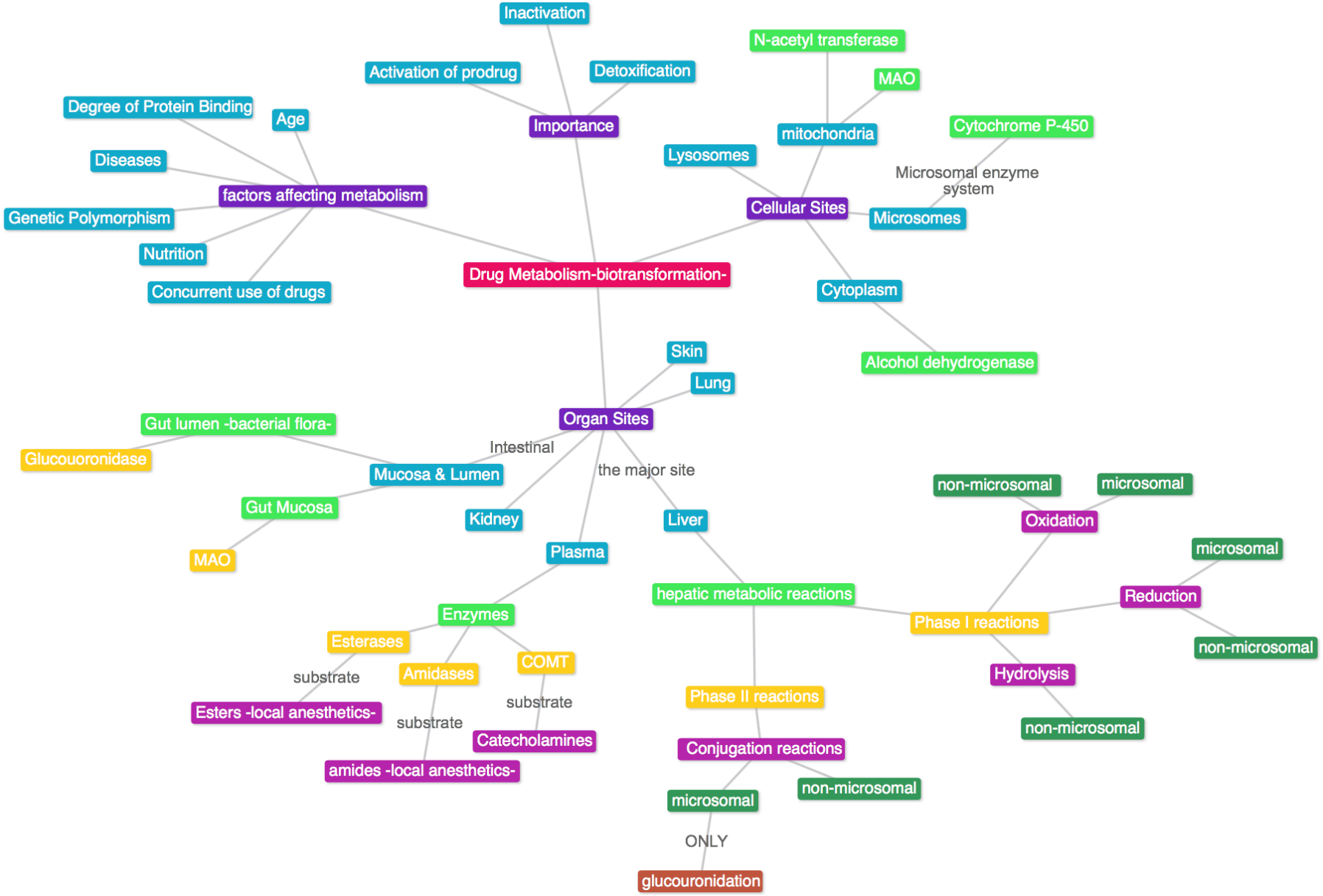
Lecture 3

Pharmacokinetics : drug metabolism III

Objectives:

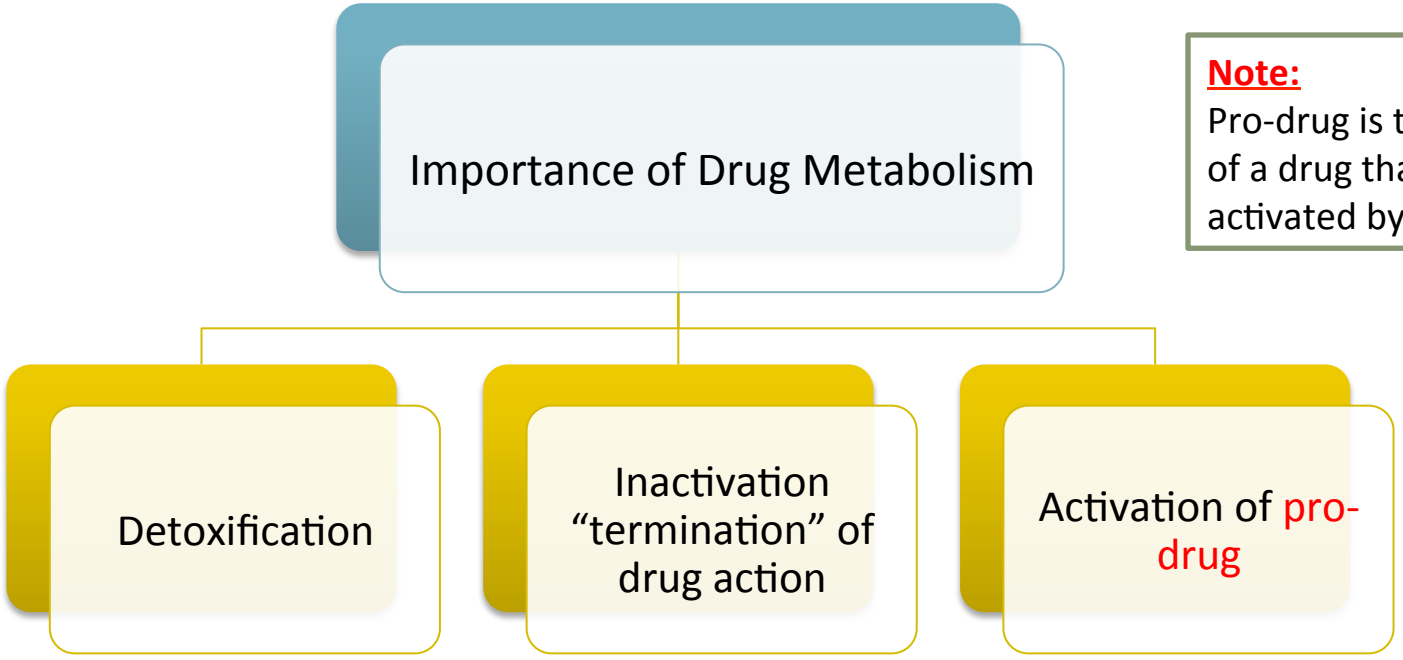
1. Recognize the importance of biotransformation
2. Know the different sites for drug metabolism
3. Define the major phase I and phase II metabolic reactions
4. Describe the modulation of liver microsomal enzymes by inducers and inhibitors
5. Mention two drugs that are known as enzyme inducers and inhibitors
6. Know the impact of first pass metabolism on drug bioavailability

- Additional Notes
- Important
- Explanation –Extra-


Drug Metabolism-biotransformation-
Importance
Inactivation
Activation of prodrug
Detoxification
factors affecting metabolism
Degree of Protein Binding
Age
Diseases
Genetic Polymorphism
Nutrition
Concurrent use of drugs
Cellular Sites
mitochondria
N-acetyl transferase
MAO
Lysosomes
Microsomes
Cytochrome P-450
Microsomal enzyme system
Cytoplasm
Alcohol dehydrogenase
Organ Sites
Skin
Lung
Intestinal
Mucosa & Lumen
Gut lumen -bacterial flora-
Glucouoronidase
Gut Mucosa
MAO
the major site
Kidney
Liver
Plasma
Enzymes
Esterases
substrate
Esters -local anesthetics-
Amidases
substrate
amides -local anesthetics-
COMT
substrate
Catecholamines
hepatic metabolic reactions
Phase I reactions
non-microsomal
microsomal
Oxidation
microsomal
Reduction
non-microsomal
Hydrolysis
non-microsomal
Phase II reactions
Conjugation reactions
non-microsomal
microsomal
ONLY
glucouronidation

Drug Metabolism

Drugs, chemicals, and toxins are all foreign to our bodies. Our body attempts to get rid of foreign chemicals, regardless of whether they are therapeutic or harmful. Most drugs must be biotransformed, or metabolized, so they can be excreted. In **pharmacology**, the word "metabolism" often refers to the process of making a drug more polar and water soluble.



Note:
Pro-drug is the inactive form of a drug that needs to be activated by Metabolism

Sites of Drug Metabolism

Organ Sites		
1- Liver –the major site-		**2- Kidney**
3- Intestine	Gut Mucosa	Monoamine Oxidase “MAO” & Sulphatase
	Gut Lumen	Glucourindase “Bacterial Flora”
4- Plasma	Catechol O-Methyl Transferase COMT	Catechol Amines
	Estrases	Esters “Local Anesthetic”
	Amidases	Amides “Local Anesthetic”
5- Skin		**6- Lungs**

Cellular Sites	
1- Cytoplasm	Alcohol Dehydrogenase
2- Mitochondria	Monoamine Oxidase “MAO”
	N-Acetyl Tranferase
3- Microsomes	Cytochrome P450 =Microsomal Enzyme System
4- Lysosomes	Main Organelles for digestion in the cell

Monoamine Oxidase "MAO"

Substrate: Monoamine
Enzyme: Oxidase
Works in the Sympathatic Nervous system, and acts on neurotransmitters such as Adrenaline & Noradrenaline

Catechol O-Methyl Transferase "COMT"

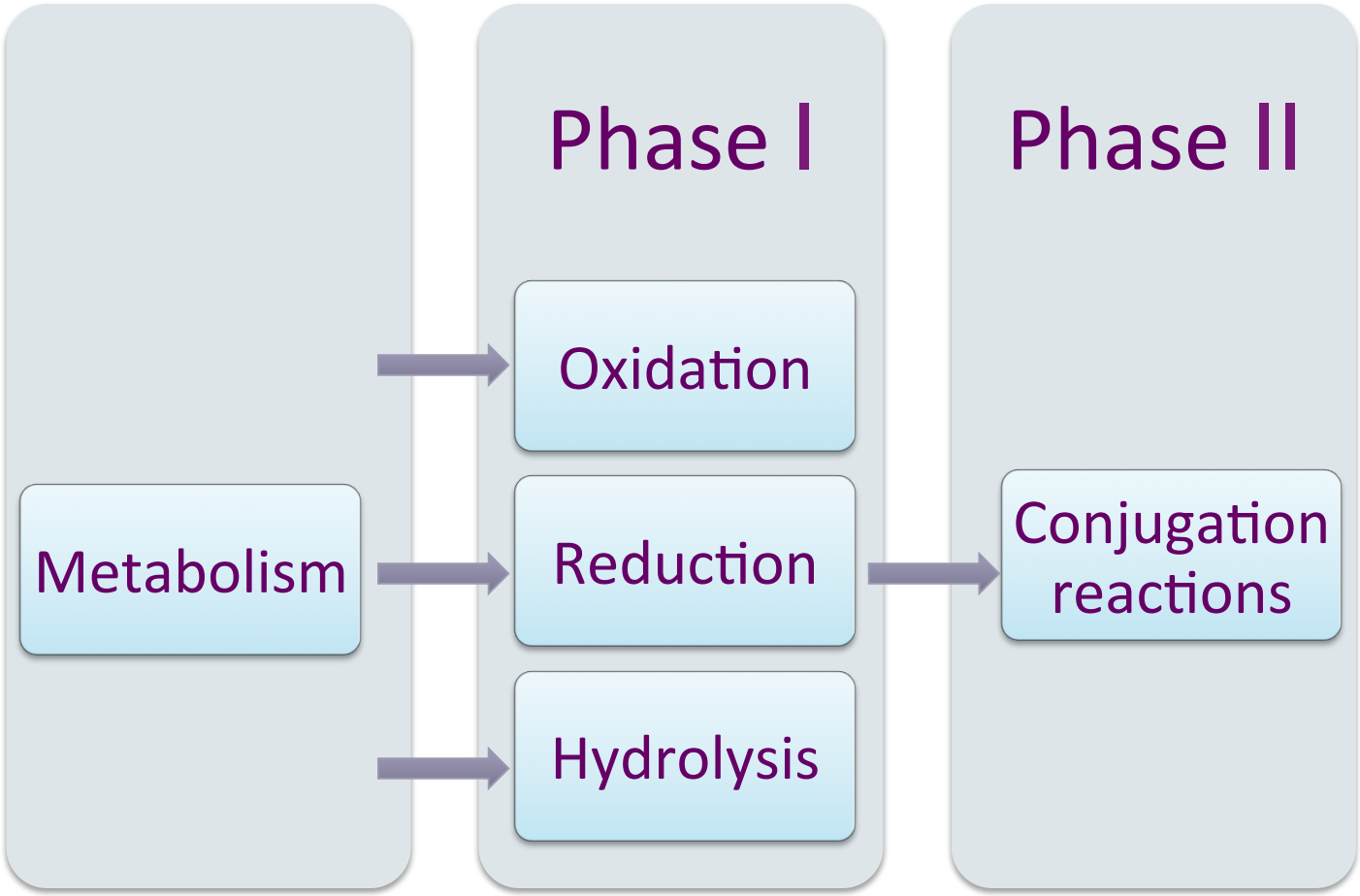
It transfers Methyl group to a catechol structure in the drug this enzyme also works on Catecholamines in the Sympathatic NS such as Adrenaline & Noradrenaline

Epinephrine = adrenaline can be metabolized by COMT or MAO

Cytochrome P450

CYP 3A4/5 carry out biotransformation of thelargest number (30–50%) of drugs. Expressed in liver and intestine (responsible for first pass metabolism at this site).

Types of Hepatic Metabolic Reactions



After Phase I the drug could be either:

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

2. Inactive = water soluble, now it can be excreted.

Phase I

Oxidation

- It is the addition of oxygen or removal of hydrogen.
- It is the most important drug metabolizing reaction.
- It May be microsomal or non-microsomal.

- Microsomal Oxidation

e.g. Cytochrome P450 enzymes, NADPH and oxygen

-Non-Microsomal Oxidation

occurs in cytosol or mitochondria

~Dehydrogenases

Alcohol **dehydrogenase** & aldehyde dehydrogenase

~Oxidases

Monoamine oxidase (MAO): metabolism of catecholamines as *adrenaline* and *serotonin*

e.g. moclobemide is MAO inhibitor and used as antidepressant since it increases serotonin in brain.

Xanthine oxidase: metabolism of *xanthine*

Hypoxanthine ⟶ xanthine ⟶ uric acid → uric acid accumulation ⟶ GOUT

Allopurinol is an inhibitor of xanthine oxidase and used in **gout**

Reduction

- Removal of oxygen or addition of hydrogen.
- may be microsomal or non-microsomal.

Examples: ***levodopa*** + DOPA-decarboxylase >>> dopamine

Hydrolysis

All are ***non microsomal*** occurs by addition of water molecules in presence of enzymes as (esterase or amidases)

Esterase: hydrolyze drugs that are esters, such as **acetylcholine** (neurotransmitter).

Acetylcholine $\xrightarrow[\text{esterase}]{}$ acetate + choline.

Amidases: hydrolyze drugs that are amides, such as **lidocaine** (used as local anesthetic)

Phase I reactions can result in

1- Activation of pro-drug

e.g. **levodopa** to **dopamine**

2- Inactivation of drug (termination of action)

3- Conversion of active drug to active metabolite

4- Conversion of nontoxic drug to toxic metabolite

Paracetamol → hepatotoxic metabolite (hepatic necrosis)

5- Product might still active and undergo phase II reaction

Phase II

Conjugation reactions

Conjugation of metabolite coming from (phase I) with endogenous substance as methyl group, acetyl group, sulphate, amino acid or glucouronic acid to produce conjugate that is water soluble and easily excreted in urine or bile.

- All are non microsomal **except** glucouronidation , Glucouronide conjugation is a **microsomal** process (the most common).
- Deficiency of glucouronyl transferase enzyme in neonates may result into toxicity with chloramphenicol (**Gray baby syndrome**).

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

#Characteristics of Phase II

Products

- Usually pharmacologically inactive.
- Polar
- more water soluble.
- Easily excreted in urine

Factors affecting metabolism

- ***Age:*** ↓ rate of metabolism in neonates & elderly
- ***Diseases:***↓ rate of metabolism in liver diseases
- ***Degree of Protein Binding:*** ↓ rate of metabolism
- Concurrent use of drugs: Induction & inhibition
- ***Nutrition***: malnutrition ↓ rate of metabolism
- ***Genetic polymorphism:***

  Existence of more than one phenotype due to genetic variation in rate of metabolism

  E.g. Isoniazid (anti- tuberculosis drug)

  Slow acetylator phenotype → peripheral neuropathy

  Rapid acetylator phenotype → hepatitis.

Enzyme Induction & Inhibition

Liver microsomal enzymes inducers

drugs that increase activities of liver microsomal enzymes & increase the metabolism of itself and other drugs.

Enzyme induction may result in:

- ↑ the metabolism and excretion of the inducer drug itself and co-administered drugs.
- ↓ the action of the inducer drug itself & co-administered drugs.
- Tolerance may occur: decrease in the pharmacological action of the drug by repeated administration.
- Drug interactions may occur: decrease in action of one drug by administration of another drug

  e.g. oral contraceptives & phenytoin (inducer).
- Failure of oral contraceptive may lead to pregnancy if combined with phenytoin.

Liver microsomal enzymes inhibitors

drugs that decrease activities of liver microsomal enzymes & decrease the metabolism of itself and other drugs.

Enzyme inhibition may :

- ↓ Delay the metabolism and excretion of the inhibitor drug and co-administered drugs.
- ↑ Prolong the action of the inhibitor drug & co-administered drugs.

  e.g. warfarin & erythromycin (inhibitor).
- Inhibition of warfarin metabolism may lead to increase

  its anticoagulant effect (bleeding).

Examples

Enzyme inducers	Enzyme inhibitors
Alcohol	Grape fruits
Cigarette smoking	Cimetidine
Phenobarbitone hypnotic	Erythromycin (antibiotic)
Phenytoin (antiepileptic)	Ketoconazole (antifungal)
Rifampicin (Anti TB)	

Check your understanding here ! –MCQ's-

http://www.onlineexambuilder.com/pharmacokinetics-iii/exam-10877

You still don't understand very well ? Checkout this video!

http://www.youtube.com/watch?v=ztsBn8gsfHw

✸ summary

1-Recognize the importance of biotransformation

changing drugs from lipid-soluble form to water-soluble form.

2-Know the different sites for drug metabolism

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

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

Phase I

-Activation of pro-drug

- Inactivation of drug (termination of action)

-Conversion of active drug to active metabolite

-Conversion of nontoxic drug to toxic metabolite

-Product might undergo phase II

Phase II

All are non microsomal except glucouronidation

Glucouronide conjugation is a microsomal process (the most common).

Deficieny of glucouronyl transferase enzyme in neonates may result into toxicity with chloramphenicol (Gray baby syndrome).

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

->Liver microsomal enzymes inducers: increase activities of liver microsomal enzymes and increase the metabolism.

->Liver microsomal enzymes inhibitors: decrease activities of liver microsomal enzymes and decrease the metabolism.

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

Inducers: Phenytoin (antiepileptic)

Rifampicin (Anti TB)

Inhibitors: Erythromycin (antibiotic)

Ketoconazole (antifungal)

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

First pass metabolism reduce the bioavailability. (due to the fraction of lost drug during first pass effect)