glycine)
- Methyl group (as SAM) S. Adenosyl-L-Methionine
- Acetyl group (as acetyl CoA)
- Glutathione (tripeptide)

Aim of Conjugation

(attack) رح يعمل ، [O, N, S]

وهيك بيرتبط عليها

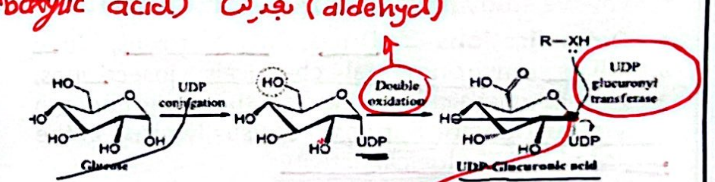


شرطها

- Hetero atoms like X = O, N, S have lone pair of electrons
- Phenol, alcohol and carboxylic acid Amine (aliphatic and aromatic), Thiol

From Glucose to UDP Glucuronic Acid

يعني اول شي بيتحول إلى (carboxylic acid) بعدين (aldehyd)



الدواء الي عنده (R-XH) بواسطة (UDP glucuronyl transferase)

رح يعمل (attack) على هاد الكربونة لانها صارت

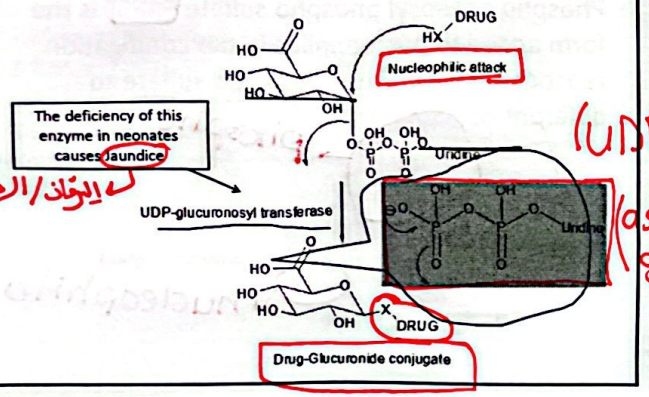
(highly electrophilic) وهادي فائدة UDP

لانه (P. group) هم (highly electronegative) ، رح يسحبوا الالكترونات

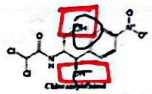
بتهتم ، فيخلوا الكربونة (very electrophile) ، واول ما يشوفها الدوا الي عنده (x.group) رح يعمل (attack) عليها

بيطلع (UDP) وضل الدوا رابط مع (glucuronic acid).

Mechanism of conjugation Glucuronidation reaction

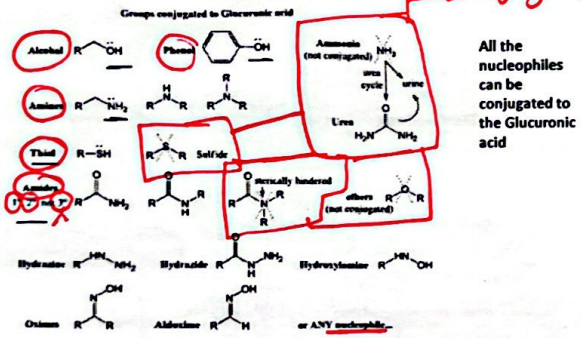


Chloramphenicol



- Sometimes UDP-glucuronosyl transferase enzyme is deficient in the newborns that their livers are immature after delivery which results in "Neonate Jaundice", in those babies any drug that needs to be conjugated in order to be eliminated will accumulate in their bodies.
- For example, "Chloramphenicol", an antibacterial agent, has two alcohols that can be conjugated so if there is no enough glucuronide conjugation due to problems in the liver, "Grey-Baby syndrome" will be result (Babies that have immature livers with little amount of UDP-glucuronosyl transferase, so they tend to accumulate chloramphenicol in their bodies and terminating at Grey color).

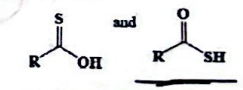
Candidates for Glucuronidation reaction



All the nucleophiles can be conjugated to the Glucuronic acid

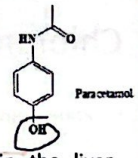
Candidates for Glucurodination reaction

- 1. Aliphatic alcohols, Aromatic alcohols (Phenols)
- 2. Aliphatic amines, Aromatic Amines
- 3. Carboxylic acids
- 4. Thiols
- 5. Amides
- 6. Thioacids (it's abundant in liver)



Thioacids

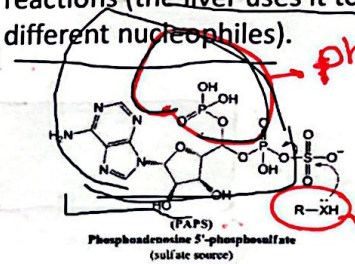
Paracetamol toxicity



- The Glucuronic acid stores are large stores in the liver although they can be consumed and cause toxicity.
- After administration of large toxic dose of certain drug, for example if a patient administered 20 tablets of Paracetamol at once (each tablet contains 500mg so 20 tablets contain 10g) it can reach the toxic dose because it depleted all the Glucuronic acid stores and therefore it will start having toxicity, But under normal clinical doses usually the amount of Glucuronic acid is enough to help in detoxification of the drugs.

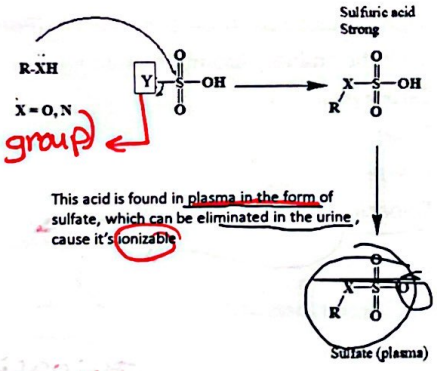
Sulfate conjugation

- Phospho adenosyl phospho sulfate "PAPS" is the form added to nucleophiles in the conjugation reactions (the liver uses it to add sulfate to different nucleophiles).



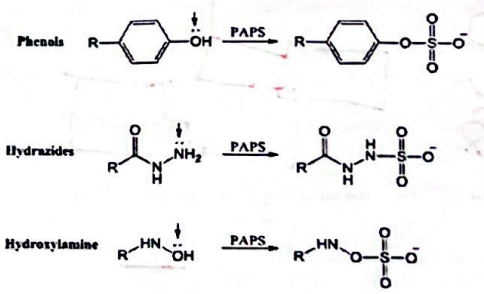
" phenols " ممكن يصير للباراسيتامول

Sulfate conjugation



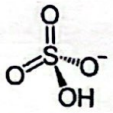
PAP ← (leaving group) ← اي

Candidates for sulfation

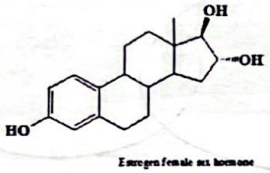


Candidates for sulfation

1. phenols (Aromatic alcohols) (not aliphatic)
2. Anilines (Aromatic amines) (not aliphatic)
3. Hydroxyl amines

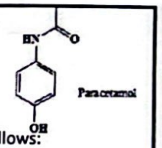


Majority of the sulfation process happens on the internal substrates like: (Bile salts, steroidal hormones such as testosterones, estrogens)



Paracetamol

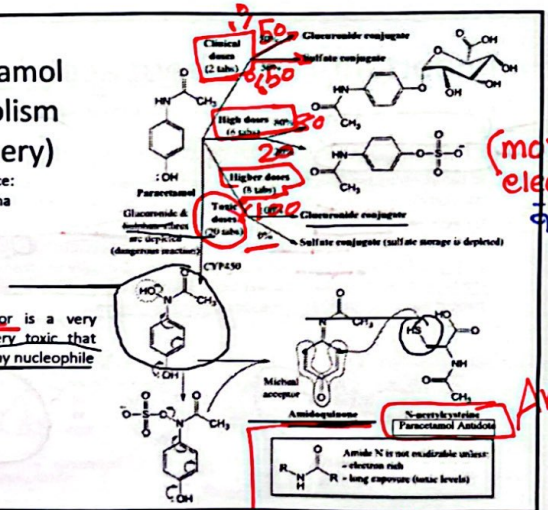
Paracetamol



- If taken in a clinical low dose we will see it in the urine as follows:
- 1. 50% Sulfate conjugate
- 2. 50% Glucuronide conjugate
- If the dose is high the majority of the dose is excreted as Glucuronide conjugate
- The amounts of sulfates in the liver are much lower than the Glucuronic acid, for example the three previous groups that can be sulfated also can be conjugated to Glucuronic acid, so under low clinical doses there is a competition between sulfate conjugation and glucuronide conjugation (50:50), but if the clinical dose increases the sulfate will be reduced (depleted) and the glucuronide will be higher than it (higher clinical doses results in depletion of the sulfate and therefore the glucuronide will be higher than the sulfate).

Paracetamol metabolism (Summery)

Reference:
Prof. Taha



Micheal acceptor is a very reactive and very toxic that can react with any nucleophile

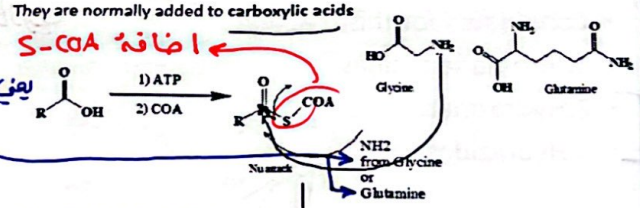
highly reactive

Antidote

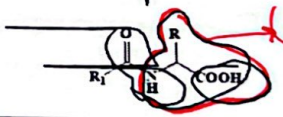
Amino Acid conjugation

Carboxylic acids are the only substrates for amino acid conjugation

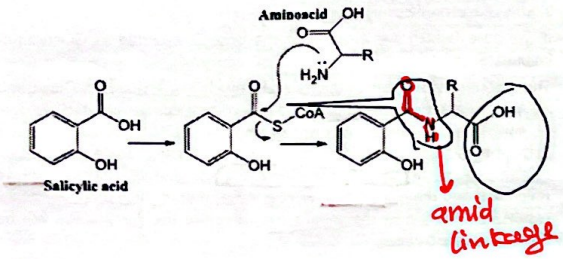
- They are normally added to carboxylic acids



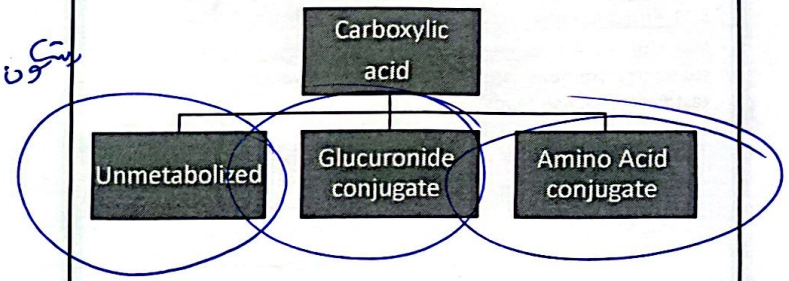
This reaction is catalyzed by Glycine transferase or Glutamine transferase



Example

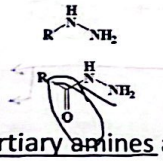


Fate of carboxylic acids in the body



Acylation reactions

- Candidates for this reaction
- 1. Aromatic amines
- 2.Hydrazines
- 3.Hydrazides

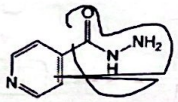


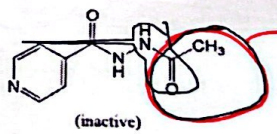
- Secondary and tertiary amines are not acetylated.

Important facts about acetylation

First Fact: People are divided into two groups according to the Acetylation:

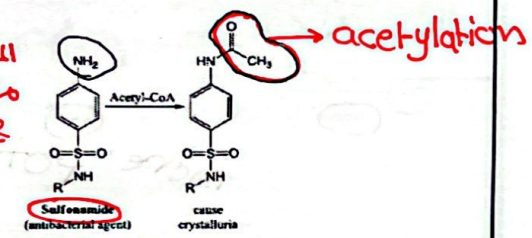
- A- Slow acetylators 50%
- B- Fast acetylators 50%
- So before giving the Drug to a patient we should check if our patient is a slow or a fast acetylator especially if the drug is to be given for long period of time.
- For example, "Isoniazide" drug that used for tuberculosis against *Mycobacterium* should be taken for long period of time (the treatment duration is 6 months to 2 years), so if the patient was fast acetylator we should modify the dose (increase the dose) to accommodate the fact the individual is a fast acetylator while if the patient was a slow acetylator we should decrease the dose.


Isoniazid
(active)


(inactive)

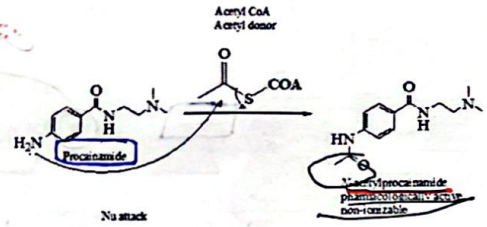
Second fact

- We said that the aim of Phase 2 reactions is increasing the water solubility of the compounds, but in Acetylation we are adding an acetyl group to the compound which increases its lipophilicity!
- So, Acetylation makes the compounds less water soluble and leads to their precipitation in the kidney and causes "Crystalluria" or "Kidney stones"



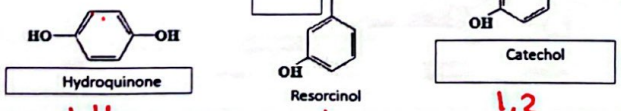
Example

- The product in this case is less soluble than the starting drug (special case)



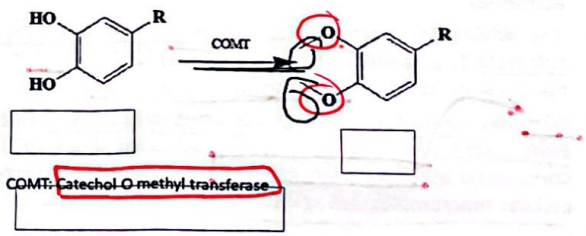
Methylation reaction

- Candidates for this reaction:
  - 1. Amines
  - 2. Alcohols
  - 3. Catechols (majority)
  - 5. Resorcinol
  - 6. Hydroquinones



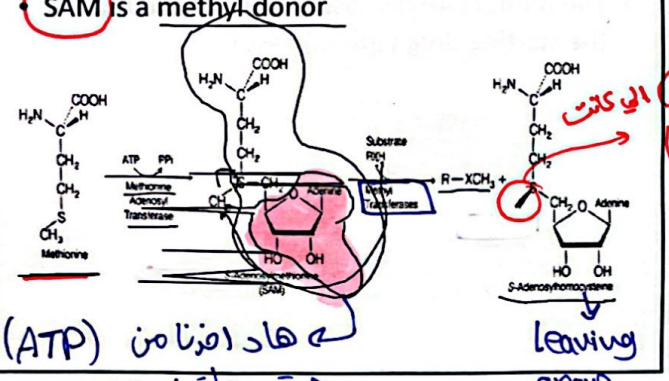
Methylation reaction

- COMT carries out O-methylation of such important neurotransmitters as epinephrine and dopamine and thus terminates their activity



S-Adenosylmethionine SAM

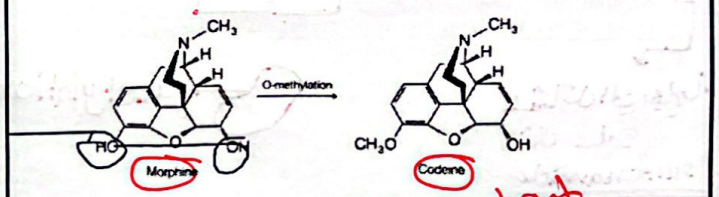
- SAM is a methyl donor



PPi وطلعنا (ATP) هاد اخذنا من SAM حتى يعطيها leaving group

هون اخذها (CH3) الميثايل

S-Adenosylmethionine SAM

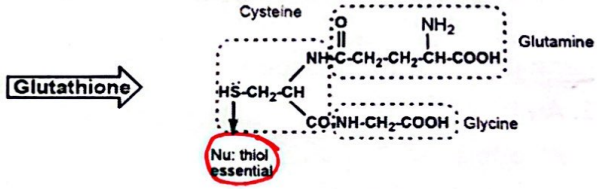


more potent

[4] Glutathione or Mercapturic Acid Conjugation

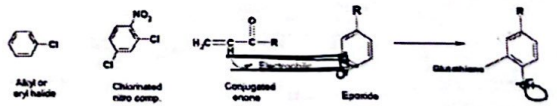
- GSH is tripeptide: [γ-glutamyl cysteinyl glycine] found in most tissues.
- Glutathione combines with activated drug (GSH is not activated).
- the driving force for this reaction is the electrophilicity of substrate (e.g. arene oxide and epoxide) & the reactivity of nucleophilic GSH towards elecrtophilic substrates.
- GSH may prevent any damage occurring to macromolecules (DNA , RNA , Proteins) by some activated drugs so it is considered as *detoxifying pathway* that function to protect cellular macromolecules against harmful electrophiles.

Donor : Glutathione tripeptide = Cysteine + glutamine + glycine
(activated inside the body)



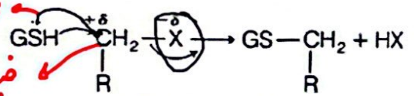
Acceptor : ***Electrophilic species*** (electron deffecient)

e.g . Alkyl or aryl- halide , Epoxide , Chlorinated nitro compound , Organic nitrate & Conjugated enone



GSH or Mercapturic Acid Conjugates

- Glutathione (GSH) protects vital cellular constituents against chemically reactive species by virtue of its nucleophilic SH group.
- The SH group reacts with electron-deficient compounds to form S-substituted GSH adducts



R = Alkyl, Aryl, Benzylic, Allylic
X = Br, Cl, I, OSO_3^-, OSO_2R, $OPO(OR)_2$

(attack)

(CH2)

more electrophilic)

(attack)

(nucleophilic)

(GSH)

(conjugation)

GSH or Mercapturic Acid Conjugates