METABOLISM

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ARKAN ACADEMY

❖ Alcohol metabolism

- Ethanol (C_2H_5OH): has a hydrophilic and hydrophobic nature which allows it to cross membranes easily
  - ➢ It can reach the **brain**
  - ➢ It has an **inhibitory** effect on the central nervous system, by:
    - ✓ Binding inhibitory receptors such as GABA receptors
    - ✓ Inhibition (blocking) of excitatory receptors such as aspartate and glutamate
- A small amount of ethanol is immediately metabolized in the stomach
  - ➢ The remaining is absorbed by gastrointestinal tract (stomach and upper small intestine)
- There are 3 pathways of ethanol metabolism:

♦ The major pathway (liver and muscles)

- Ethanol enters the liver cells and oxidized into acetaldehyde by ***Alcohol Dehydrogenase (ADH)*** which converts NAD^+ into NADH
- Acetaldehyde either leaves the cell to the blood stream or transferred into the mitochondria for farther oxidation to produce Acetate by ***Acetaldehyde dehydrogenase (ALDH)*** which also produces NADH
- Acetate (acetic acid) leaves liver cells into the **muscles** where it is converted into acetyl CoA by ***Acetyl CoA synthetase (ACS)*** which enters the TCA cycle
- Alcohol consumption causes:
  - ➢ High $NADH/NAD^+$
  - ➢ Inhibition of FA oxidation
  - ➢ Inhibition of gluconeogenesis
  - ➢ Lactic acidosis

The lingering odor of the alcoholic individuals is due to the smell of **acetaldehyde**

Can cause liver cirrhosis

♦ MEOS: Microsomal Ethanol Oxidizing System (Liver)

- Involves primarily the ***cytochrome P450 2E1 (CYP2E1)*** which is associated with NADPH-cytochrome P450 reductase in the **ER** of the **liver**
- CYP2E1 oxidizes ethanol into acetaldehyde which conversion of NADPH into $NADP^+$ and produces 2 water molecules by reducing O_2
- Acetaldehyde is then converted into acetate by ALDH
- This pathway is an alternative pathway that metabolizes 10-20 % of alcohol
  - ➢ CYP2E1 has a high Km (low affinity), so it doesn't act when there are low concentration of alcohol
  - ➢ This pathway increases the oxidative stress in the liver cells by increasing reactive oxygen species (ROS) such as s hydrogen peroxide (H_2O_2), hydroxyethylradical (HER·), hydroxylradical (OH^-) and superoxide (O^-)
  - ➢ It can be done for any toxic material that enter the body not only alcohol (Detoxification)

♦ MEOS: Microsomal Ethanol Oxidizing System (Liver)

- A minor (not a key) pathway depends on ***catalase*** enzyme in the **peroxisomes**
  - ➢ Catalase is expressed in almost all the cells
  - ➢ The major function of catalase is to deal with ROS (decreases oxidative stress)
  - ➢ Catalase is expressed by **colonic floras** which lead to acetaldehyde production in the lower GI tract
- ADH has 5 classes or isoenzymes, where different isoforms are expressed in different tissues such as liver, lung, stomach and esophagus
- People with different races inherit different sets of ADH isoenzymes:

➢ **African Americans** have isoform with a **high maximal velocity** resulting in fast ethanol metabolism

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