Metabolism of xenobiotics

XENOBIOTICS

= compounds foreign to the body

1. ENTRANCE TO THE BODY

→digestive tract → blood → LIVER

→lungs → blood

→skin → blood

Xenobiotics are metabolized at the place of „their entrance or exit"

2. BLOOD TRANSPORT

! chemical nature of the xenobiotic !

hydrophilic (polar)

→ water soluble

→ difficult transport through membranes

→ rapidly eliminated with the urine

2. BLOOD TRANSPORT

! chemical nature of the xenobiotic !

lipophilic (nonpolar, hydrophobic)

→ poorly soluble in water

→ **need a blood transporter** (albumin)

→ freely diffuse through membranes

→ can be stored in membranes

→ slowly eliminated from the body

Xenobiotics bound to transport proteins

→ the binding is reversible
→ ionic and hydrophobic interactions
→ competition of compounds
→ only free fraction of the xenobiotic is biologically active
→ the binding to proteins decreases elimination
of the xenobiotic from the body

Metabolism of xenobiotics can lead to

a) lowering their toxicity
b) increasing their toxicity
c) their bioactivation
d) increasing their water solubility

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3. FATE OF XENOBIOTICS

1) utilizable substances can enter the body´s intermediary metabolism (e.g. ethanol → energy)

2) unutilizable substances are transformed to more water soluble products and excreted with the

→ urine (small molecules: to Mr = 300)

→ bile → stool (larger molecules)

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3. FATE OF XENOBIOTICS

BIOTRANSFORMATION

2 phases of the conversion *(proceed both or separately)*

Phase I (biotransformation)

⇒ free polar functional groups in the molecule

Phase II. (conjugation)

⇒ polar endogenic substance bound to the xenobiotic

↓

inactivation

↑ water solubility

excretion from the body

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Phase I- biotransformation

- localization

- the liver - membranes of ER, cytoplasm
- other tissues - lungs, intestine, skin, kidneys

- enzymes

- hydrolases (esterases, peptidases, ...)
- monooxygenases (= hydroxylases, cytochrome P450 = Mixed Function Oxidases = MFO)

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- properties of the enzymes
  - metabolism of endogenic substances
  - broad substrate specificity
  -inducibility (*e.g. cyt P-450*)

- reactions
  - hydrolysis
  - oxidation (e.g. hydroxylation, epoxidation)
  - oxidative cleavage: e.g. dealkylation, deamination
  - reduction
  - methylation

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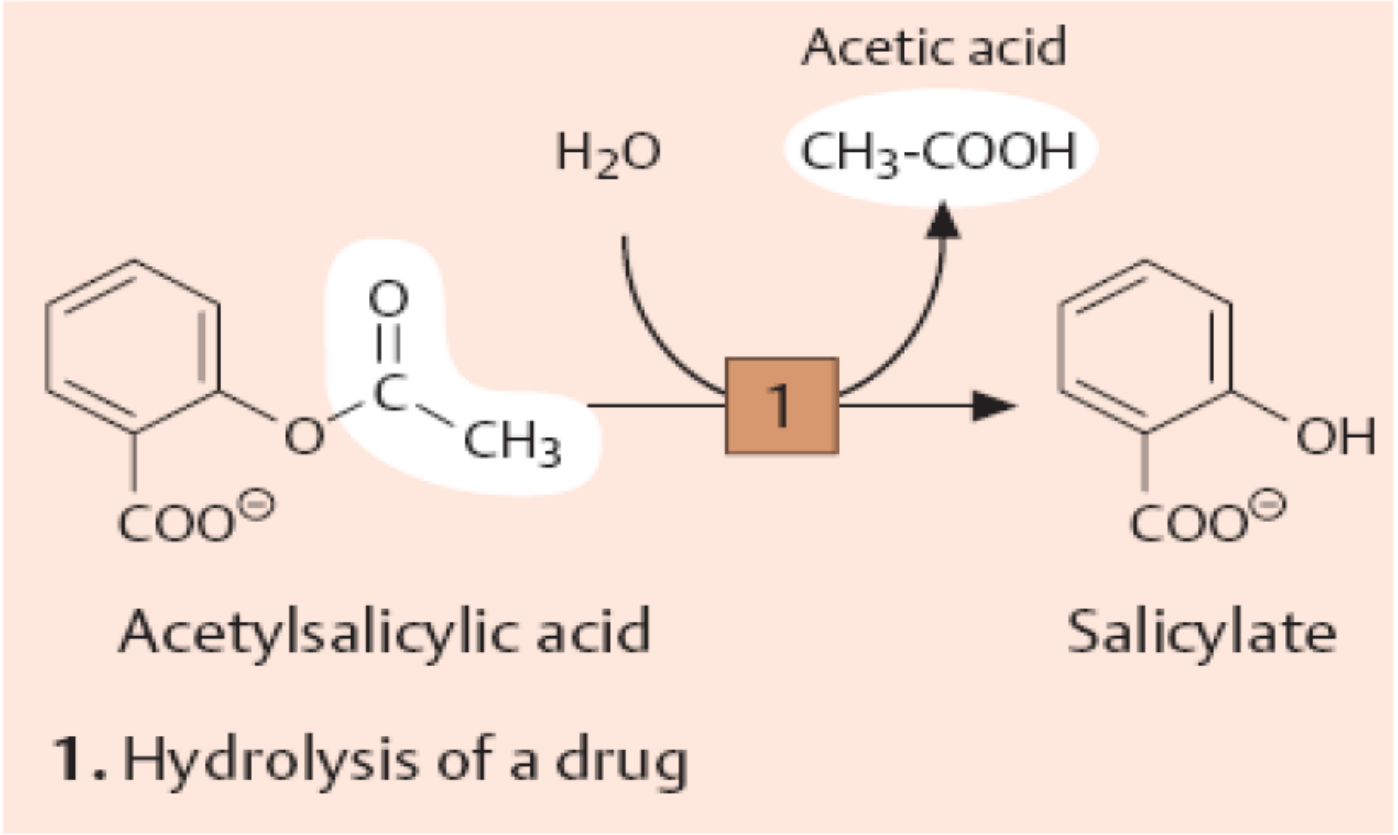
- **results**
  - increased polarity of xenobiotics (water solubility)
  - inactivation of xenobiotics (detoxification)

or

  - **bioactivation of some xenobiotics** (drugs x procarcinogens)

danger of cell and body damage

Example of a reaction catalyzed by a hydrolase



The figure is from: Color Atlas of Biochemistry / J. Koolman, K.H.Röhm. Thieme 1996. ISBN 0-86577-584-2

Cytochrome P450
(monooxygenase, hydroxylase, MFO)

- belongs among **hemoproteins**
- many types of cyt P450, polymorphism
- coenzyme: **NADPH**
- NADPH-cytochrome P450-reductase
- membranes of ER or mitochondria
- common reaction:

$$RH + O_2 + NADPH+H^+ \rightarrow R\text{-}OH + H_2O + NADP^+$$

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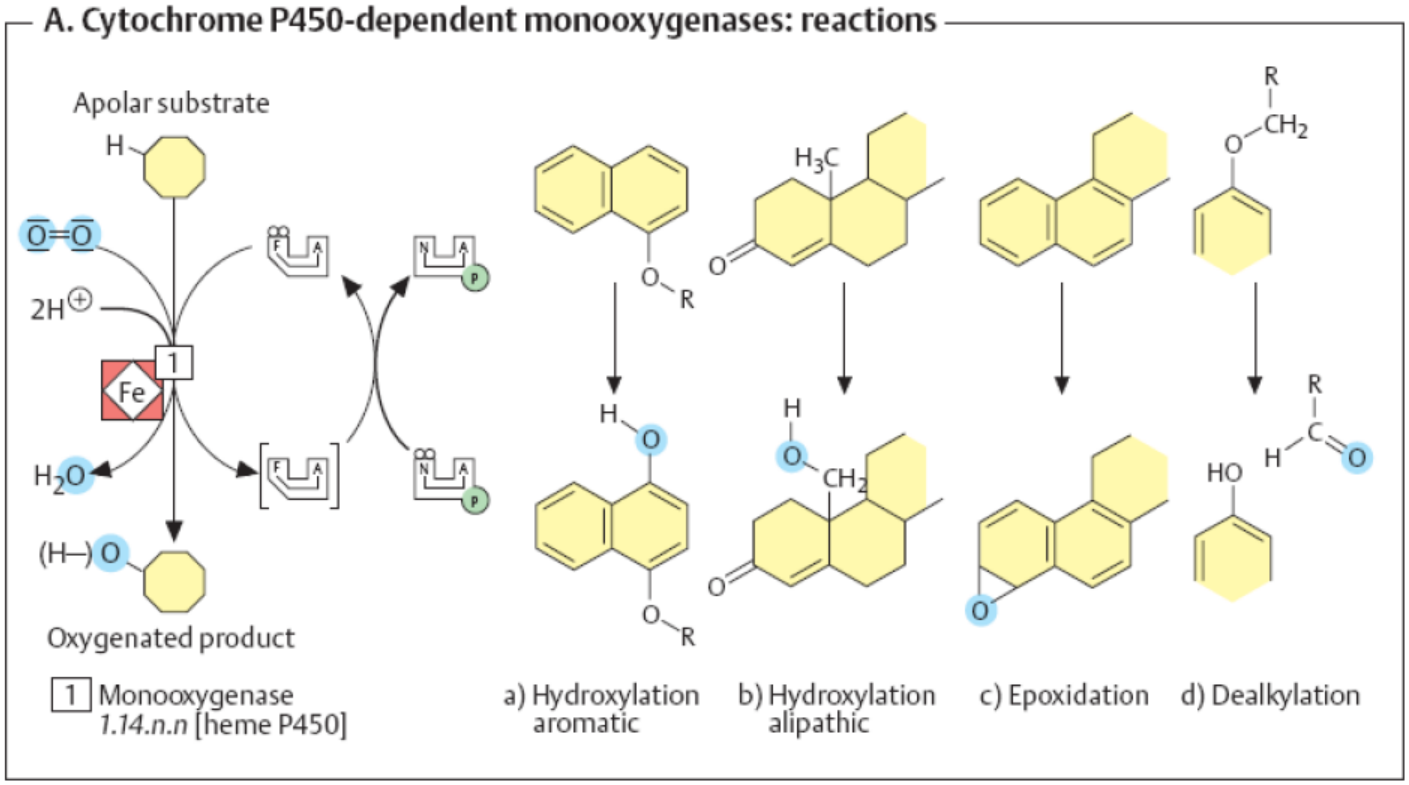
Example of a reactions catalyzed by cyt P450



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Phase II - conjugation

- **localization**
  - liver (intestine mucosa, skin): ER, cytoplasm

- **properties**
  - need of an **endogenic substance**
  - synthetic reactions
  - energy consumption

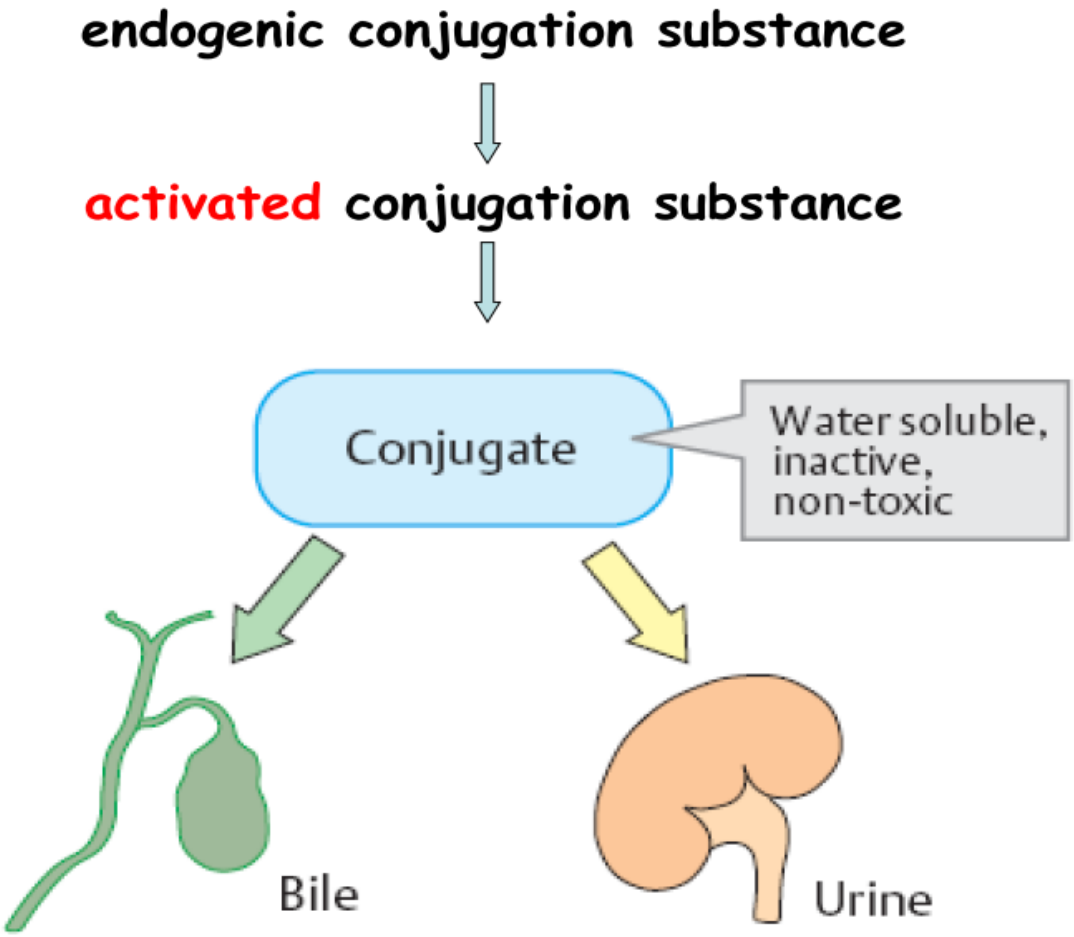
- **results**
  - highly polar conjugates (↑ water solubility)
  - decreased toxicity

Conjugation endogenic substances *(substrate):*

- **glucuronic acid** *(UDP-glucuronate)*
- **sulfate** *(PAPS = „active sulfate")*
- **acetate** *(acetyl-CoA)*
- **cysteine** *(glutathione = γ-glu-**cys**-gly)*
- **-CH_3** *(SAM = S-adenosyl **methionine**)*
- **glycine, glutamine**

Enzymes: **transferases**

TEST



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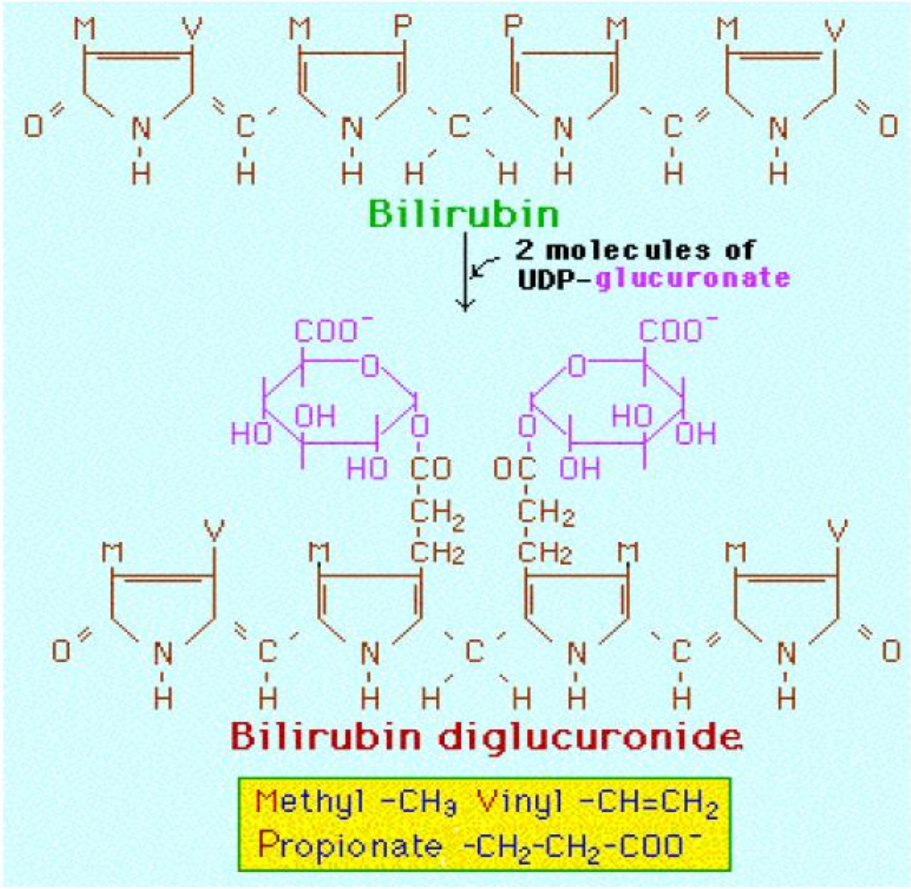
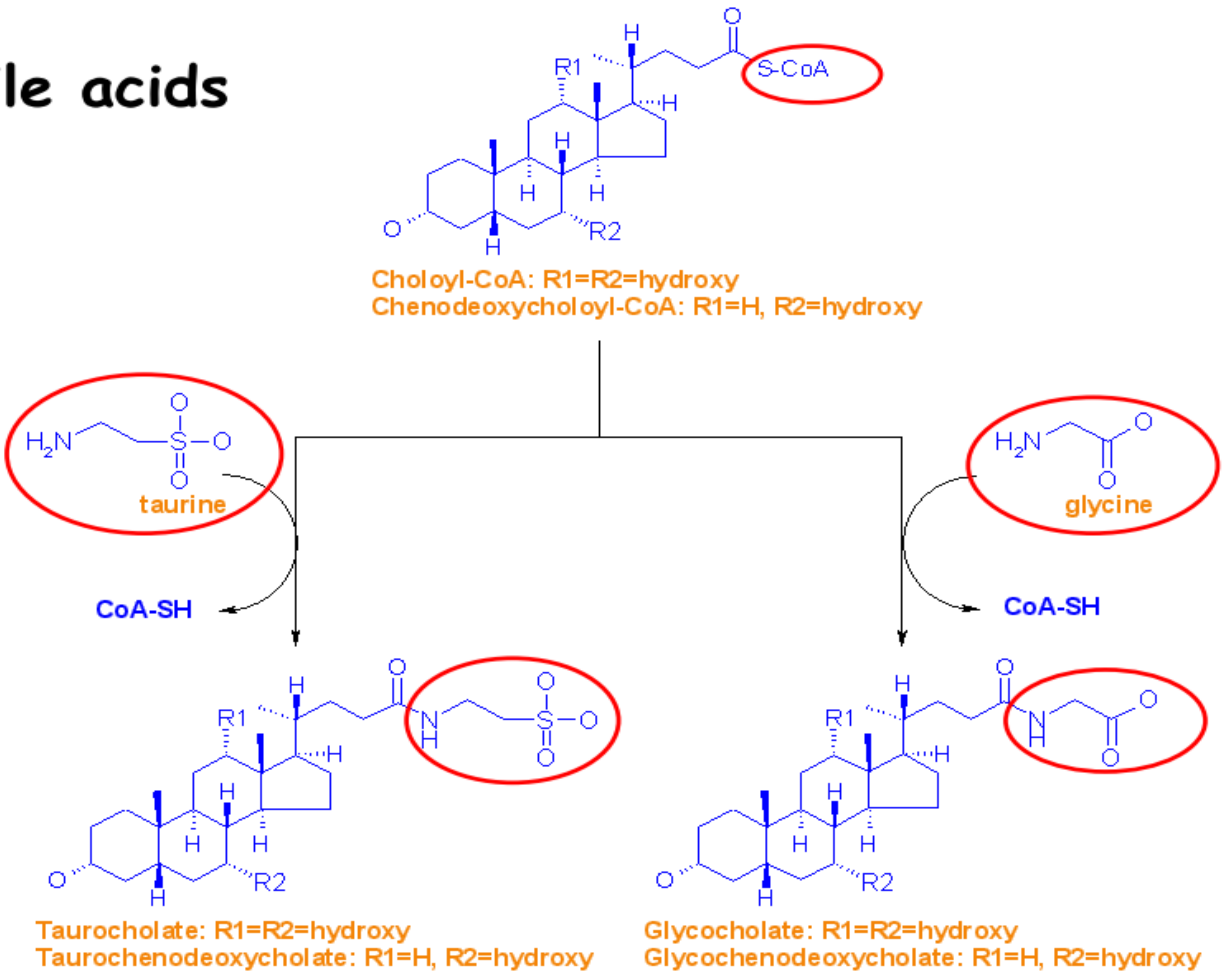
Examples of conjugation of endogenic molecules



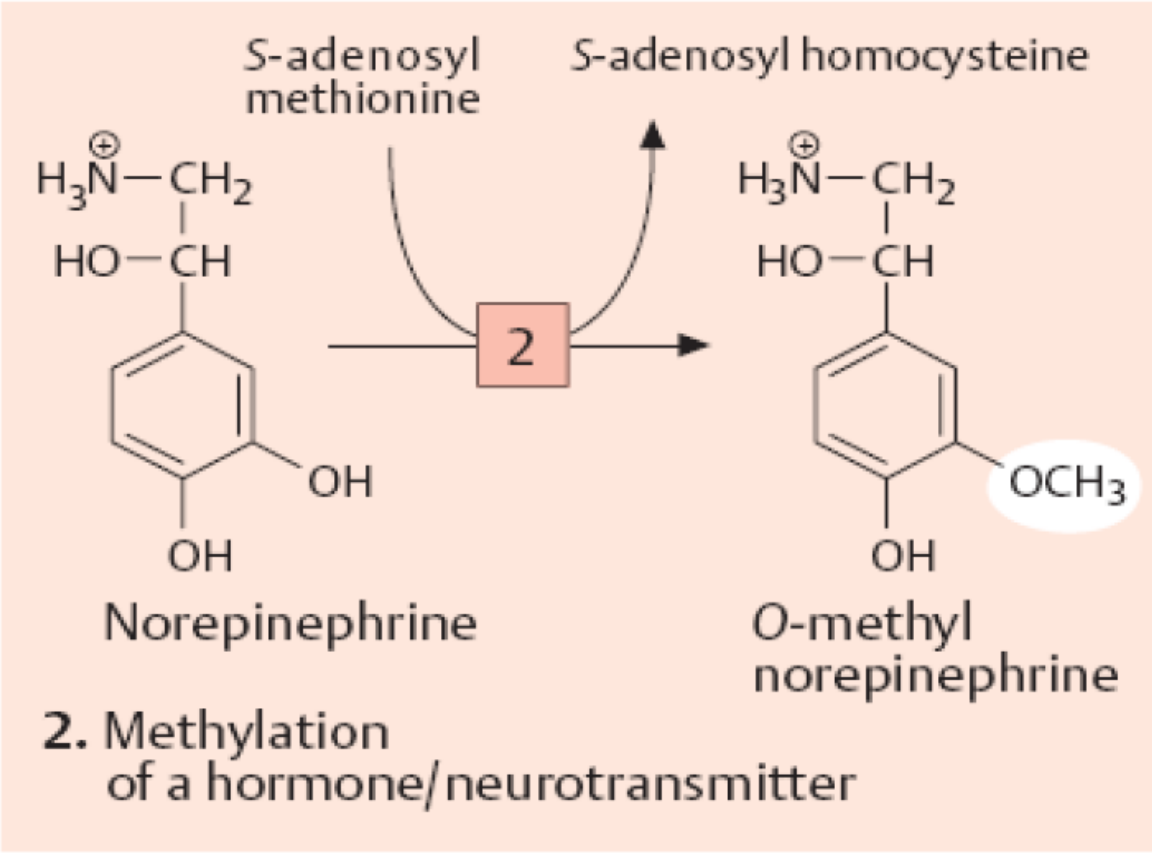
Bilirubin

The figure is found at
http://www.umanitoba.ca/faculties/medicine/units/biochem/coursenotes/blanchaer_tutorials/Frank_II/congBili.gif (May 2007)

Bile acids



The figure is found at http://www.med.unibs.it/~marchesi/bile_salts.gif (May 2007)



Neurotransmitter

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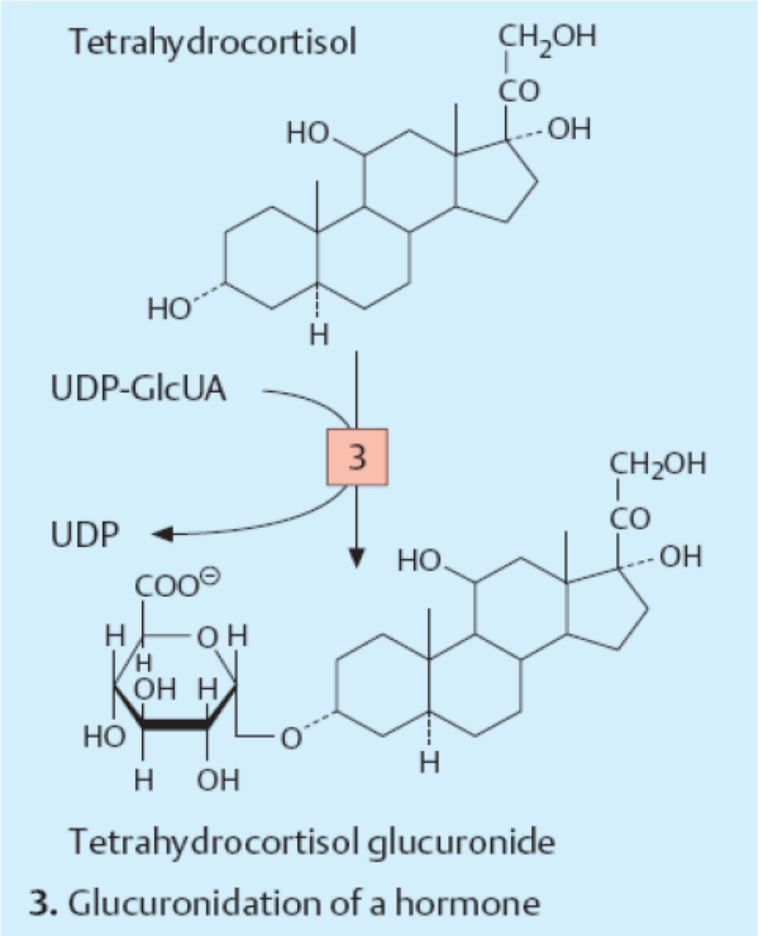
Hormone



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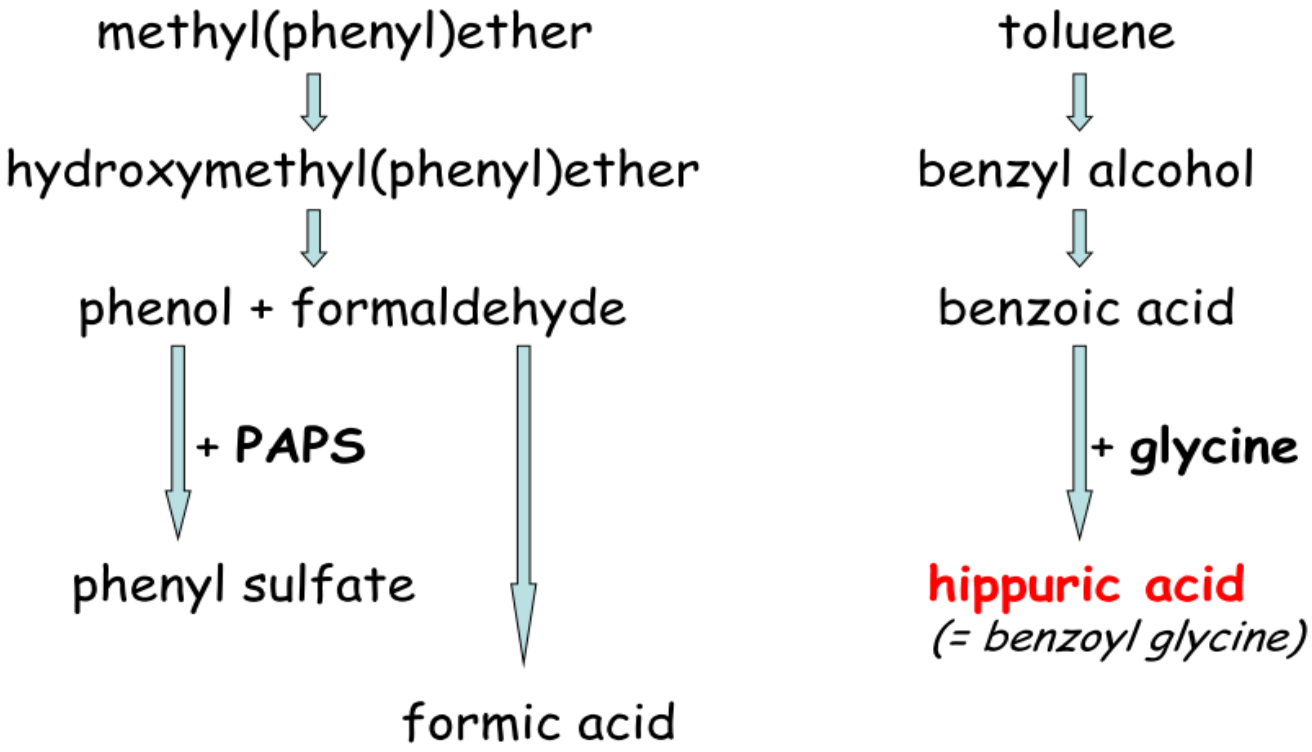
Examples from metabolism of xenobiotics



Examples from metabolism of xenobiotics

electrophilic xenobiotic

(e.g. epoxide)

+ GSH
+ acetyl CoA

mercapturic acid

(= conjugate of the xenobiotic)

generally: S-substituted N-acetyl cysteine

Summary BIOTRANSFORMATION

1. a foreign substance including a polar functional group
   - original molecule
   - or **product of the Phase I.**

(biotransformation)

2. activation of a conjugation endogenic substance

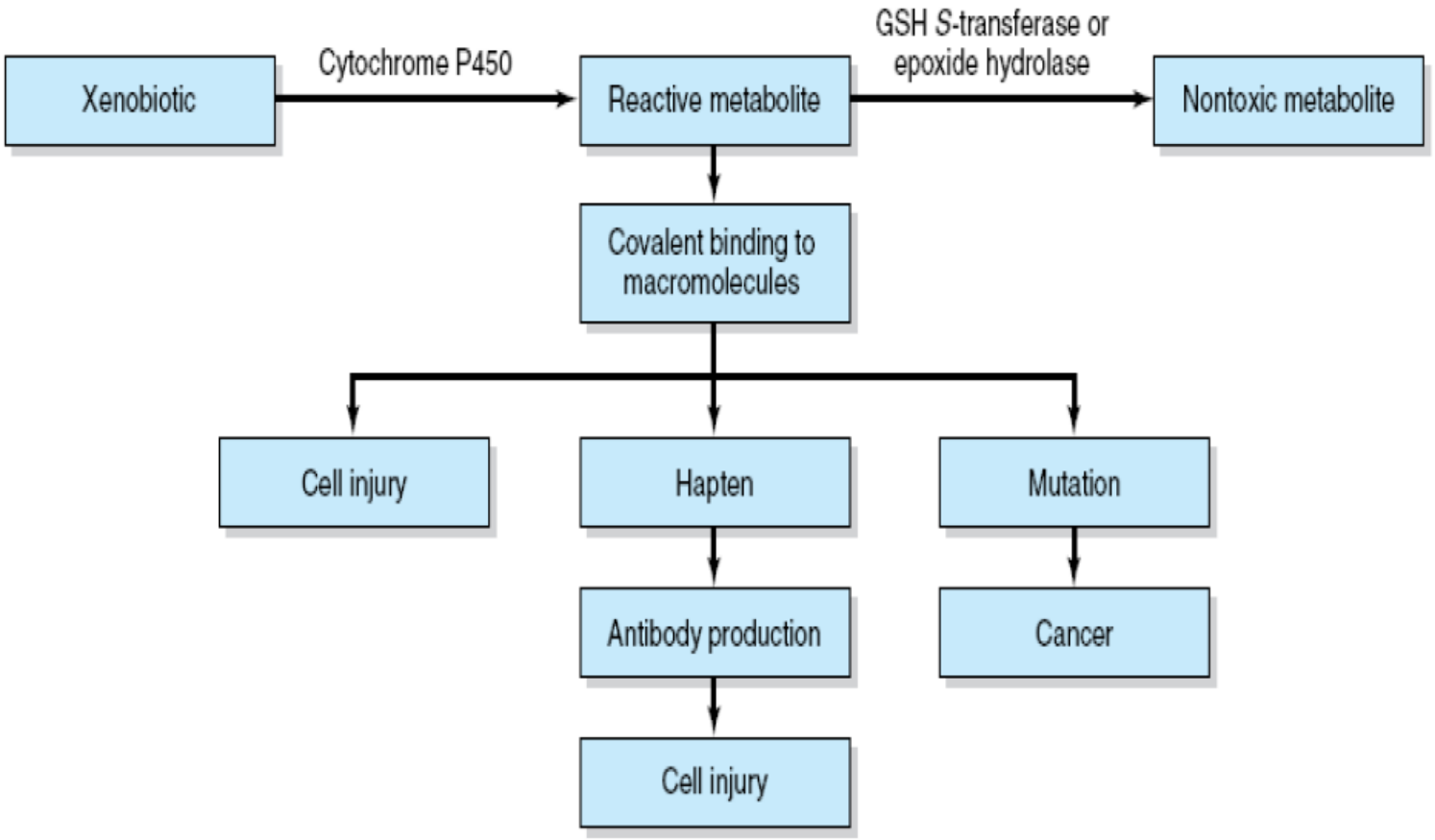
3. formation of a conjugate

4. excretion from the body

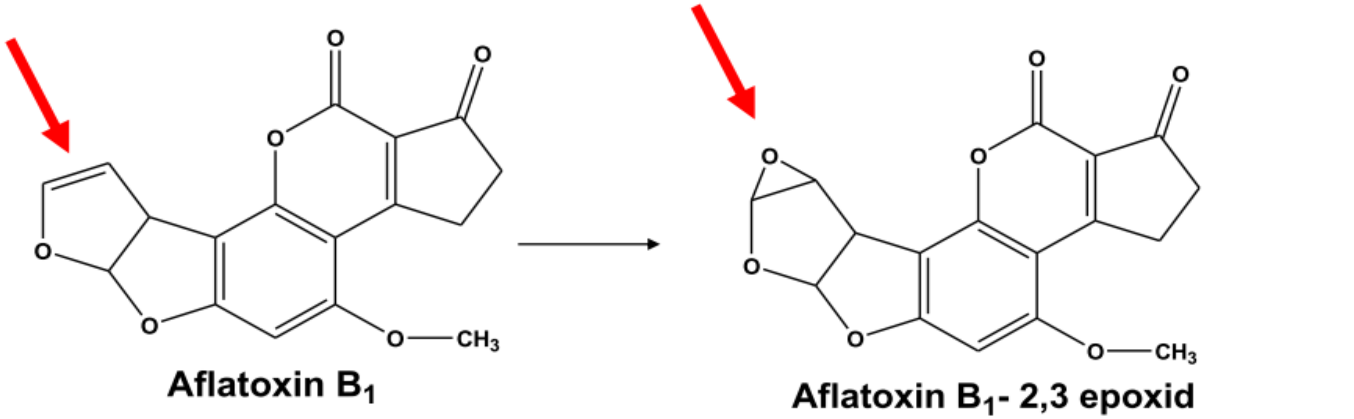
The metabolism proceed mostly in the LIVER

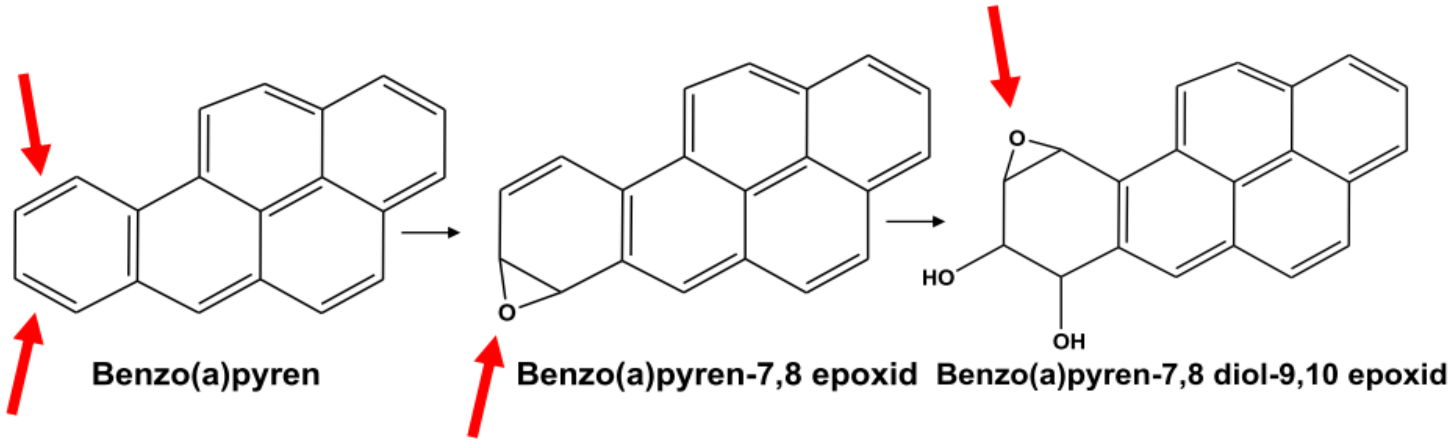
Biotransformation does not mean detoxification in all cases, it can also increase the biological activity!

(see indirect carcinogens)

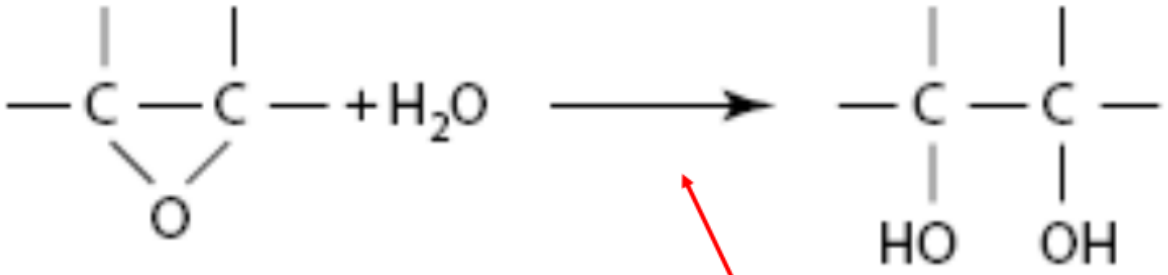


The figure was adopted from Harper´s Illustrated Biochemistry / R.K.Murray ed., 26. vyd., McGraw-Hill Comp, 2003. ISBN 0-07-138901-6

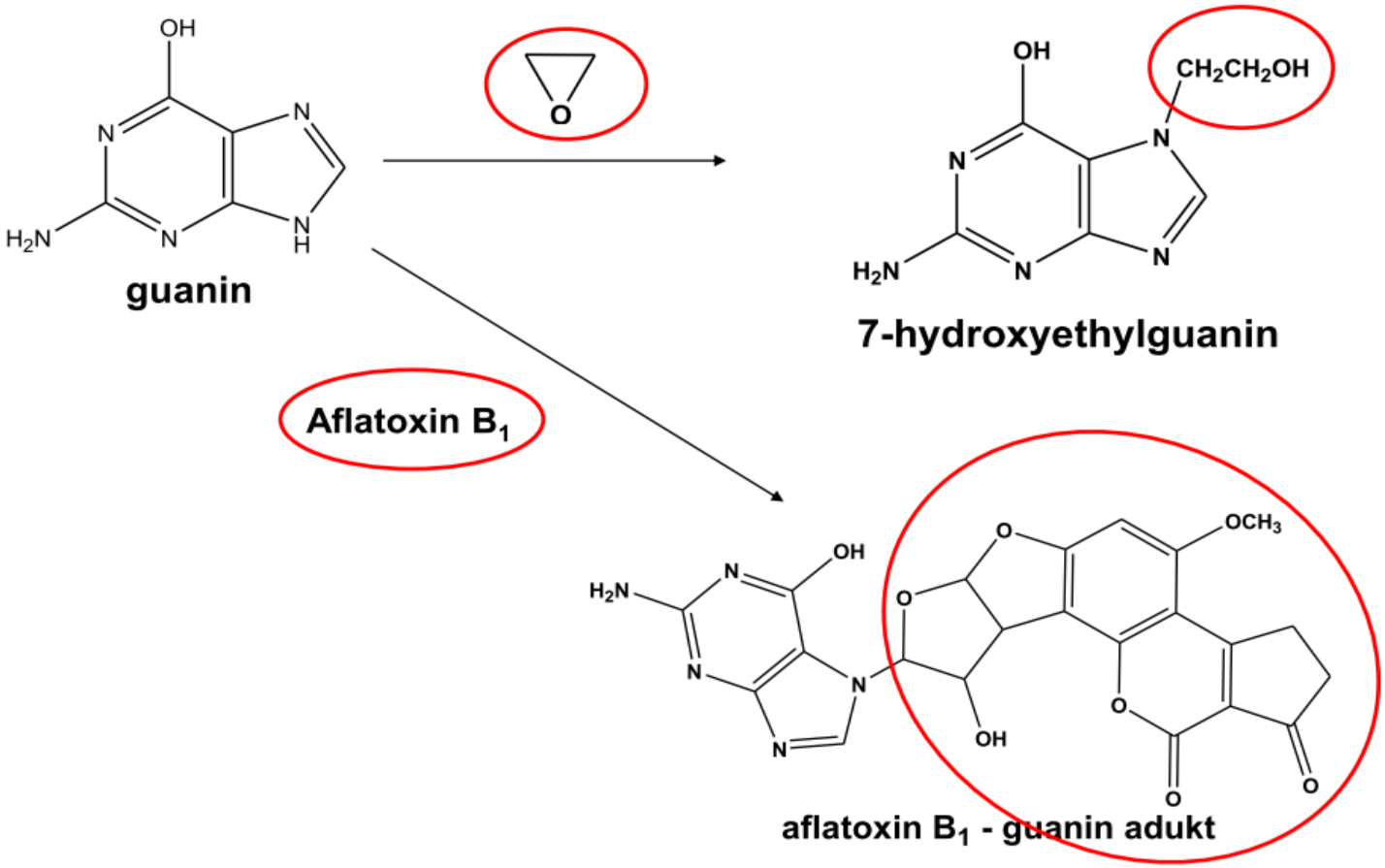




The figures are adopted from the lecture General toxicology / P. Tůma



an epoxide can be metabolized by
epoxide hydrolase (= deactivation)
or
it can react with bases of nucleic acids
(= mutagenic or carcinogenic effect)



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Cytochrome P-450

a) is a hemoprotein
b) is disolved in a cytoplasm
c) needs NADPH
d) participates in steroid metabolism

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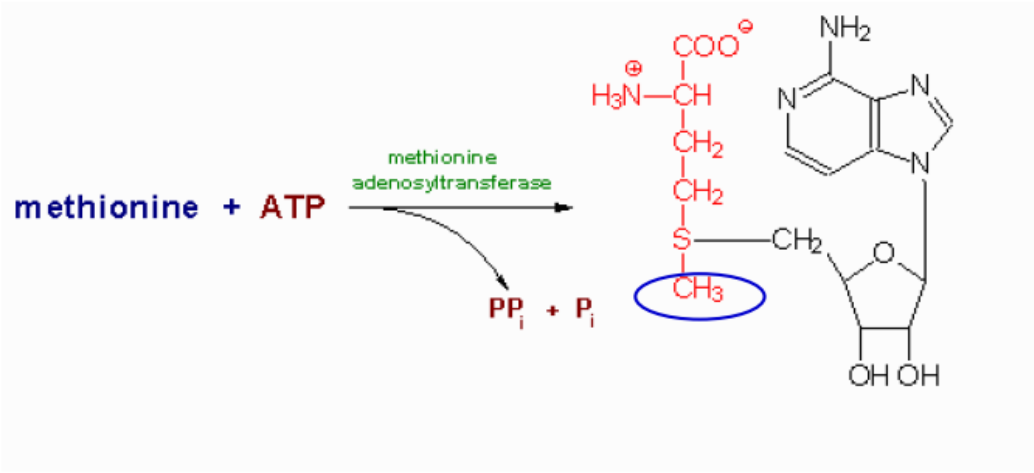
Choose correct statement(s) about biotransformations:

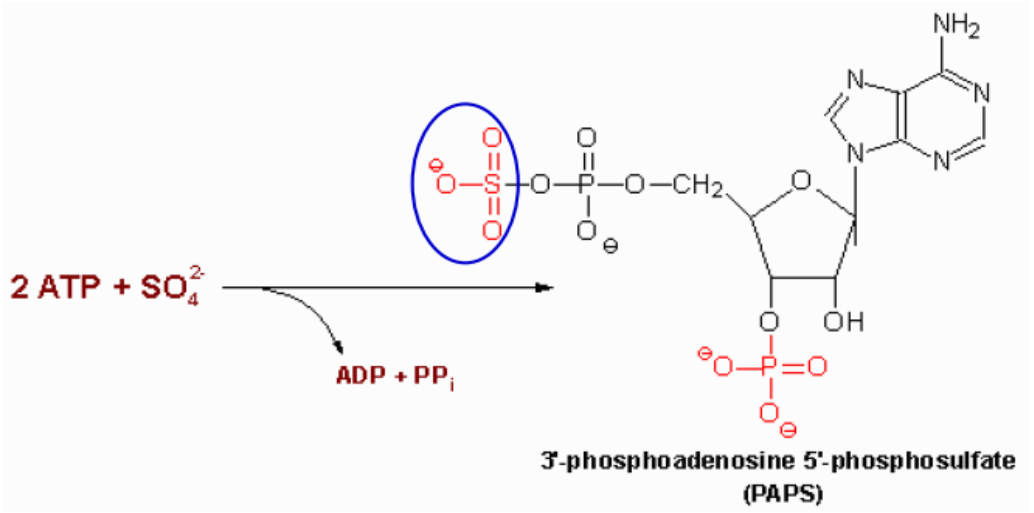
a) a hydrocarbon can be oxidized to an alcohol
b) an ester can be hydrolyzed to 2 alcohols
c) an aldehyde can be reduced to a carboxylic acid
d) a carbonyl compound can be reduced to an alcohol

e) an unsaturated or an aromatic hydrocarbon can be transformed to an epoxide
f) an amide bond can be hydrolyzed to an acid and an amine
g) benzoic acid can be transformed to hippuric acid
h) UDP-glucuronate can be formed by reduction of UDP-glc

Choose correct statement(s) about conjugation reactions:

a) UDP-glucuronyl transferase synthetizes glucuronides
b) PAPS is an active form of sulfuric acid
c) SAM is a derivative of methionine
d) glutathione contains 3 peptide bonds

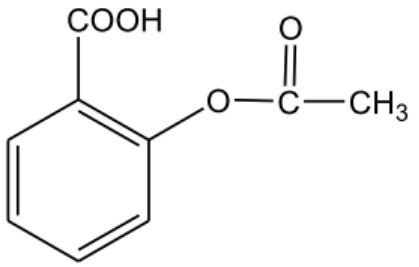




The figures are found at http://web.indstate.edu/thcme/mwking/amino-acid-metabolism.html (May 2007)

Examples from metabolism of xenobiotics

a) nonpolar acetylsalicylic acid



- an active substance of Aspirin
- irreversible inhibition of synthesis of PG, PGI and TX (cycloxygenase)
- bound to plasma proteins
- hydrolyzis of its ester bond (intesine, blood)
- conjugation in the liver with glycine → salicyluric acid
- excretion of the conjugate with urine

Examples from metabolism of xenobiotics

b) polar alcohols

CH_3CH_2OH

ETHANOL

- absorbed in the stomach
- 10 % ecreted with the urine, breath, perspiration
- 90 % metabolized (mainly in the liver)
- oxidation: ethanol → acetaldehyde → acetic acid
- enzymes:
  - alcohol dehydrogenase (cytoplasm, NAD +)
  - aldehyde dehydrogenase (mitochondria, NAD +)
  - or cyt P450 (MEOS) → oxidative stress

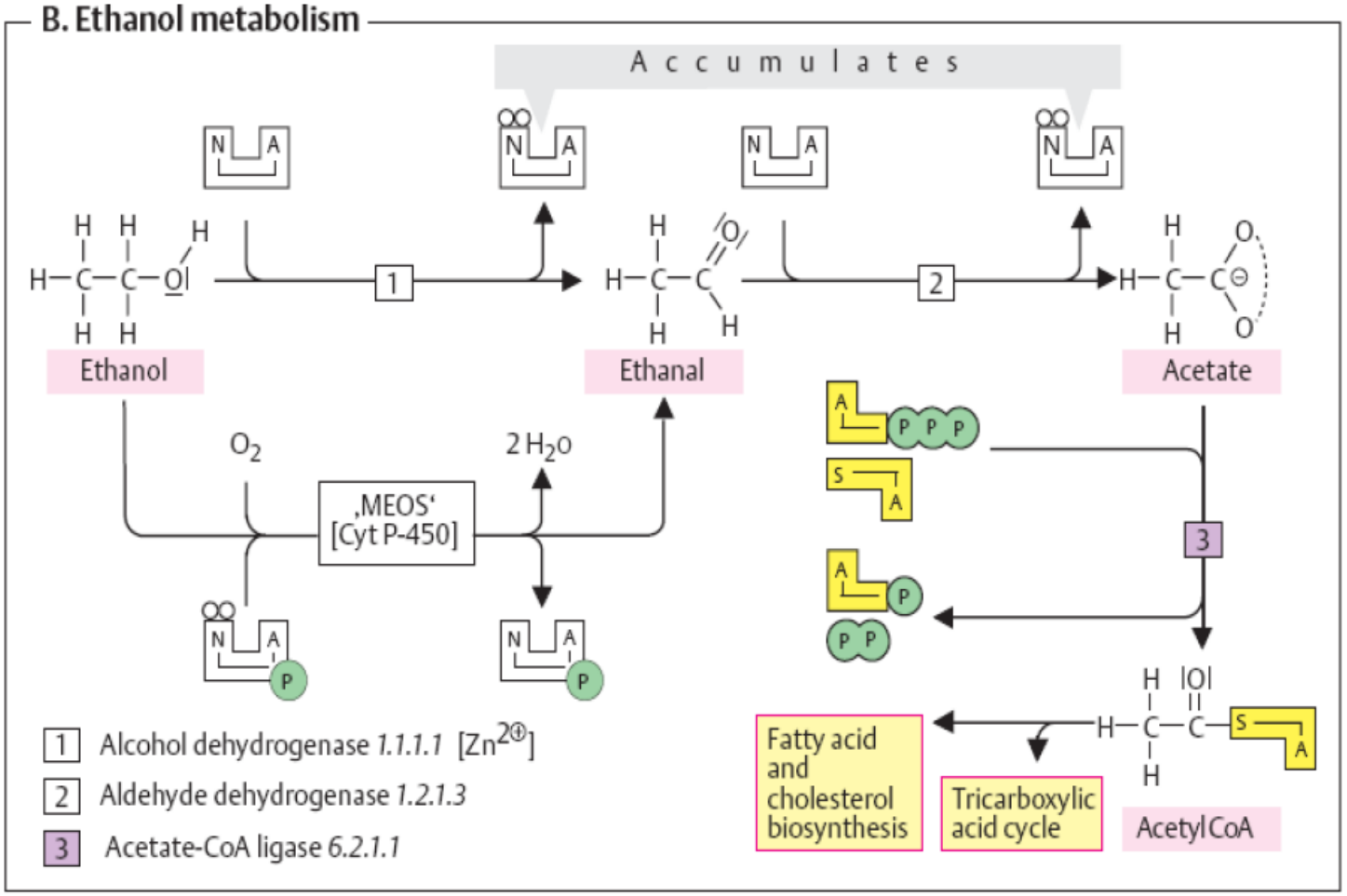
- excess of NADH
  - inhibition of beta-oxidation and citrate cycle
  - inhibition of gluconeogenesis

- acetaldehyde can damage proteins

- acetic acid metabolized mainly in the heart:
  acetyl-CoA → citrate cycle, RCH → CO 2 , H 2 O

- acetate, lactate → metabolic acidosis

- accumulation of TAG in the liver



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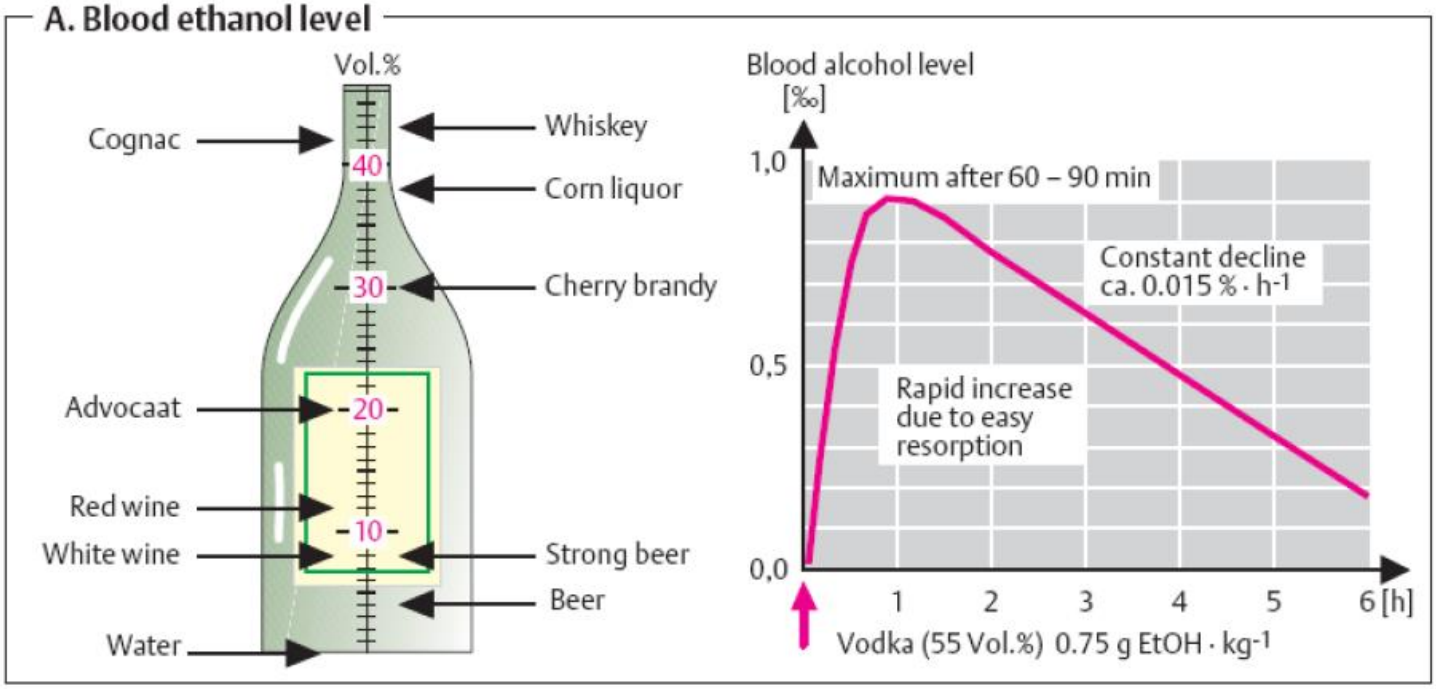

0,5 L of beer (4%) ~ 20 mL of ethanol = 16 g

70 kg man: 0,7 x 70 = 49 kg (L) water

i.e. 16 g etOH / 49 L = 0,33 g / L = 0,33 ‰

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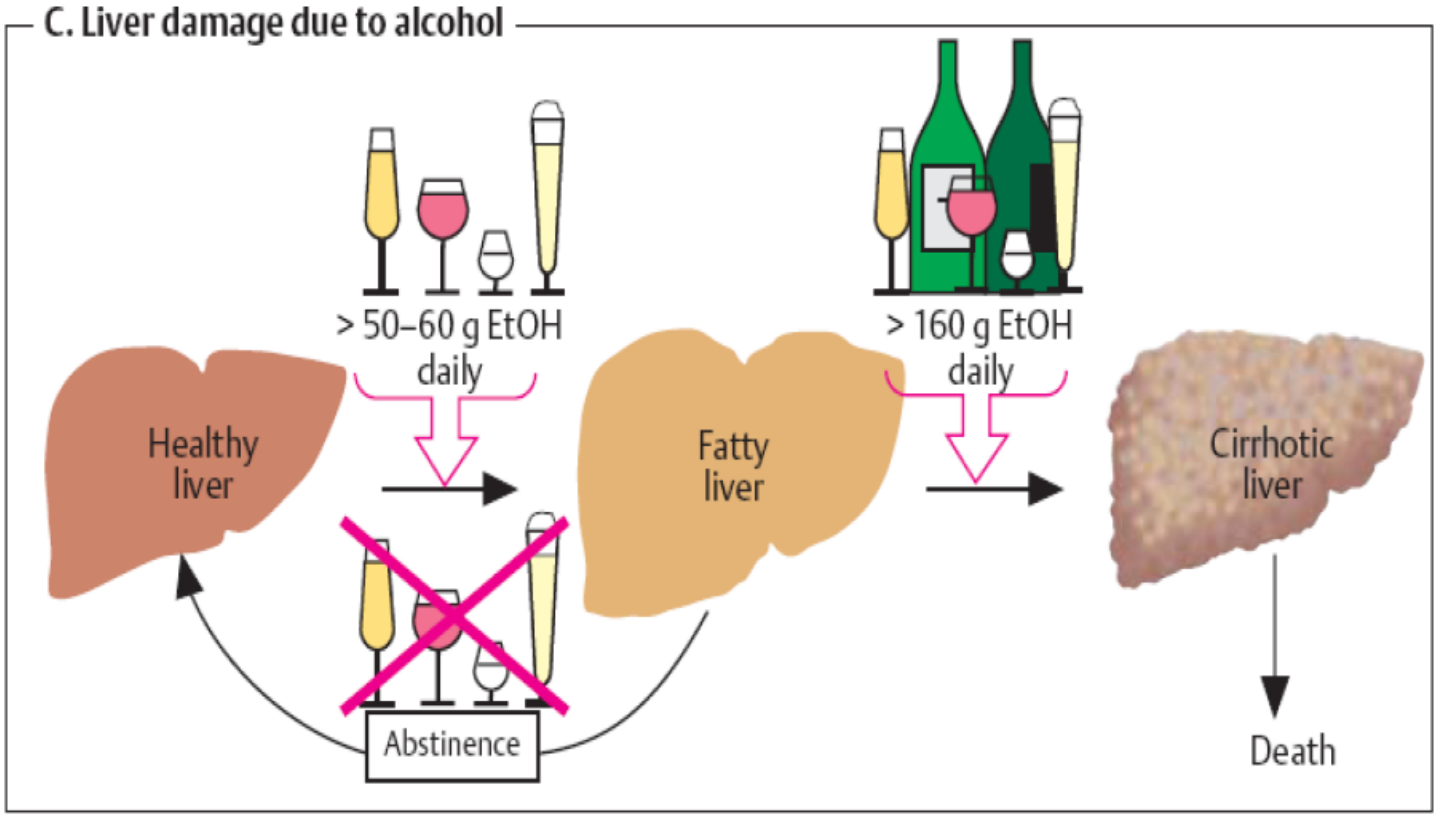

29,4 kJ/g of ethanol

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Examples from metabolism of xenobiotics

b) polar alcohols

CH_3OH

METHANOL

- lower narcotic effect than ethanol
- slower excretion from the body → longer drunkenness
- metabolized by the same enzymes as ethanol
- causes harder sickness (formaldehyde)
- serious intoxication: 5 – 10 ml (lethal dose ~ 30 ml)
- no symptoms immediately after drunkenness (6 – 30 h.)
- headache, pain in back, loss of sight
- metabolic acidosis
- therapy: ethanolemia ~ 1 ‰ (1 - 2 days), liquids

Ethanol

a) can be reduced to CH 3 CHO
b) can be metabolized by cyt P450
c) is a secondary alcohol
d) consumes NADH if metabolized

Increased ratio of NADH / NAD +

a) activates conversion of lactate to pyruvate
b) inhibits citrate cycle
c) activates β-oxidation
d) inhibits gluconeogenesis