Ethanol Metabolism

Lecturer Alexander N. Koval

Gomel State Medical University
Biochemistry Department

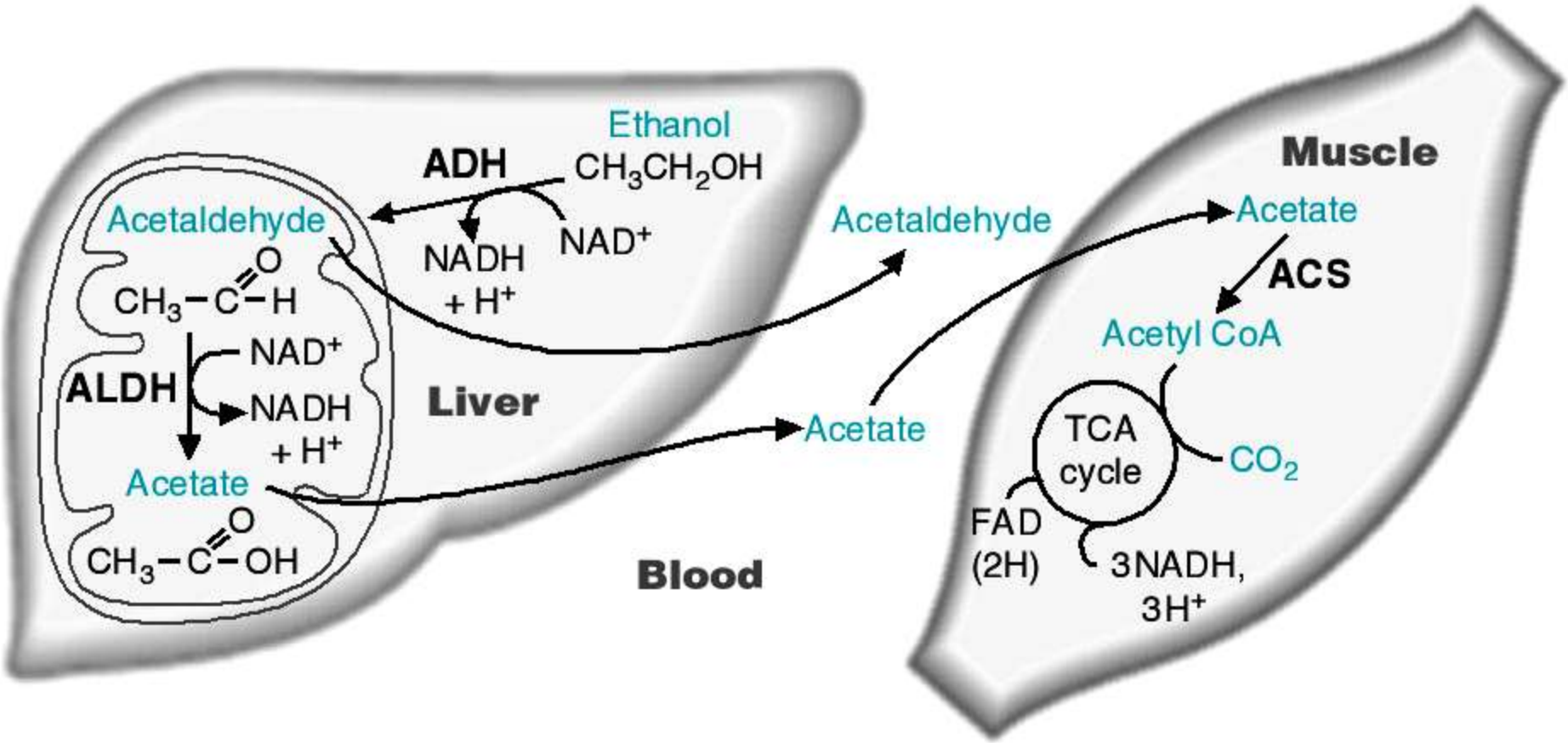
Introduction

- Ethanol is the dietary fuel that is metabolized to acetate principally in the liver, with the generation of NADH.
- The principal route for the metabolism of ethanol – through hepatic alcohol dehydrogenase.

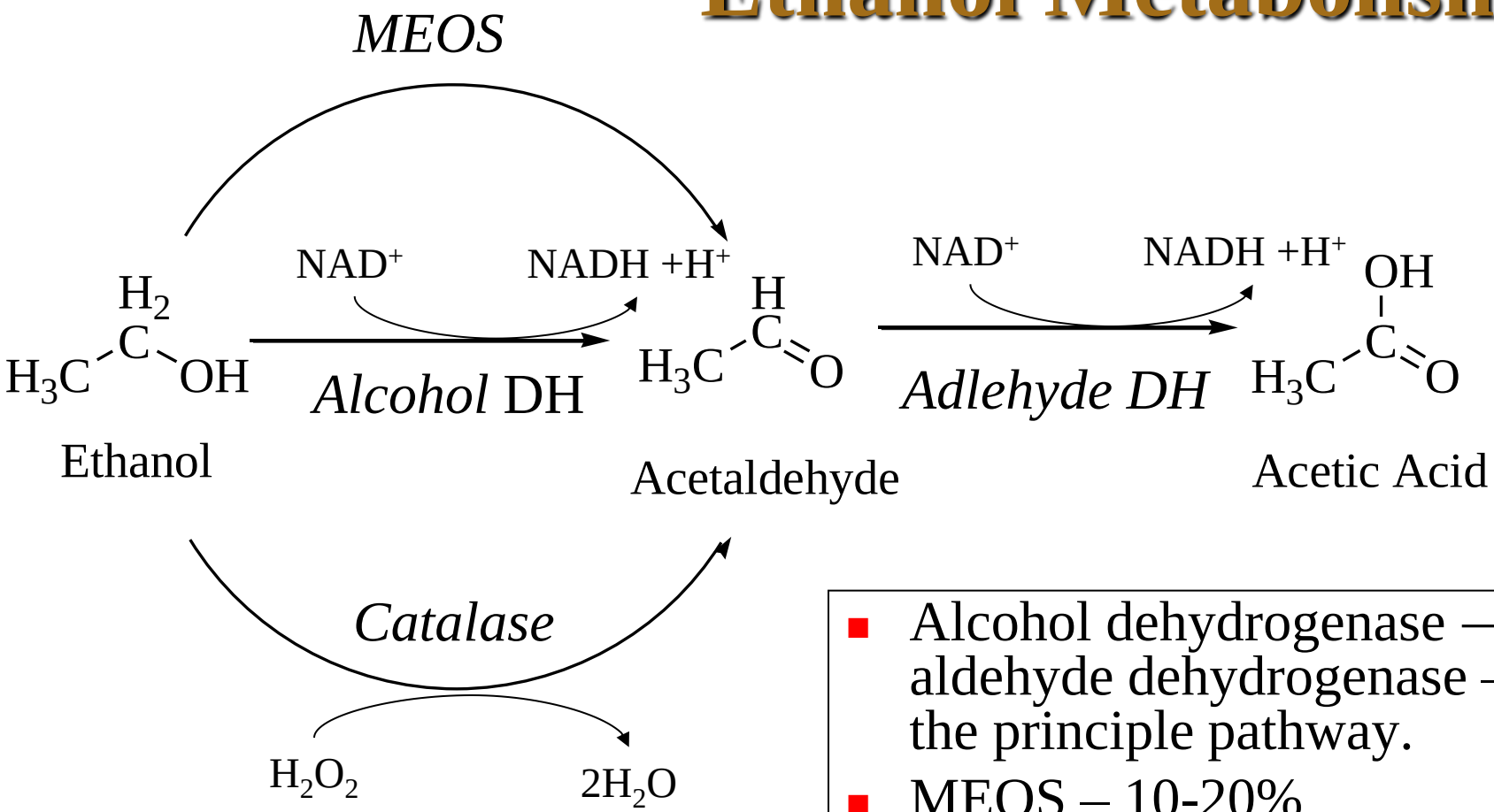
Ethanol + NAD^+ → acetaldehyde + NADH + H^+
catalyzed by ADH

- Metabolism of ethanol increases cytosolic load of NADH, this drives the LDH and MDH reaction in the direction of lactate and malate production, respectively.
- Both of these results severely impairs the capacity of the liver to carry out gluconeogenesis.

Ethanol as a Dietary Fuel

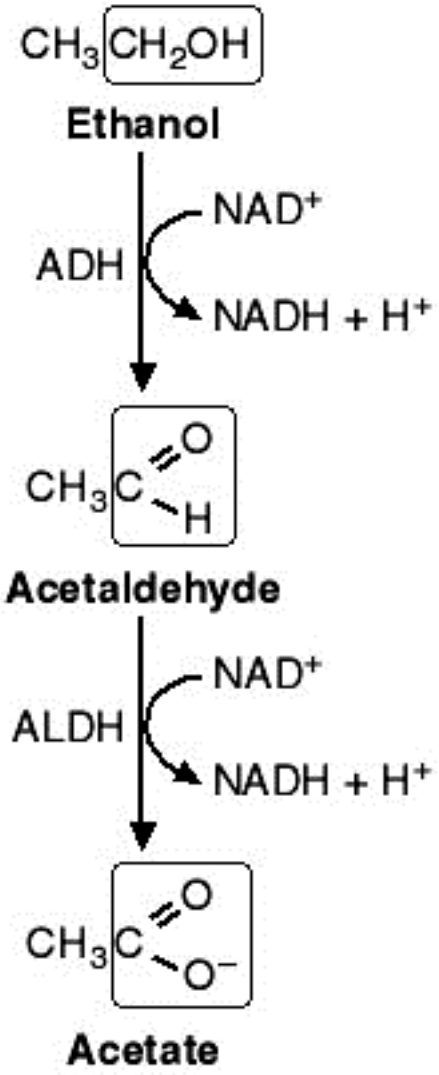


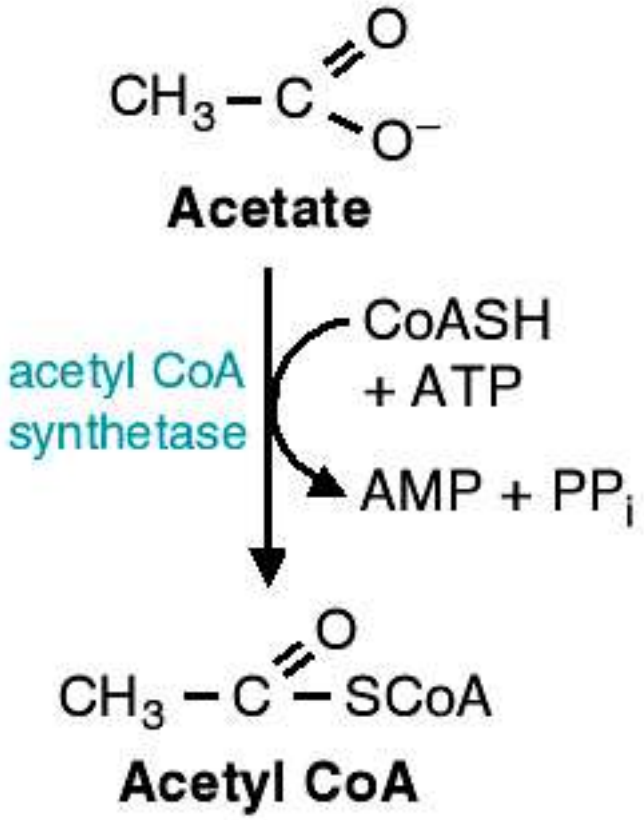
The Pathways of Ethanol Metabolism



- Alcohol dehydrogenase → aldehyde dehydrogenase – is the principle pathway.
- MEOS – 10-20%
- Catalase -3-5%

Acetate Metabolism





- ADH – alcohol dehydrogenase,
- ALDH – aldehyde dehydrogenase.

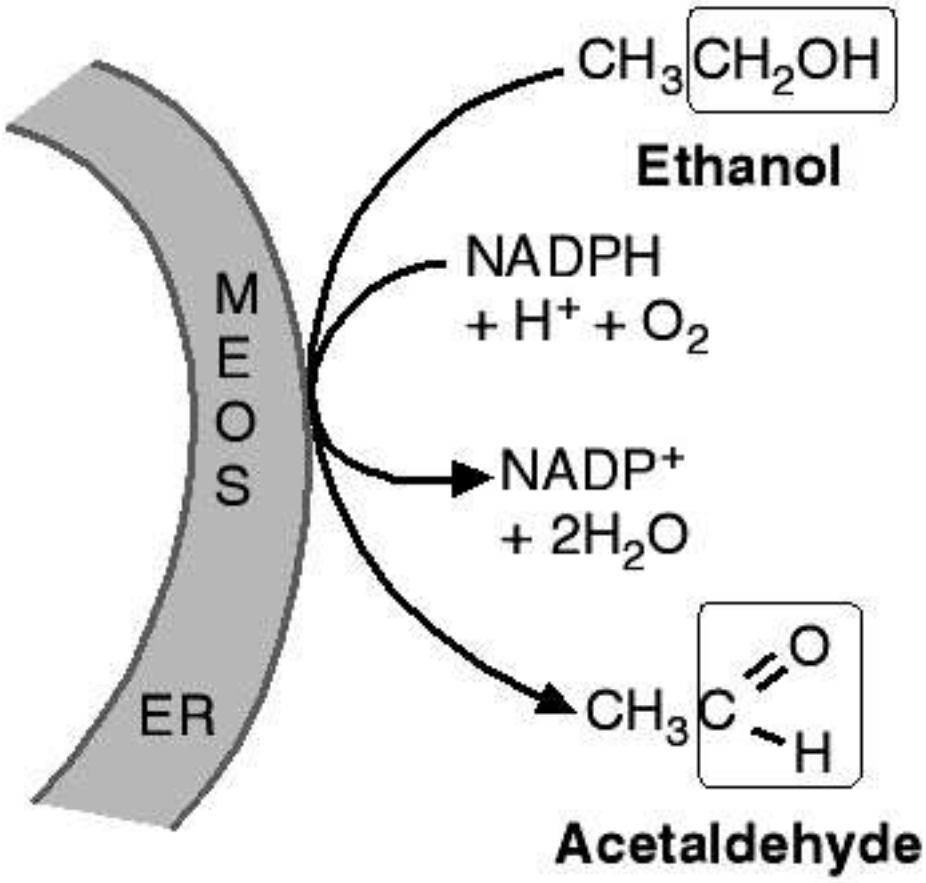
Isozymes of Alcohol Dehydrogenase

Class	Gene	Sub-unit	Tissue	Properties
I	ADH 1	α	Most abundant in liver, adrenal glands.	Km 0.05-4 mM
	ADH 2	β		
	ADH 3	γ		
II	ADH 4	π	Liver, lower GIT	Km 34 mM
III	ADH 5	χ	Liver, germinal cells	long-chain alcohols, ω-OH acids
IV	ADH 7	σ	upper GIT, not in liver	Km 28 mM, retinal
V	ADH 6	-	fetal liver	-

Acetaldehyde Dehydrogenases

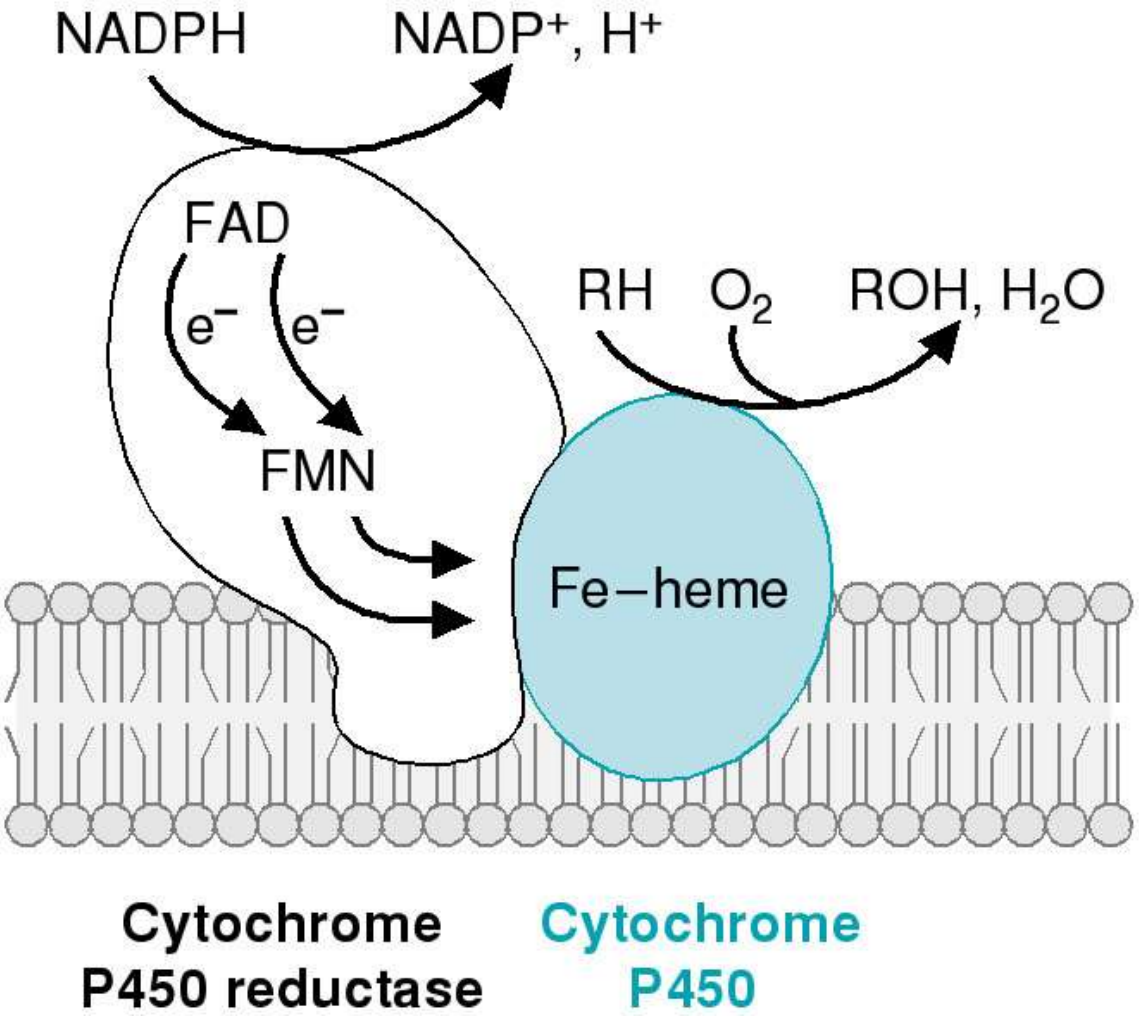
- > 80% of acetaldehyde oxidation in the liver is normally catalyzed by mitochondrial acetaldehyde dehydrogenase (ALDH2):
  - High affinity to acetaldehyde
- Other – cytosolic acetaldehyde denydrogenase (ALDH1).
- Additional ALDH.

Microsomal Ethanol Oxidizing System (MEOS)



- Appr. 10-20% of ingested ethanol is oxidized through MEOS, comprising cytochrome P450 enzymes in the endoplasmic reticulum.

Cytochrome P450 Functioning

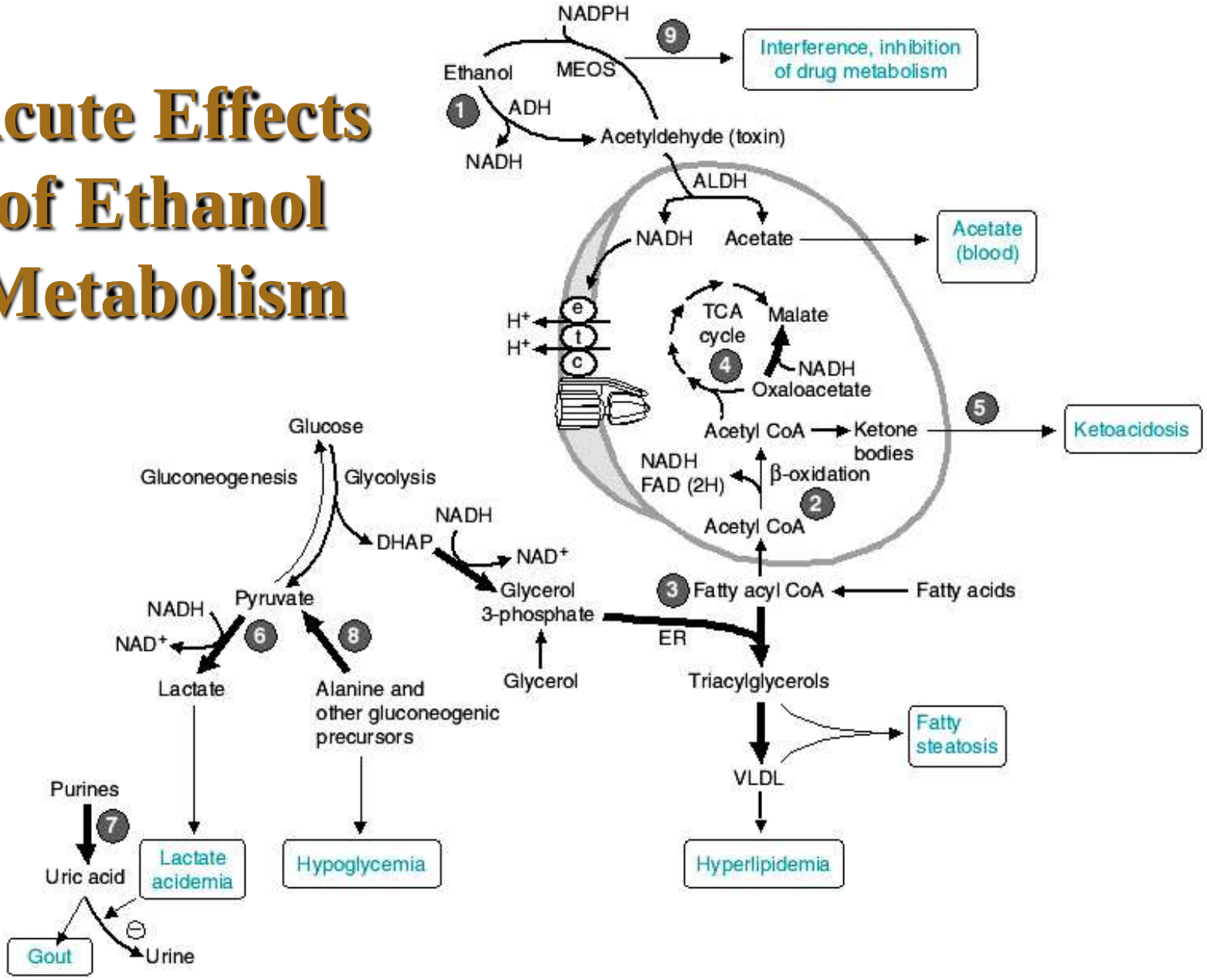


- CYP2E1 has a high *Km* for ethanol and is inducible by ethanol.
- Therefore, the proportion of this metabolism is greater
  - at high ethanol concentrations, and
  - after chronic consumption of ethanol.

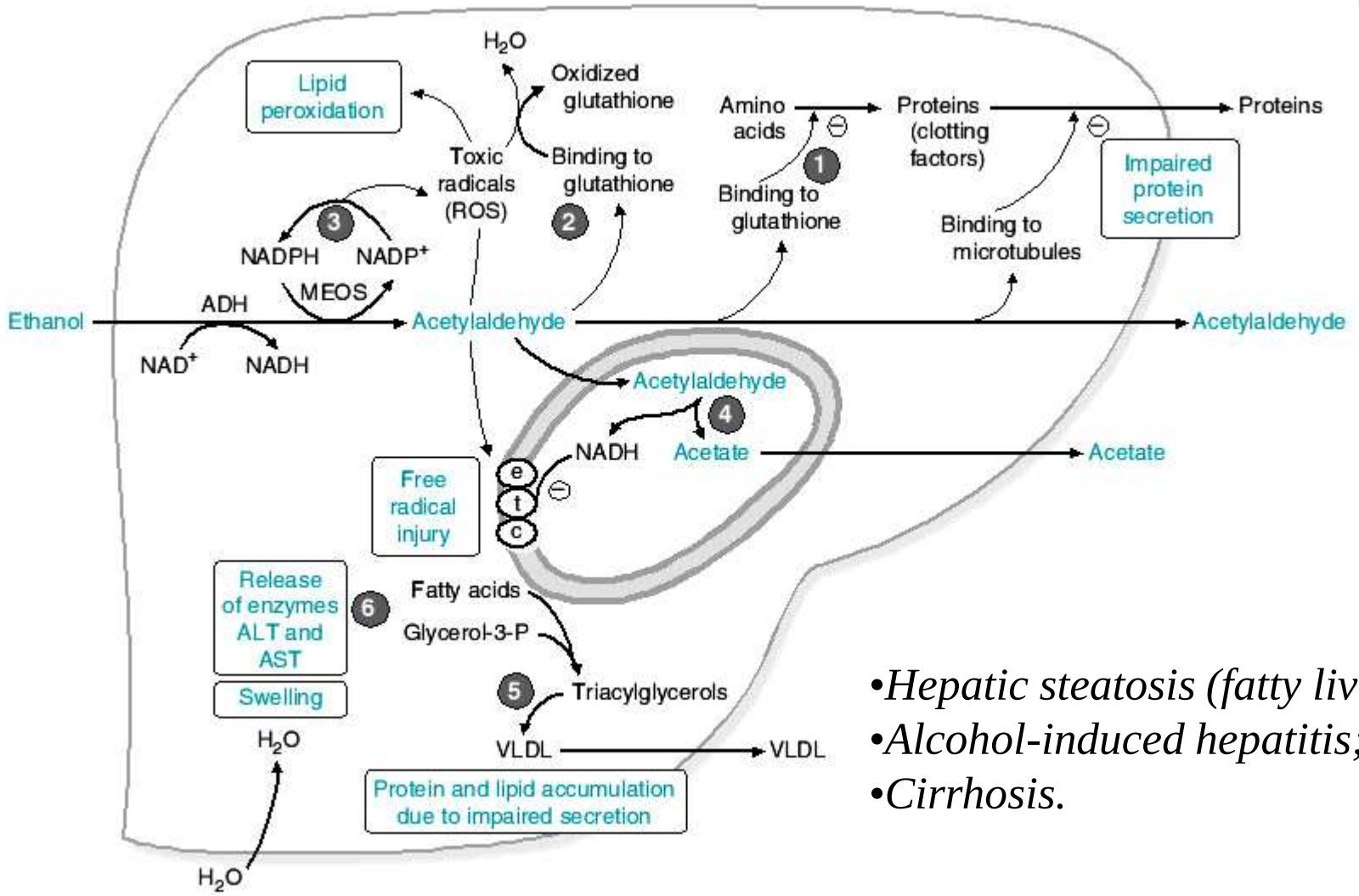
Acute Effects of Alcohol Ingestion

- Acute effects of alcohol ingestion arise principally from the generation of NADH, which greatly increases the NADH/NAD^+ ratio of the liver.
  - As a consequence, fatty acid oxidation is inhibited, and ketogenesis may occur.
  - The elevated NADH/NAD^+ ratio may also cause lactic acidosis and inhibit gluconeogenesis.

Acute Effects of Ethanol Metabolism

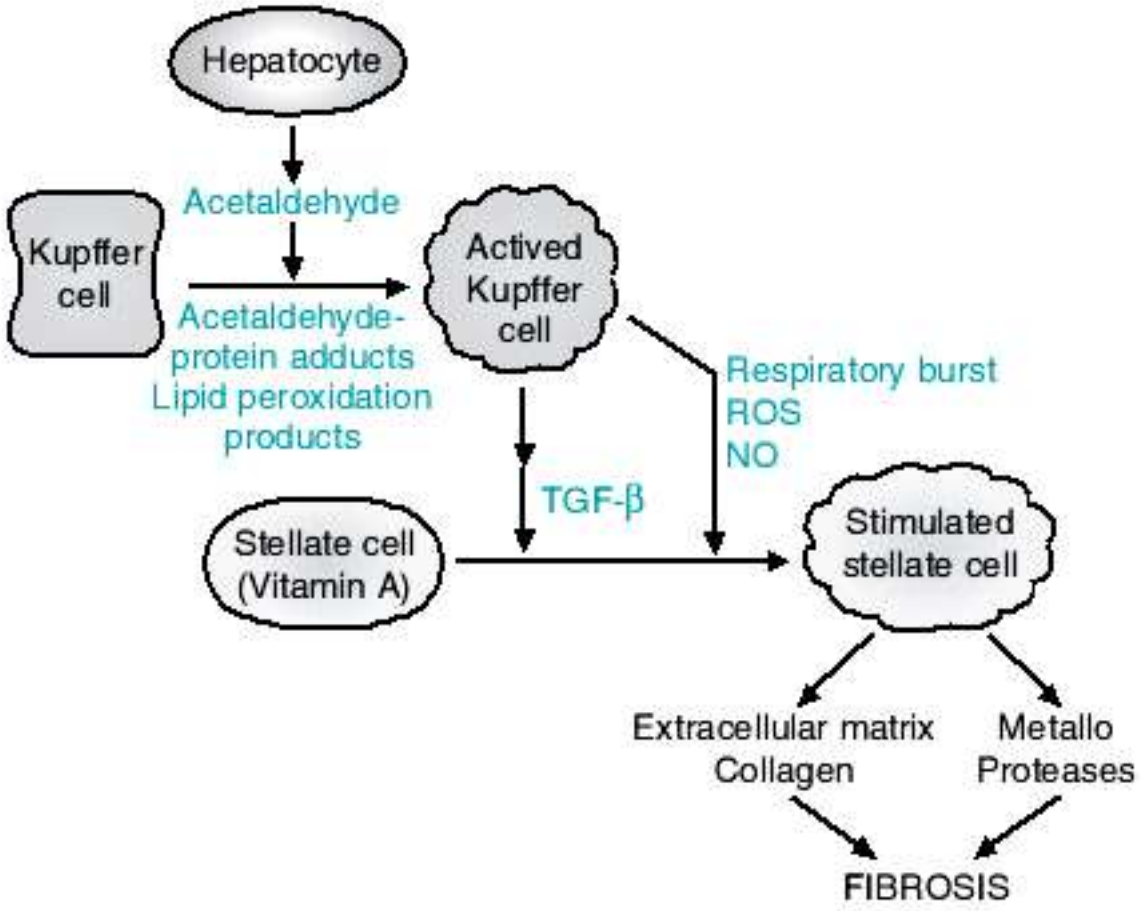


Alcohol-induced Liver Disease (After Chronic Ethanol Intoxication)

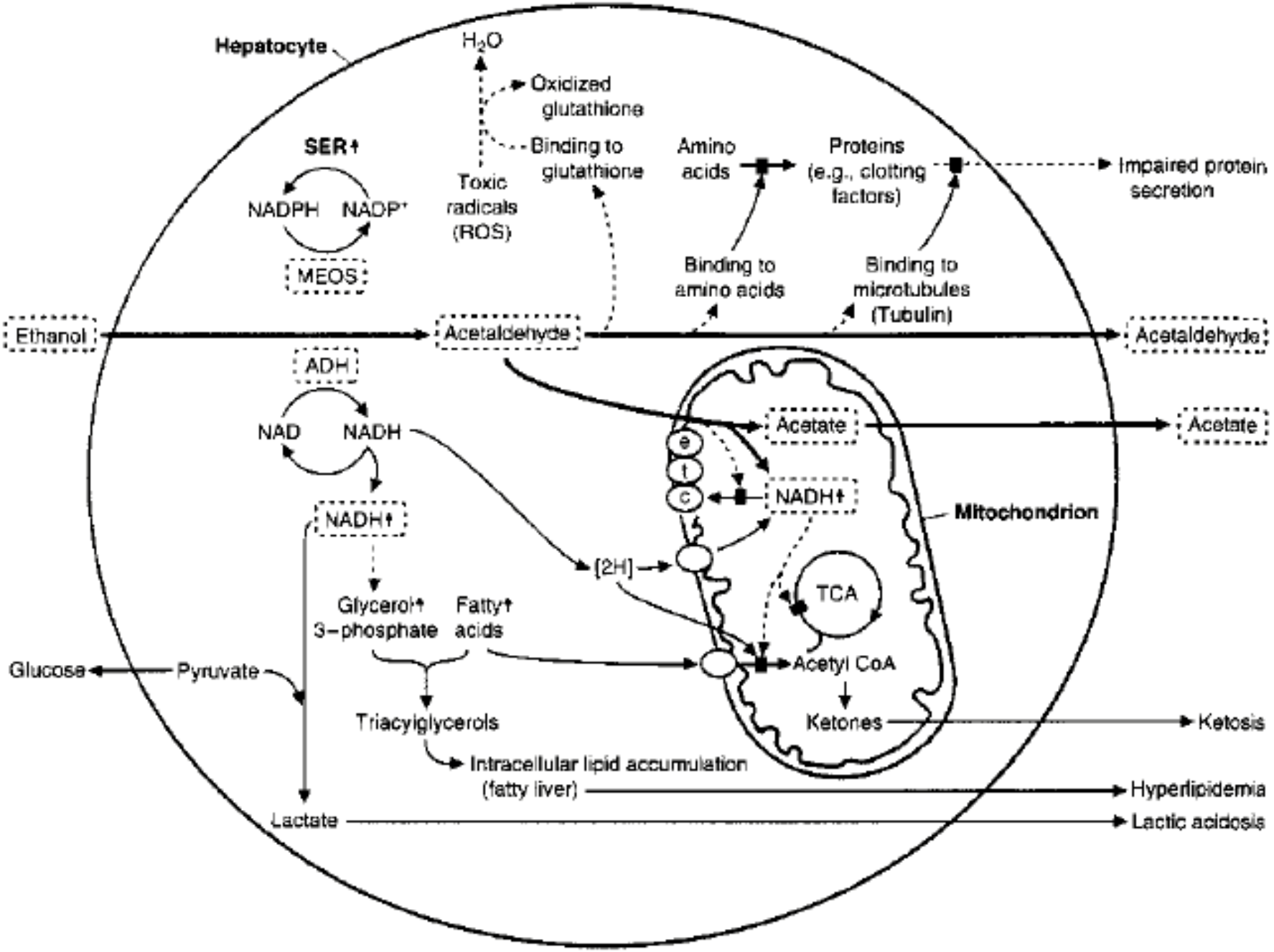


- *Hepatic steatosis (fatty liver);*
- *Alcohol-induced hepatitis;*
- *Cirrhosis.*

Development of Hepatic Fibrosis



- Hepatocytes, Kupfer cells, and stellate (Ito) cells are involved.
- ROS – reactive oxygen species;
- NO – nitric oxide;
- TGFβ1 – transforming growth factor β1.


Hepatocyte
H_2O
Oxidized glutathione
Binding to glutathione
Toxic radicals (ROS)
SER↑
NADPH
$NADP^+$
MEOS
Amino acids
Proteins (e.g., clotting factors)
Impaired protein secretion
Binding to amino acids
Binding to microtubules (Tubulin)
Ethanol
Acetaldehyde
Acetaldehyde
ADH
NAD
NADH
Acetate
Acetate
e
l
c
NADH↑
Mitochondrion
NADH↑
[2H]
TCA
Glycerol 3-phosphate↑
Fatty acids↑
Glucose
Pyruvate
Acetyl CoA
Triacylglycerols
Ketones
Ketosis
Intracellular lipid accumulation (fatty liver)
Hyperlipidemia
Lactate
Lactic acidosis

Conclusion

- The main toxic products of ethanol metabolism is acetaldehyde and free radicals.
- Acetaldehyde forms adducts with proteins and other compounds.
- The hydroxyethyl radical and others radicals produced during inflammation cause irreversible damage to the liver.
- Many other tissues are adversely affected by ethanol, acetaldehyde, or by the consequences of hepatic dysmetabolism and injury.
- Genetic polymorphisms in the enzymes of ethanol metabolism may be responsible for individual variations in the development of alcoholism or the development of liver cirrhosis.


Thank you
for your attention