PHARMACOLOGY
433

King Saud University
College of Medicine
Foundation Block

Pharmacokinetics III ; Drug Metabolism

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Objectives

-Recognize the importance of biotransformation.

-Know the different sites for drug metabolism.

-Define the major phase I and phase II metabolic reactions.

-Describe the modulation of liver microsomal enzymes by inducers and inhibitors.

-Mention two drugs that are known as enzyme inducers and inhibitors.

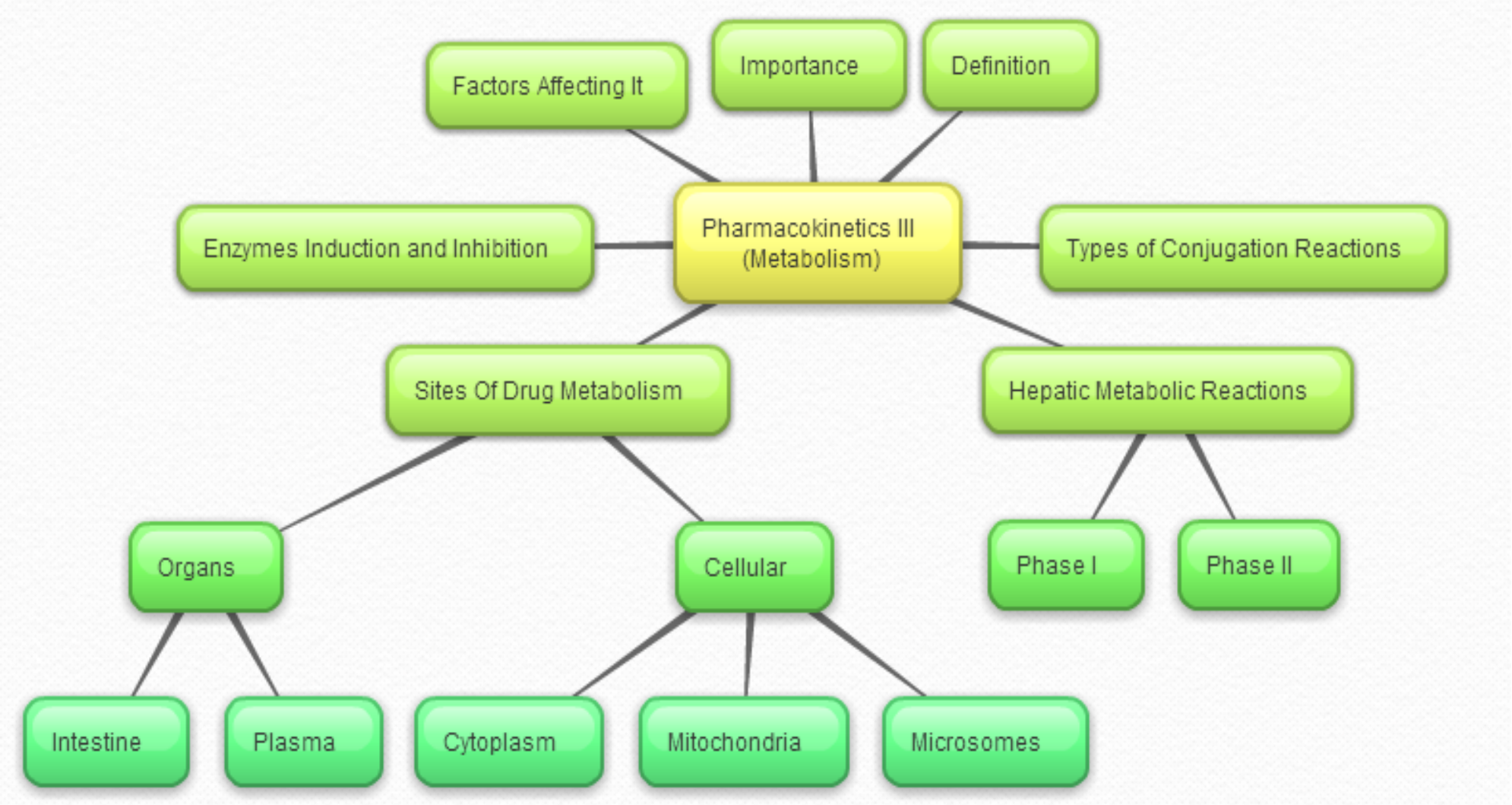
-Know the impact of first pass metabolism on drug bioavailability.

Key Words

*Metabolism
*Biotransformation
*Toxins
*Enzymes and Substrates
*Oxidation and Reduction
*Conjugation Reactions
*Induction and Inhibition

This lecture has a lot of Chemistry, so remember ;

*LEO the lion goes GER
Loss of Electrons is Oxidation
Gain of Electrons is Reduction
*The suffix “ase” means enzyme.
*Hydrolysis means addition of WATER.



Drug Metabolism (Biotransformation) :

Chemical reactions which occur in the body and lead to change of drugs from lipid soluble form to water soluble form that is easily excreted. Metabolism increases the renal excretion.

Importance of Metabolism

1. Detoxification : remove toxins from the drug.

2. Inactivation (termination) of drug action.

3. Activation of prodrug : prodrug means the inactive form of a drug that should be activated after administration by Metabolism.
Most of the drugs that we take are in the active form, but some of them might be prodrugs, so they get activated after administration.

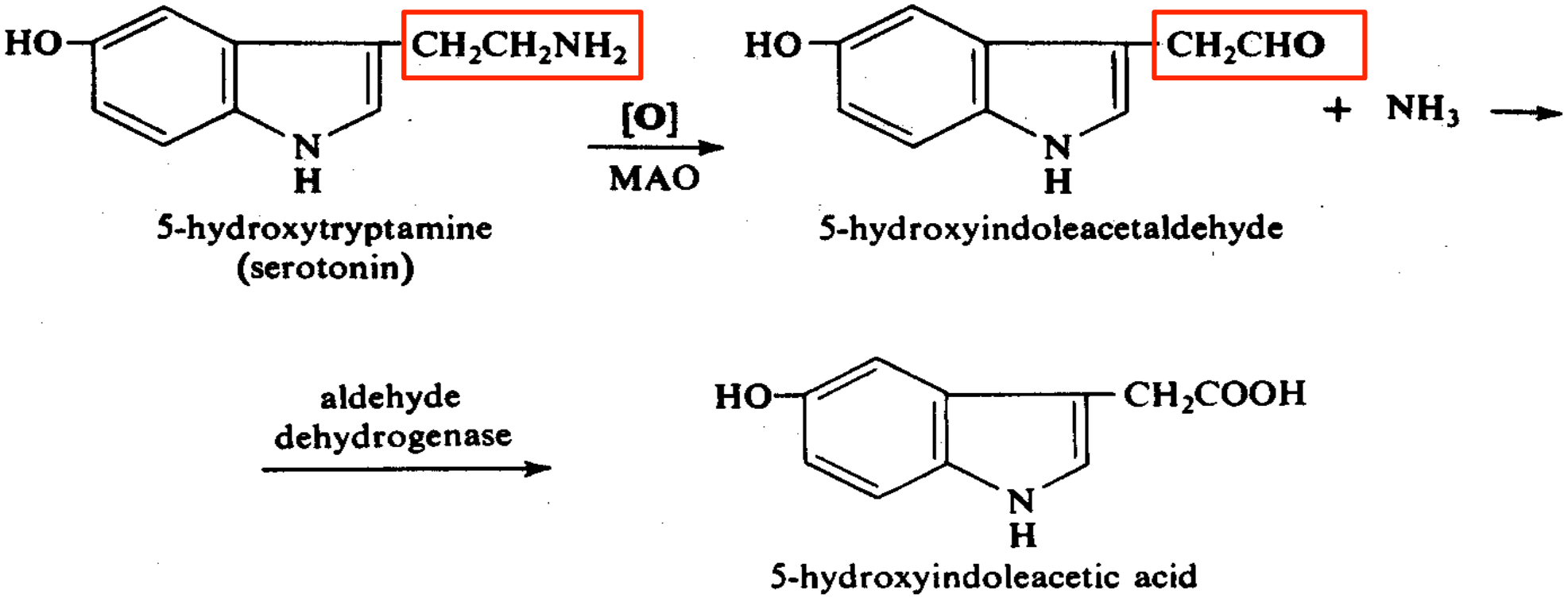
Organ Sites of Drug Metabolism

Site	Drug Metabolism	
Liver	It is the **major** site of drug metabolism	
Intestine	**Gut Mucosa**	1.Monoamine Oxidaze (MAO). 2.Sulphatase.
	Gut Lumen "Bacterial Flora"	1.Glucouronidaze. 2.Azoreductase (N=N). "split the N=N bond, to result as NH_2 and NH_2"
Kidney	Because it receives a substantial portion of the cardiac output.	
Plasma	**Enzyme**	**Substrate**
	Catechol O-Methyl Transferase (COMT)	Catecolamines
	Esterases	Esters (local anesthetics)
	Amidases	Amides (local anesthetics)
Skin	Has many enzymes that play a role in drug metabolism.	
Lungs	Lungs are pharmacologically active organs that affect drug metabolism.	

Monoamine oxidase (MAO)

"Monoamine is the substrate, Oxidase is the enzyme.

This enzyme work in the Sympathetic Nervous System as it acts on Adrenaline and Noradrenaline.



5-hydroxytryptamine (serotonin)

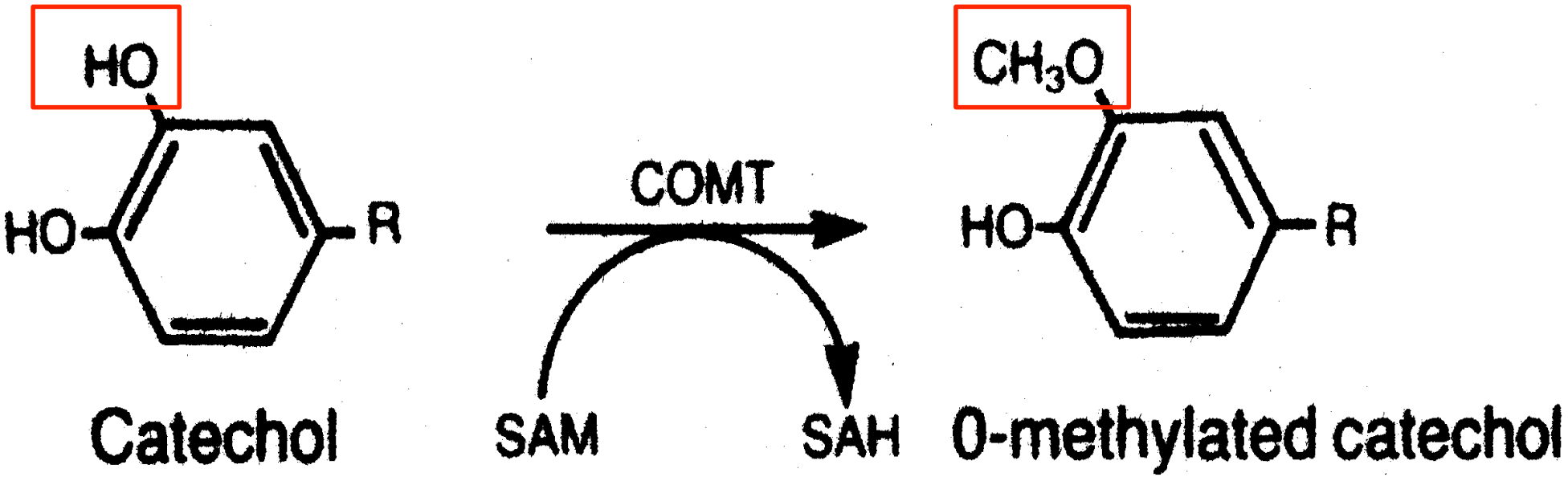
5-hydroxyindoleacetaldehyde

5-hydroxyindoleacetic acid

Catechol O-Methyl Transferase (COMT)

COMT is an enzyme that transfer a methyl group to a chatecol structure in the drug.

This enzyme also acts on : **Adrenaline** and **Noradrenaline** in the Sympathetic Nervous System. Note that adrenaline is the same as epinephrine, and noradrenaline is the same as norepinephrine.



Cellular Sites of Drug Metabolism

Organelle	Drug Metabolism
Cytoplasm	e.g. Alcohol dehydrogenase : Oxidation of alcohol. **Ethanol** Alcohol dehydrogenase → **Acetaldehyde** Aldehyde dehydrogenase → **Acetic Acid** **$CH_3CH2OH \rightarrow CH_3CHO \rightarrow CH_3COOH$**
Mitochondria	1.Monoamine Oxidase Enzyme (MAO) : Oxidation of catecholamines 2. Acetylation by N-acetyl transferase: introduction of acetyl group (CH_3COO^-)
Microsomes	Microsomal enzyme system => mixed function oxidase => mono-oxygenase => Cytochrome P450
Lysosomes	As they are the main organelles for digesting in the cell.

Types of Hepatic Metabolic Reactions:

There are two phases,

Phase I

- Oxidation • or
- Reduction. • or
- Hydrolysis.

Now the drug could be either :

Active= lipid soluble and it means it should enter the second phase to become water soluble.

Inactive= water soluble, now it can be excreted.

Phase II

Phase II reactions include:

- Conjugation reactions

The drug after this phase always become in water soluble form

PHASE I

Oxidation Reactions

Microsomal

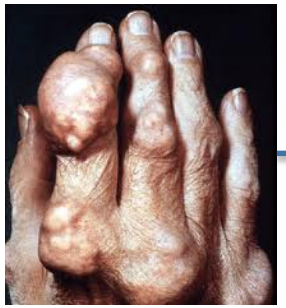
Oxidation by : Cytochrome P450 enzymes present in "microsomes"

Non-Microsomal

Oxidation by : Soluble enzymes in Cytosol or Mitochondria of cells as ; Oxidases and Dehydrogenases.

Reduction Reactions

Hydrolysis



Oxidases :

-Monoamine oxidase (MAO): metabolism of Catecholamines

-Xanthine oxidase: metabolism of Xanthine

Hypoxanthine ⟶ Xanthine ⟶ Uric acid.

***Uric Acid Accumulation ⟶ GOUT "النقرص"**

Dehydrogenases :

-Alcohol dehydrogenase.
-Aldehyde dehydrogenase.

PHASE I

Oxidation Reactions

Reduction Reactions

Microsomal

Nitrobenzene -> Aniline
NO_2 -> NH_2

Non-Microsomal

Chloral hydrate ->
Trichloroethanol (active)
$CCl_3–CHO$ -> $CCl_3 – CH_2OH$

Hydrolysis

-All are **Non-Microsomal**. "in cytoplasm or Mitochondria"

-Occurs by enzymes that are (Esterases or Amidases).

-Drugs (substrates) affected are either Esters or Amides.

Amides as Lidocaine :
used as local Anesthetic

$$R_1\text{- CONH} – R_2 \xrightarrow{\text{amidase}} R_1\text{- COOH} + R_2NH_2$$

Esters as Acetylcholine :
Neurotransmitter in Parasympathetic NS

Acetylcholine →choline + acetate.

$$R_1\text{-COOR}_2 \xrightarrow{\text{esterase}} R_1\text{COOH} + R_2\text{OH}.$$

Phase I Reactions Can Result In :

***Inactivation of drug (termination of action).** "usually 50% of the drug becomes inactive after the 1st phase, which means it's now ready to be excreted, and no need to undergo the 2nd phase."

***Conversion of active drug to another active metabolite.** "this result means the drug should go to the 2nd phase to become inactive (the purpose of metabolism)"

***Conversion of drugs to toxic metabolites.**

Paracetamol → hepatotoxic metabolite

***Activation of pro-drug** "goes to the 2nd phase."

***Product might undergo phase II.** "except for the drugs that became inactive after this phase."

Remember that :

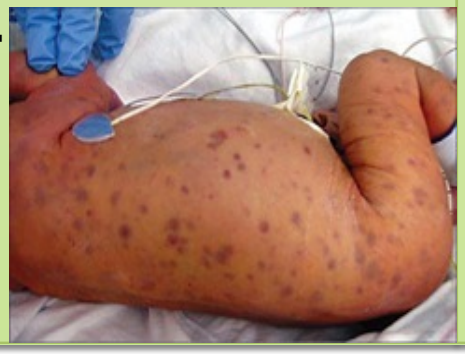
*The enzyme MAO metabolizes drugs in:
Non-microsomal Oxidation Reactions→
in the Mitochondria→
in the Gut Mucosa.

*Microsomal reactions are associated with the enzyme Cytochrom P450

Both (MAO) and (COMT) are enzymes acting on the Sympathetic NS,

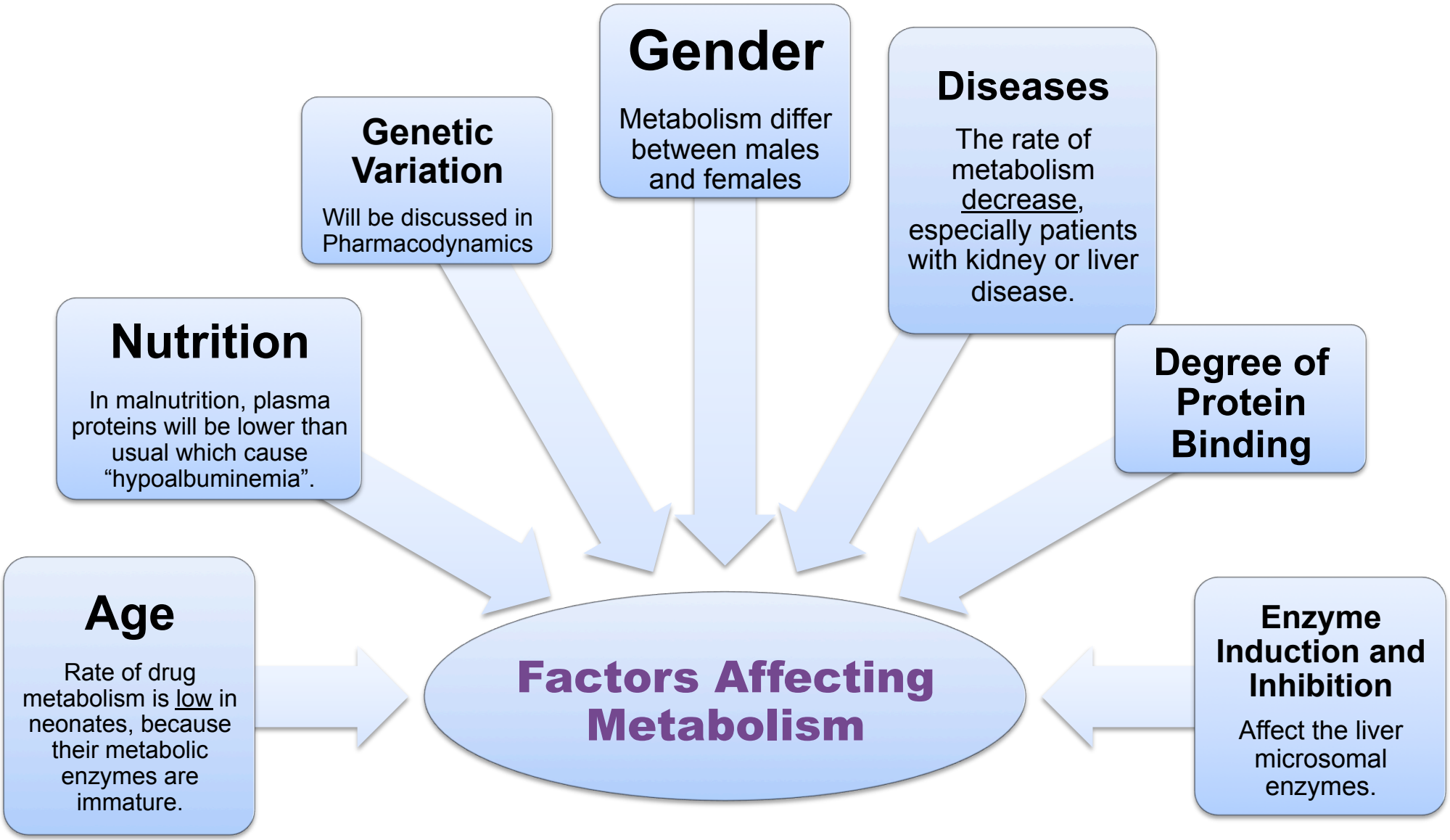
Whereas Acetylcholine is in the Parasympathetic NS.

Phase II

Conjugation Reactions	Reactions	Characteristics of Phase II Products
-What is it? Conjugation of metabolite coming from (phase I) with endogenous substance. **-Examples of those substances?** Methyl group, Acetyl group, Sulphate, Amino Acid or Glucouronic Acid. **-Why does it happen?** to produce conjugate that is water soluble and easily excreted.	1.All are **Non-Microsomal** except Glucouronidation. 2. The most common is : **Glucouronide conjugation** and it is a Microsomal process. 3.Deficiency of Glucouronyl-Transferase enzyme in neonates "حديثي الولادة" may result into toxicity with chloramphenicol (Gray baby syndrome). 	1.Usually pharmacologically inactive. 2.Polar 3.More water soluble. 4.More readily excreted in urine.

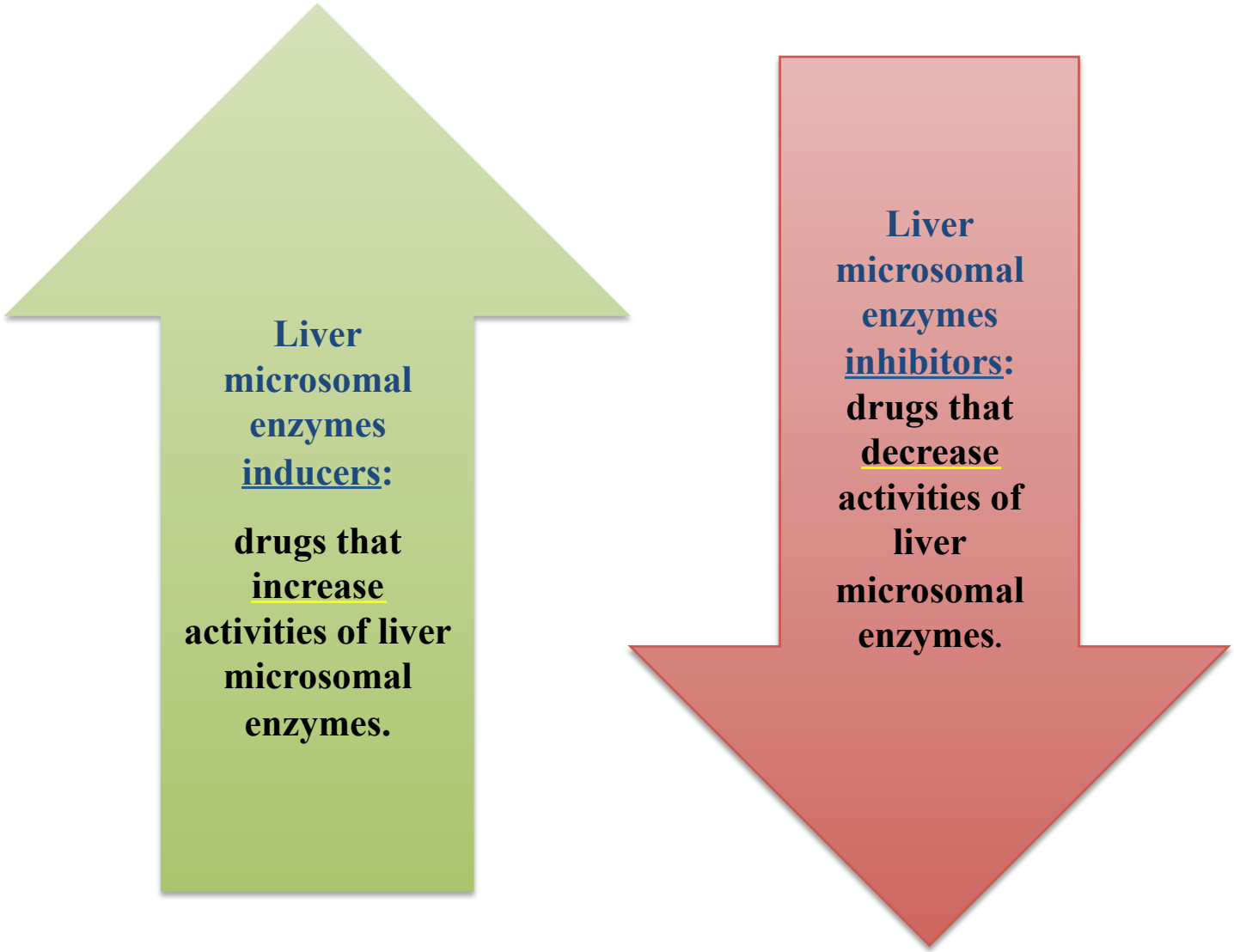
Types of conjugation reactions

Conjugation Reaction	Enzyme Required
glucouronide conjugation	Glucouronyl transferase
Acetylation (CH_3COO^-)	N-acetyl transferase
Sulphation (SO_4^{--})	Sulfo transferase
Methylation (CH_3)	methyl transferase
Amino acids conjugation	Glycine conjugation


Gender
Metabolism differ between males and females
Genetic Variation
Will be discussed in Pharmacodynamics
Diseases
The rate of metabolism decrease, especially patients with kidney or liver disease.
Nutrition
In malnutrition, plasma proteins will be lower than usual which cause "hypoalbuminemia".
Degree of Protein Binding
Age
Rate of drug metabolism is low in neonates, because their metabolic enzymes are immature.
Factors Affecting Metabolism
Enzyme Induction and Inhibition
Affect the liver microsomal enzymes.

Enzyme Induction & Inhibition

Activities of liver microsomal enzymes may be changed by administration of some drugs..



Microsomal inducers	Microsomal inhibitors
Cigarette smoking	Grape Fruits
Alcohol	Cimetidine
Phenobarbitone hypnotic	Erythromycin (antibiotic)*
Phenytoin (antiepileptic)*	Ketoconazole (antifungal)*
Rifampicin (Anti TB)*	
Grisofulvin (antifungal)	* important

Enzyme induction	Enzyme inhibition
1. Increase metabolism of the inducer drug. 2. Tolerance قدرة التحمل : decrease in its pharmacological action "in response to the drug because increasing of metabolism". 3. Drug interactions: increase the metabolism and excretion of co-administered drugs	1. Delay (decrease) the metabolism and excretion of the inhibitor drug and co-administered drugs. "co means at the same time" 2. Prolong the action of the inhibitor drug and co-administered drugs.
e.g. phenytoin & oral contraceptives. Failure of contraceptive may lead to pregnancy if combined with phenytoin.	e.g. erythromycin & warfarin. Inhibition of warfarin metabolism may lead to increase its anticoagulant effect.

Summary

- ***Recognize the importance of biotransformation :***

  These chemical reactions change the lipid soluble drugs into a water soluble form to be easily excreted.

  Used for:

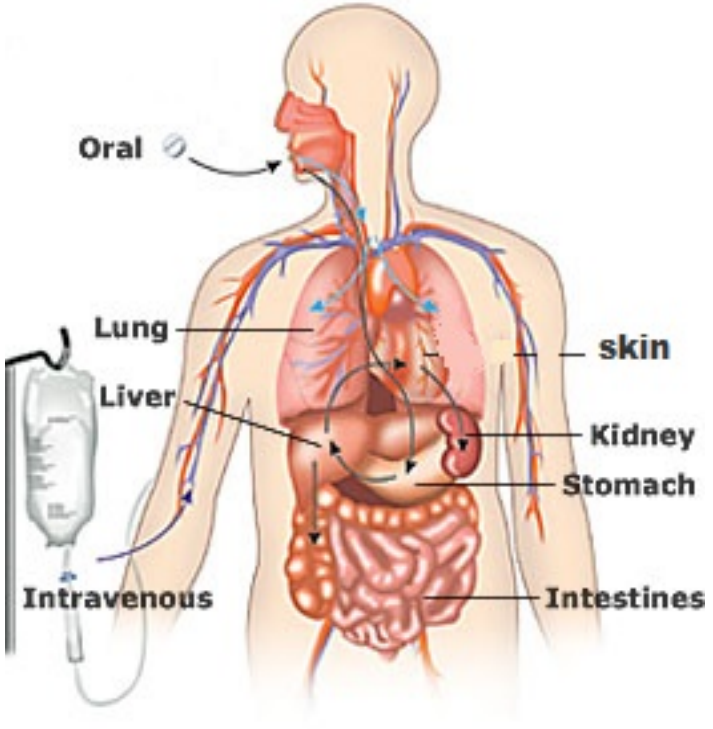
- **Detoxification**
- **Inactivation\termination of drug action**
- **Activation of prodrug**

- ***Know the different sites for drug metabolism :***

  - **Liver (major site)**
  - **Intestinal Mucosa and Lumen**
  - **Plasma**
  - **Kidney**
  - **Skin**
  - **Lung**

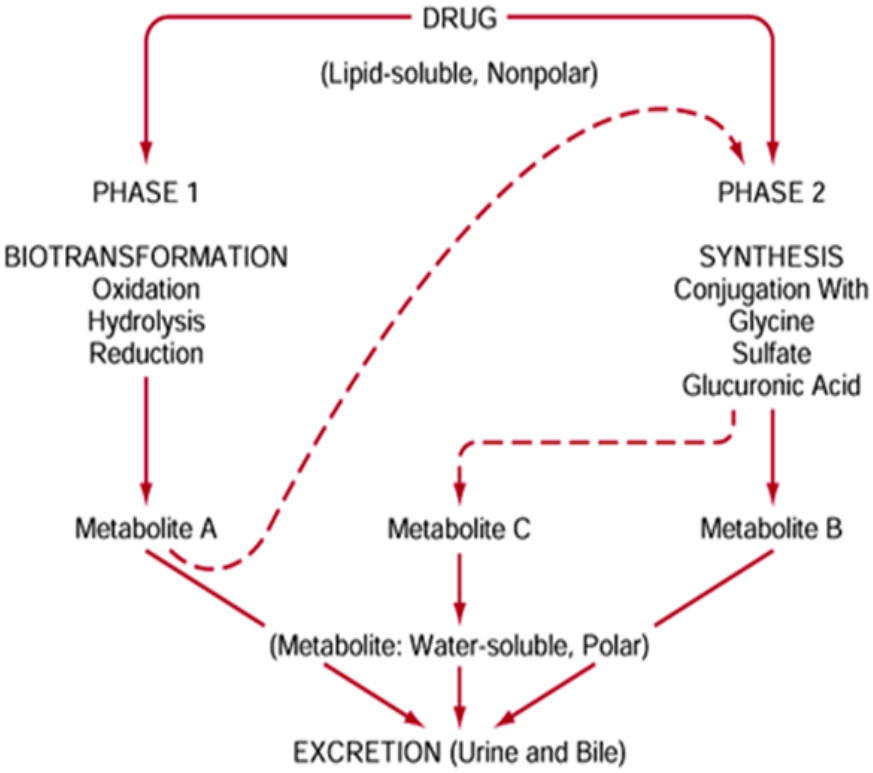
Cellular sites:

- **Cytoplasm**
- **Mitochondria**
- **Lysosomes**
- **Microsomes**



Summary

- ***Define the major phase I and phase II metabolic reactions :***



- ***Describe the modulation of liver microsomal enzymes by inducers and inhibitors***
- ***Mention two drugs that are known as enzyme inducers and inhibitors :***

Inducers: drugs that increase activities of liver microsomal enzymes.

- **Examples: Alcohol, Phenytoin.**

Inhibitors: drugs that decrease activities of liver microsomal enzymes.

- **Examples: Grape fruits, Erythromycin.**

- ***Know the impact of first pass metabolism on drug bioavailability :***

- **REMEMBER THAT:**

Bioavailability: is the fraction of the drug that reaches the blood without any changes.

First Pass Metabolism DECREASE the drug's bioavailability.

MCQs

1. The major site of drug metabolism is:

A- Kidney
B- Liver
C- Lung
D- Skin

2. An intestinal mucosa enzyme :

A- Esterases.
B- MAO.
C- Glucouronidase.
D- COMT.

3. Example of liver microsomal enzymes inhibitors:

A- Cigarette smoking.
B- Grape fruit.
C- Cimetidine.
D- Both B & C.

4. Oxidation by cytochrome P450 enzymes present in :

A- Cytoplasm.
B- Microsomes.
C- Lysosomes.
D- Mitochondria.

5. Deficiency of glucouronyl transferase enzyme in neonates may result into :

A- Increase in anticoagulant effect.
B- Decrease in pharmacological action
C- Uric acid accumulation.
D- Toxicity with chloramphenicol.

6. Phase one reactions can result in :

A- Activation of drug.
B- Inactivation of drug.
C- Conversion of drugs to toxic metabolites.
D- Both B & C.

7. Duration of action is going to be long by :

A- Conversion of active drug to another active metabolite.
B- Activation of pro-drug.
C- Inactivation of drug.
D- Conversion of drugs to toxic metabolites.

8. Responsible for oxidation of alcohol into acetic acid :

A- Alcohol dehydrogenase.
B- Alcohol dehydrogenase and aldehyde dehydrogenase.
C- MAO and cytochrome P-450
D- Xanthin Oxidase.

9. Enzyme in the Gut Lumen that splits the double bond between the N=N molecule :

A- MAO.
B- Glucouronidase.
C- Azoreductase.
D- Sulphatase.

1-B 4-B 7-A
2-B 5-D 8-B
3-D 6-D 9-C

We hope we made this lecture easier for you
Contact us for any questions or comments
Good Luck !

Nada Dammas
Ghadah AlHindi
Norah Alnaeim
Malak Alaboudi
Aseel Alghonaimy
Raneem Alotaibi
Ghaida Alawaji
Lamees Almezaini
Yara Alenezi
Latifa Alanazi
Hanan Al-Dossari

Ahmed Aldakhil

Pharmacokinetics – Metabolism
(http://www.youtube.com/watch?v=ztsBn8gsfHw**)**

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