بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Metabolism | FINAL 1

Alcohol Metabolism

Written by : NST

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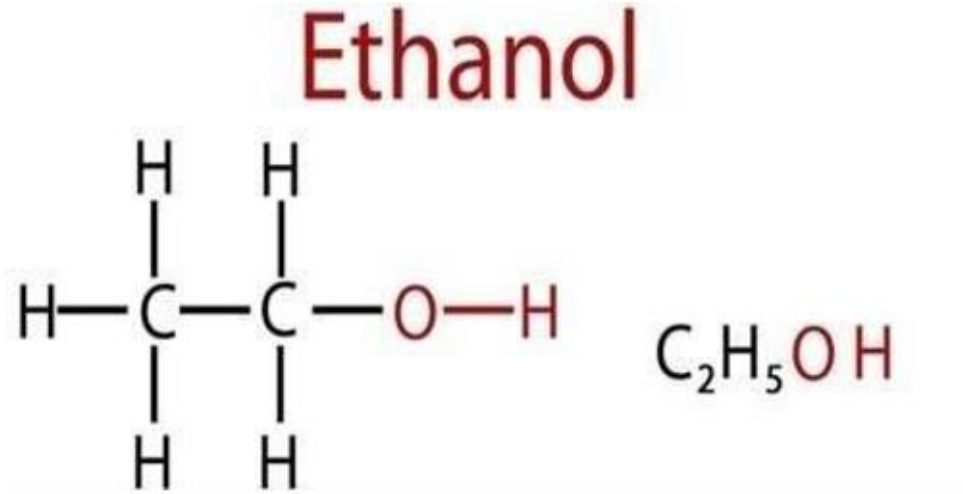
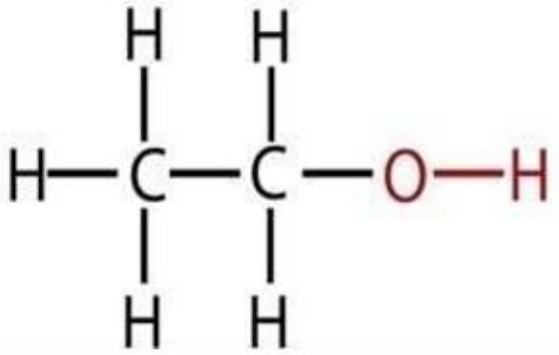


Alcohol Metabolism

Dr. Diala Abu-Hassan

https://www.agriculture.com/news/business/farm-and-ethanol-groups-ask-trump-to-intervene-on-rfs-waivers
https://www.ukessays.com/essays/chemistry/importance-of-ethanol-to-society.php

Ethanol



C_2H_5OH

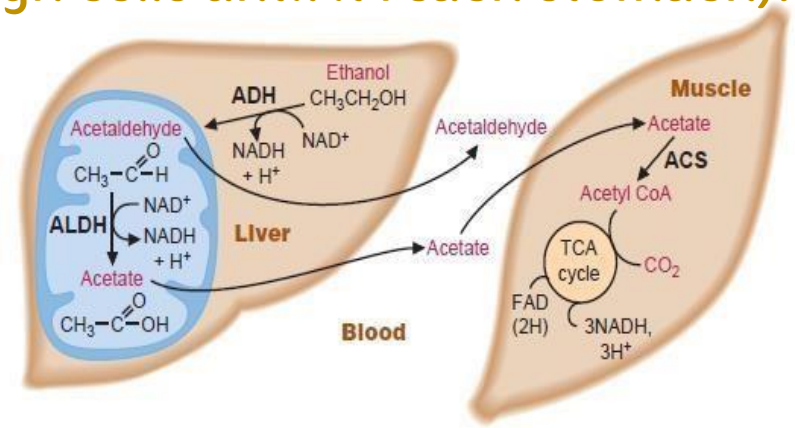
Non-Polar side Polar side

Alcoholic compound composed of 2 carbons **non-polar side** and 1(OH) group **polar side** so it's kind of **amphipathic**, which facilitates its **absorption** through stomach cells. It's present in alcoholic beverages.

we're going to discuss how the body cells get rid of it and degrade it to finish its effects on **CNS**...

Metabolism of Alcohol

- ✓ When alcohol is ingested , a small amount is immediately metabolized in the stomach.**(ethanol moves easily through cells until it reach stomach).**
- ✓ Most of the remaining alcohol is subsequently absorbed from the gastrointestinal tract, primarily the stomach and upper small intestine



ADH: Alcohol Dehydrogenase
ALDH: Acetaldehyde Dehydrogenase
ACS: Acetyl CoA Synthetase

How do you prepare acetic acid from ethanol in organic chemistry?

- ➢ Ethanol enters **hepatocytes** (liver cells) :

1. In the **cytosol of hepatocytes**, ethanol (a primary alcohol) is **oxidized** to acetaldehyde by the enzyme **alcohol dehydrogenase (ADH).**
    1. During this reaction, **NAD^+** is **reduced** to **NADH.**
    2. Reaction:
       Ethanol + NAD^+ → Acetaldehyde + NADH + H^+

2. In the mitochondria, the toxic **acetaldehyde** is **further oxidized** to **acetic acid (acetate)** by **acetaldehyde dehydrogenase (ALDH).**
    1. Again, **NAD^+** is **reduced** to **NADH.**
    2. Reaction:
       Acetaldehyde + NAD^+ → Acetate +

Metabolism of Alcohol

➢ The resulting **acetate** can :

- Leave the hepatocyte and enter the **bloodstream**, where it is taken up by **muscle cells**.
- In muscles, **acetate** is converted to **acetyl-CoA** by **acetyl-CoA synthetase**, which then enters the **Krebs cycle** for energy production.

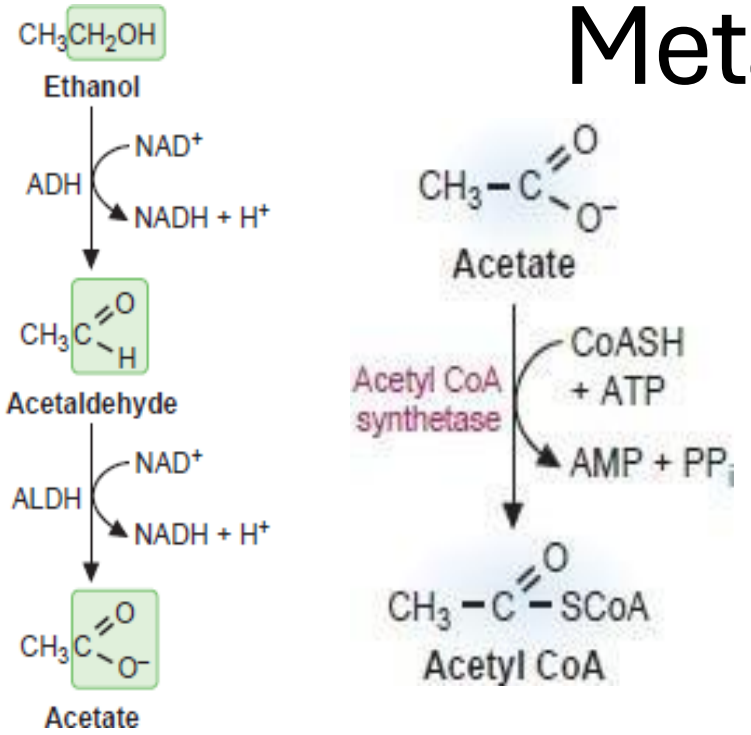
However, **Acetaldehyde** itself is **highly toxic** and **carcinogenic**.

- **Acetaldehyde (can go to the bloodstream directly, without being converted to Acetate)**If it accumulates, it can cause **cellular damage** and even promote **cancer development**.

- Acetaldehyde also has a **strong odor**, which is why you can often **smell alcohol** on someone who has been drinking.

This pathway — involving **alcohol dehydrogenase** and **acetaldehyde dehydrogenase** — is the **main route** for ethanol metabolism in humans

Metabolism of Alcohol-Steps



What happens when a high amount of Ethanol is metabolized?

- ✓ High NADH/NAD+
- ✓ Inhibition of FA oxidation
- ✓ Inhibition of gluconeogenesis
- ✓ Lactic acidosis

➢ Consequences of Ethanol Metabolism :

- Ethanol is metabolized in two oxidation steps :

1. Ethanol → Acetaldehyde (by alcohol dehydrogenase, ADH) :
    1. Occurs in the cytosol
    2. $NAD^+ \rightarrow NADH$

2. Acetaldehyde → Acetate (by acetaldehyde dehydrogenase, ALDH) :
    1. Occurs in the mitochondria
    2. $NAD^+ \rightarrow NADH$

Both reactions **consume** NAD^+ and produce NADH, which **raises the** $NADH/NAD^+$ **ratio** inside hepatocytes.

Metabolism of Alcohol

Major Metabolic Consequences :

a. Inhibition of the Krebs (TCA) Cycle :

- **High NADH** levels **inhibit** key **dehydrogenase enzymes** in the **Krebs cycle.**
- This **reduces energy (ATP) production** from normal oxidative metabolism.

b. Lactic Acidosis :

- High NADH pushes the **conversion of pyruvate → lactate**, increasing lactic acid levels.
- This leads to metabolic (lactic) acidosis.
  - ❑ Reaction shift:
    Pyruvate + NADH → Lactate + NAD^+
- Occurs because there is **not enough NAD^+** to run aerobic respiration efficiently, so **anaerobic glycolysis increases.**

Metabolism of Alcohol

c. Inhibition of Gluconeogenesis :

- Gluconeogenesis requires **pyruvate, oxaloacetate, and NAD^+**.
- But high NADH:
  - Converts **pyruvate → lactate** instead of glucose precursors.
  - Converts **oxaloacetate → malate**, removing key substrates from the gluconeogenesis pathway.
- Result → **Hypoglycemia**, especially during **fasting or heavy alcohol intake.**

d. Inhibition of Fatty Acid Oxidation :

- Fatty acid oxidation also needs **NAD^+** as an **electron acceptor.**
- When NAD^+ is scarce (due to ethanol metabolism), **β-oxidation stops.**
- Unused fatty acids are converted into **triglycerides**, causing **fatty liver (hepatic steatosis).**

Metabolism of Alcohol

e. Acetate Utilization :

- The **acetate** produced in the liver can enter the **bloodstream**.
- **Muscle cells** convert acetate → **acetyl-CoA** via **acetyl-CoA synthetase** to use for energy.
- However, this doesn't offset the **metabolic imbalance** caused by excess NADH in the liver.

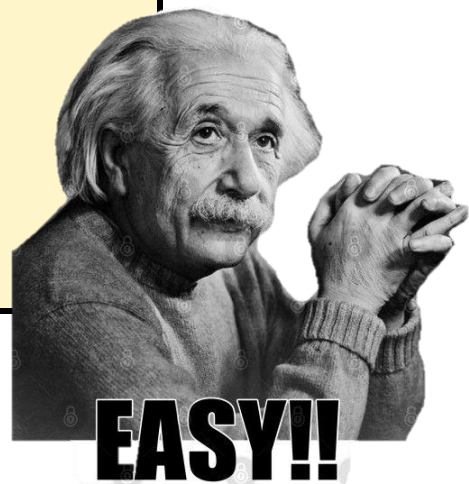
Metabolism of Alcohol

Summary: Chain of Effects:

High Ethanol Intake → ↑NADH/NAD^+ ratio → ↓Krebs cycle + ↓β-oxidation + ↓gluconeogenesis → lactic acidosis + hypoglycemia + fatty liver

Easy Way to Remember:

"Too much NADH shuts down the liver's power plants."
Stops Krebs
Stops Fat burning
Stops Glucose making
Starts Lactic acid build-up

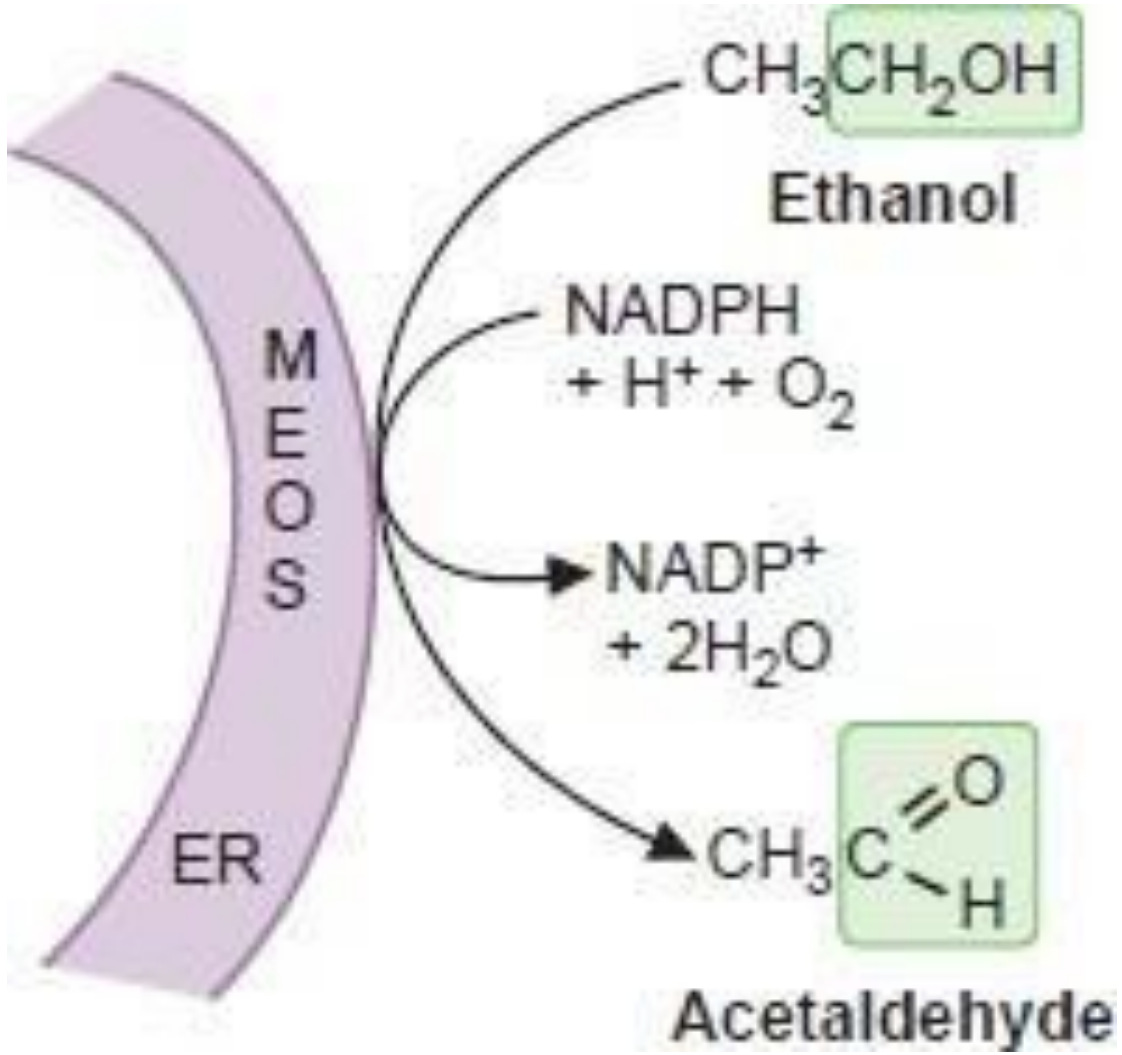


Metabolism of Alcohol

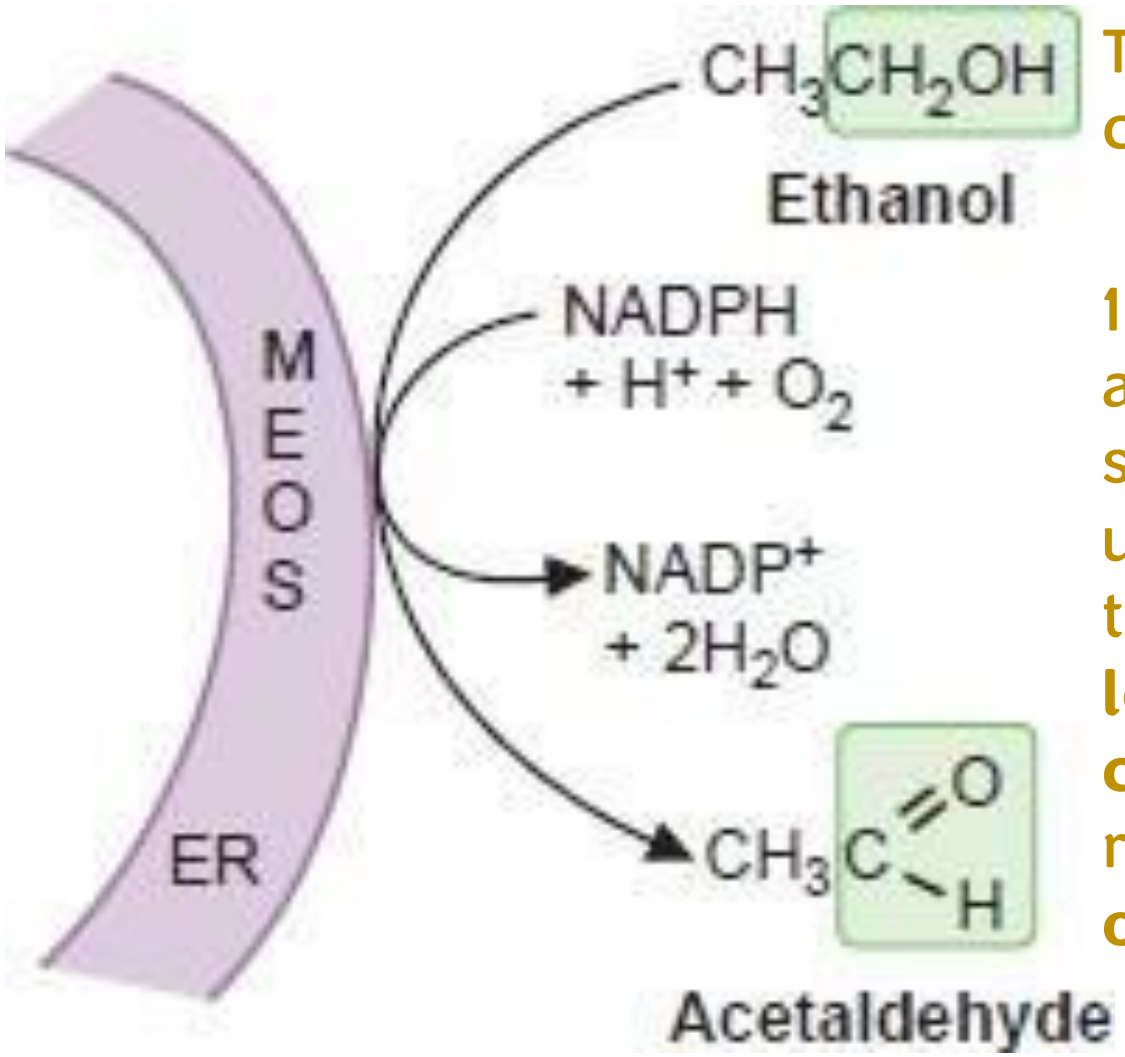
The Second most important Pathway to degrade ethanol.

MEOS: Microsomal Ethanol Oxidizing System

The second Mechanism.

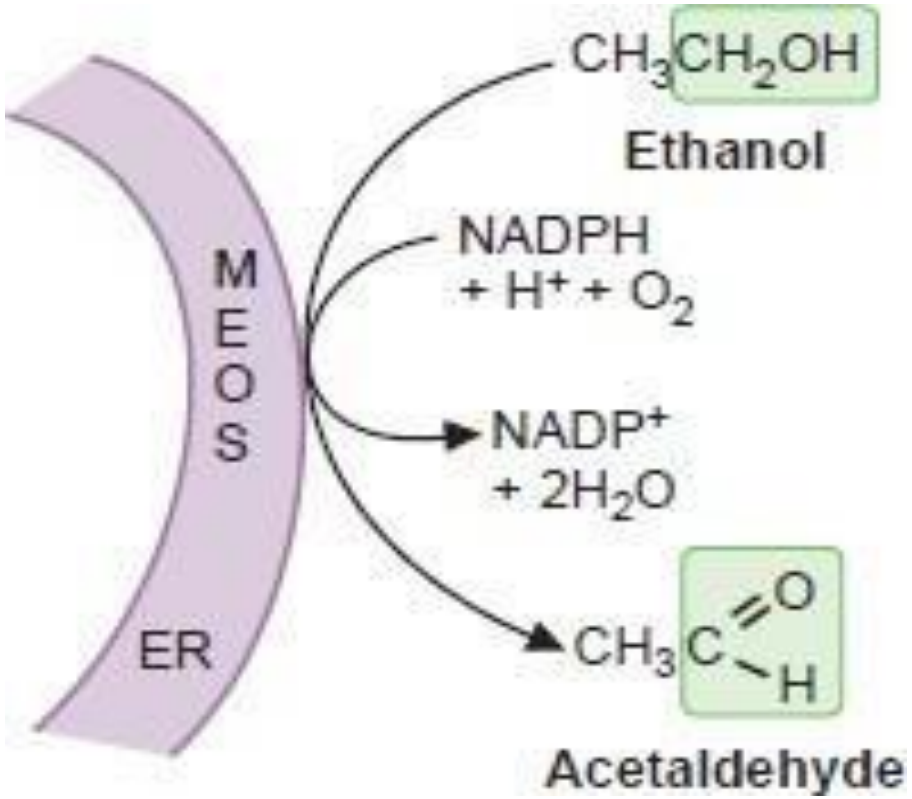


- ✓ An alternative pathway for ethanol metabolism
- ✓ **10-20**% of the ingested ethanol
- ✓ Involves primarily the **cytochrome P450 2E1 (CYP2E1).**
- ✓ CYP2E1 is associated with NADPH-cytochrome P450 reductase in the
- ✓ **High K_m for ethanol (low affinity).**
- ✓ Inducible by ethanol
- ✓ CYP2E1 is a major contributor of oxidative stress in the hepatocytes by generating several reactive oxygen species (ROS) such as hydrogen peroxide (H_2O_2), hydroxyethyl radical (HER·), hydroxyl radical (OH^-) and superoxide (O_2^-)



This one is going to depend mainly on the cytochrome P450 2E1 to do this oxidization

1) We're going to oxidise ethanol to acetaldehyde (but the enzyme used and the system used is different) in this case we will use MEOS (Microsomal Ethanol Oxidizing system) that has a **high km for ethanol** (which means **low affinity**) it has to be induced by **high concentration of ethanol** (that's why it's just responsible for metabolism of a **small amount of ethanol).**



This oxidation is associated with another **oxidation** of **NADPH to NADP+**

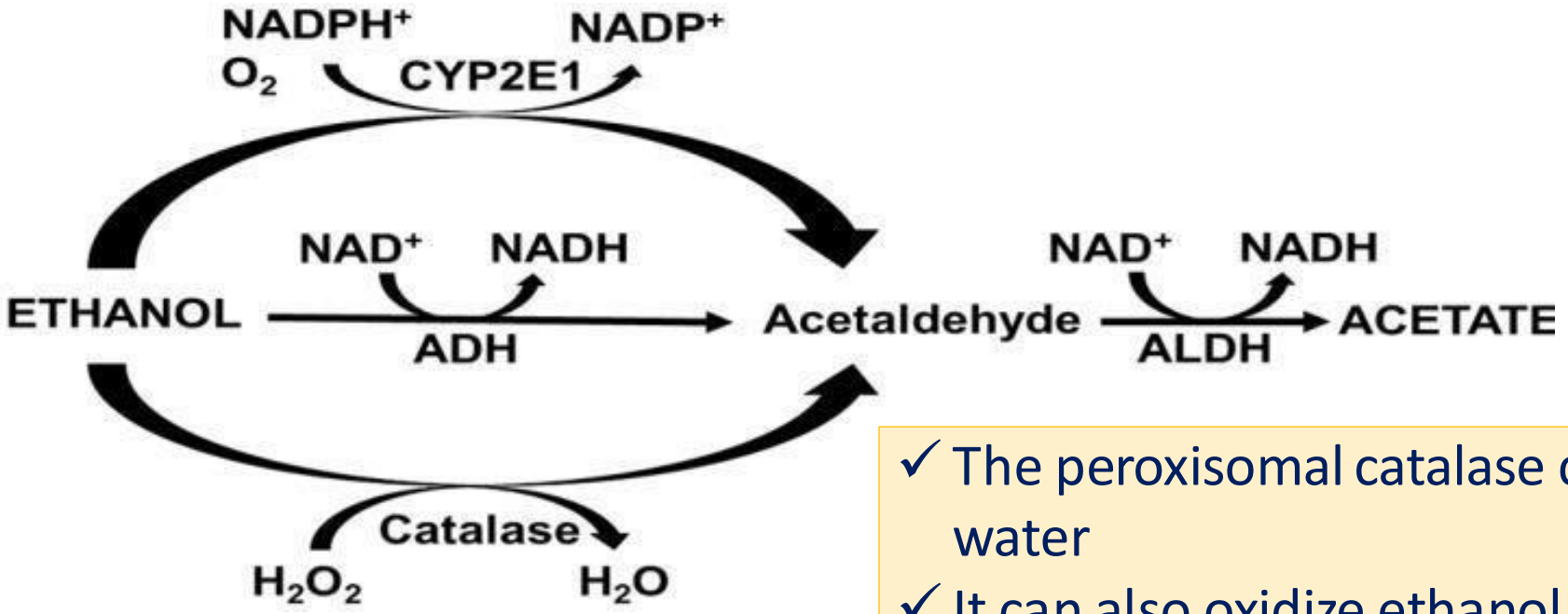
So oxygen will be reduced taking electrons from both ethanol and NADPH to reduce the oxygen molecule into **two H_2O molecules.**

This process is associated with the production of **reactive oxygen species (ROS)** such as :**H_2O_2 , hydroxyl radical ,superoxide ions…**

These are **toxic** to the **hepatocytes** where this process is going to happen.

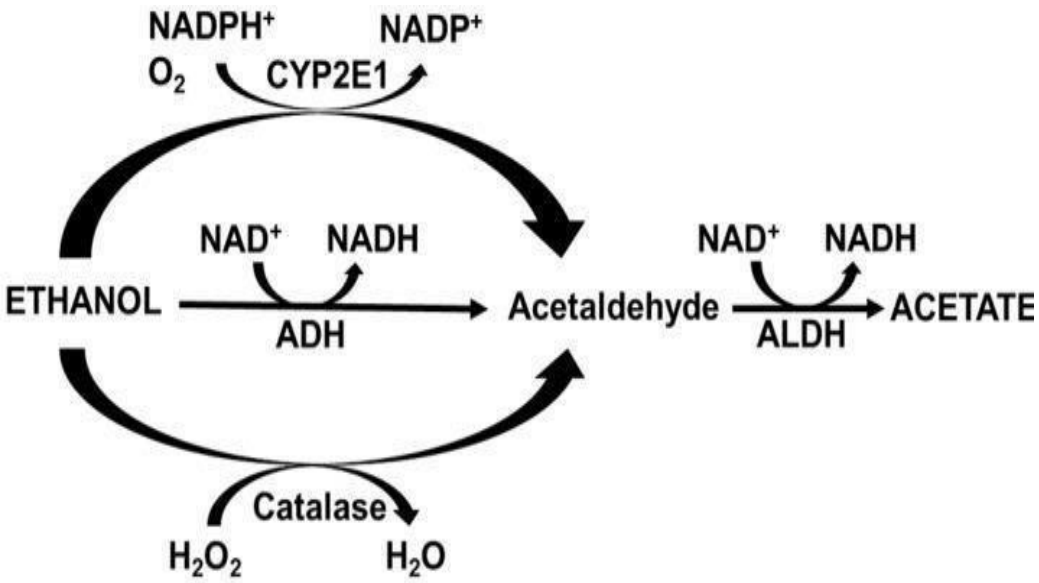
سُبْحَانَ اللَّهِ وَبِحَمْدِهِ
عَدَدَ خَلْقِهِ ، وَرِضَا نَفْسِهِ ،
وَزِنَةَ عَرْشِهِ ، وَمِدَادَ كَلِمَاتِهِ ..

Metabolism of Alcohol-Catalase



The third mechanism to get rid of alcohol.
The Ethanol will be oxidised to acetaldehyde
Same idea but using different enzyme system.

- ✓ The peroxisomal catalase converts H_2O_2 to oxygen and water
- ✓ It can also oxidize ethanol to acetaldehyde
- ✓ Is not a key pathway for ethanol elimination
- ✓ Catalase is ubiquitously expressed in almost all tissues
- ✓ Catalase is also expressed by colonic floras which may lead to acetaldehyde production in the lower gastrointestinal tract
- ✓ Catalase activity relies on the cellular level of H_2O_2

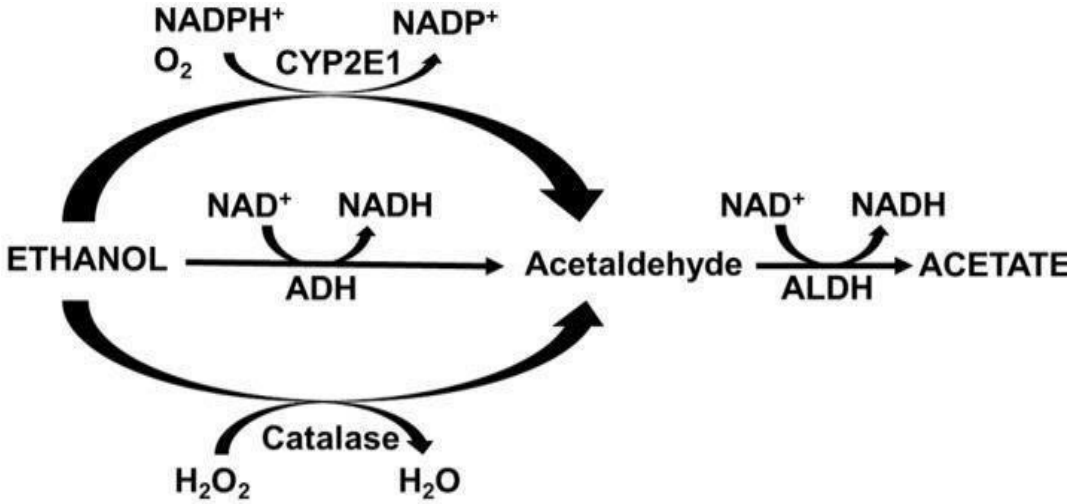


- We use **catalase** that's present in the **peroxisome.**
- peroxisomal catalase that normally gets rid of **H2O2 and makes it H2O** and **oxidise ethanol to Acetaldehyde**
- this is a very minor pathway to get rid of ethanol and eliminate it.

It's responsible for a **very small** percentage of ethanol metabolism.

This enzyme (Catalse) is also expressed by the **microflora** in the **colon** so there might be some production of **acetaldehyde in the GI tract.**

this system is connected/restricted to **H_2O_2 availability** so there has to be **H_2O_2 to be able to oxidise ethanol**
That's why it's a **minor** system for metabolism alcohol



Then after acetaldehyde is formed whether it's going to form by alcohol dehydrogenase P452E1 or catalase **it's going to be further oxidised into acetate.**

الْحَمْدُ لِلَّهِ عَدَدَ مَا خَلَقَ،
وَالْحَمْدُ لِلَّهِ مِلْءَ مَا خَلَقَ،
وَالْحَمْدُ لِلَّهِ عَدَدَ مَا فِي السَّمَاوَاتِ وَمَا فِي الأَرْضِ،
وَالْحَمْدُ لِلَّهِ عَدَدَ مَا أَحْصَى كِتَابُهُ،
وَالْحَمْدُ لِلَّهِ مِلْءَ مَا أَحْصَى كِتَابُهُ،
وَالْحَمْدُ لِلَّهِ عَدَدَ كُلِّ شَيْءٍ،
وَالْحَمْدُ لِلَّهِ مِلْءَ كُلِّ شَيْءٍ،
وَتُسَبِّحُ اللَّهَ مِثْلَهُنَّ"

Ethanol Metabolism Application

- ✓ **ADH has 5 classes or isoenzymes**
- ✓ Different isoforms are expressed in different tissues such as liver, lung, stomach and esophagus.
- ✓ People with different races inherit different sets of ADH isoenzymes, for example African Americans have an isoform with a high maximal velocity resulting in fast ethanol metabolism.

ADH has different isoforms, each one with **different kinetics** : some of them are **faster** in metabolism of ethanol than the others.

The isoforms that are **faster** are going to remove the **effect of ethanol on the CNS faster** so the people will be **more** efficient in degradation of ethanol, and they **won't get drunk easily,** whereas the **Southeast Asians** have **problems and mutations** or the so-called **polymorphisms in alcohol dehydrogenase** resulting in **less efficient and slower degradation of ethanol** that's why they **can get drunk easily in compared to other races.**

رسالة من الفريق العلمي:

For any feedback, scan the code or click on i

- Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			