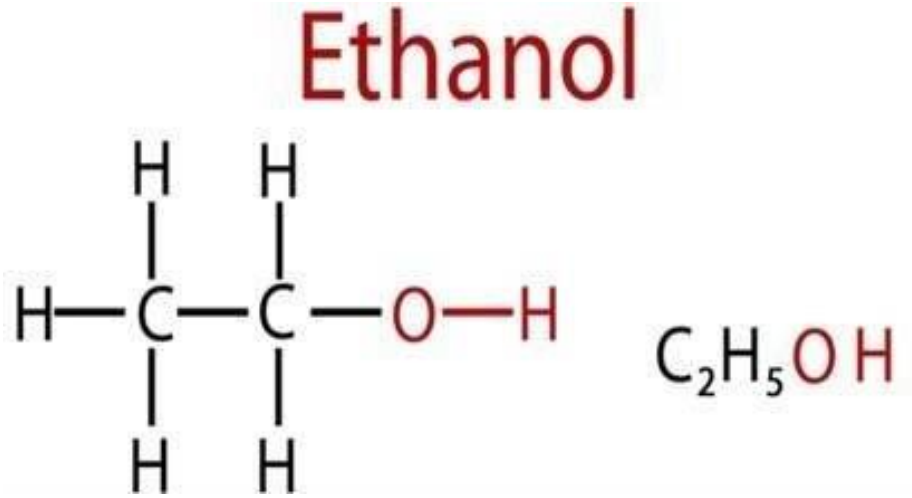
فريق طوفان الأقصى

METABOLISM

Modifide N.15

Writer: Sra'a Ali
Mahde Sabbagh

Corrector: Sra'a Ali
Mahde Sabbagh



Alcohol Metabolism

Dr. Diala Abu-Hassan

NOTE: Today, we will discuss how our cells get rid of ethanol and how ethanol affects our bodies.

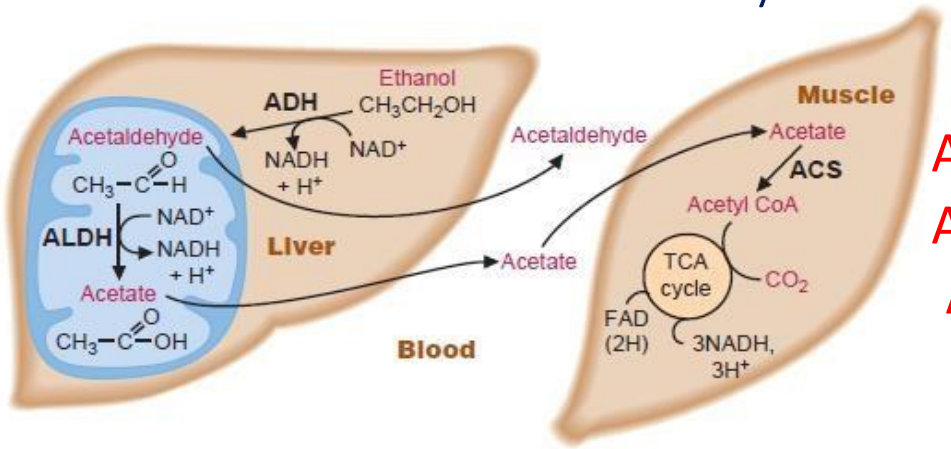
https://www.agriculture.com/news/business/farm-and-ethanol-groups-ask-trump-to-intervene-on-rfs-waivers
https://www.ukessays.com/essays/chemistry/importance-of-ethanol-to-society.php

- **The complement in this slide:** Ethanol can function as both a hydrophobic and hydrophilic molecule. Its hydrophobic nature enables it to easily pass through membranes.
- Ethanol is present in alcoholic drinks in varying proportions. When it is consumed, it enters the stomach and undergoes the absorption process. Due to its ability to easily penetrate cell membranes, it can reach different areas of the body, including the brain. In the brain, ethanol binds to multiple types of receptors, like GABA. Ethanol overactivates GABA receptors in the central nervous system, which reduces the overall function of the CNS.
- Additionally, ethanol inhibits other receptors responsible for excitatory neurotransmitters such as glutamate and aspartate. These substances not only serve as amino acids but also function as neurotransmitters. When their activity is inhibited, the overall activity of the central nervous system decreases.

- **The complement in this slide:** Once ethanol takes effect, it is metabolized to eliminate its effects. Without metabolism, its effects would persist. There are three processes that help metabolize ethanol, ranked by importance.

Metabolism of Alcohol

- ✓ When alcohol is ingested, a small amount is immediately metabolized in the stomach.
- ✓ Most of the remaining alcohol is subsequently absorbed from the gastrointestinal tract, primarily the stomach and upper small intestine



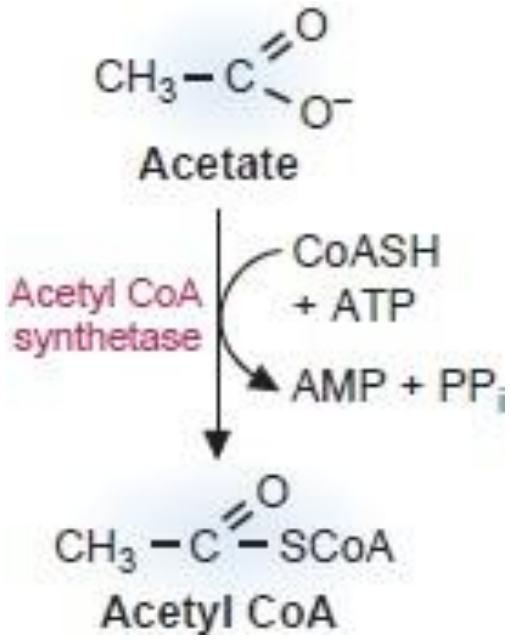
ADH: Alcohol Dehydrogenase
ALDH: Acetaldehyde Dehydrogenase
ACS: Acetyl CoA Synthetase

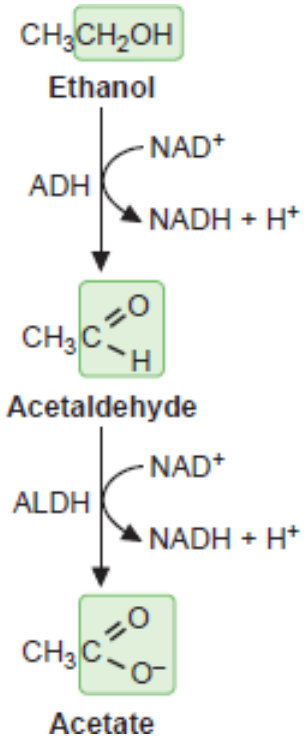
How do you prepare acetic acid from ethanol in organic chemistry?

NOTE: This pathway is responsible for 70-90% of ethanol metabolism and is specific to ethanol. The second and third pathways are not specific to ethanol.

NOTE: In all pathways, ethanol undergoes the same change (oxidation to acetaldehyde). However, different proteins and enzymes are involved in each pathway.

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

- **The complement in this slide:** In the liver, alcohol enters liver cells as ethanol and easily passes through the cell membrane. Inside the cell, ethanol is converted to acetaldehyde through a process called oxidation. This reaction involves the enzyme ADH and results in the reduction of NAD+ to NADH. Acetaldehyde can then either enter the mitochondria or leave the cell. If it enters the mitochondria, it undergoes further oxidation and is transformed into acetic acid with the help of the enzyme ALDH and results in the reduction of NAD+ to NADH. Acetic acid then leaves the liver, enters the bloodstream, and eventually reaches the muscles. In the muscles, acetic acid is converted to acetyl CoA through the enzyme ACS. Acetyl CoA can then enter the citric acid cycle.

- **The complement in this slide:** In the liver, ethanol metabolism consumes energy because NAD+ is used in oxidation and reduction reactions, which can interfere with the citric acid cycle. However, in the muscles, ethanol metabolism actually produces energy.

- **The complement in this slide:** Drinking excessive amounts of alcoholic beverages can lead to the development of liver cirrhosis.

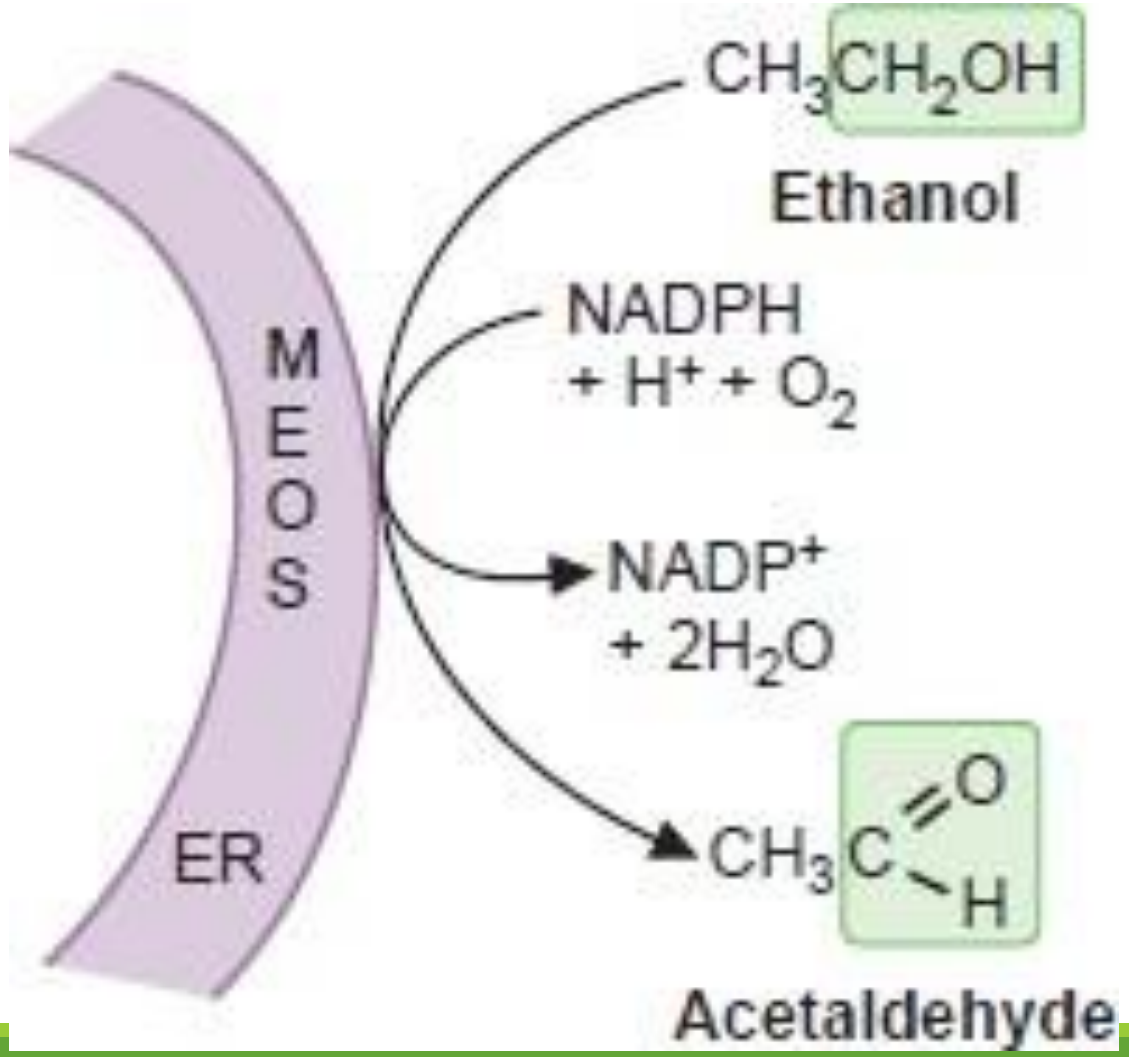
- **The complement in this slide:** In the presence of excessive alcohol consumption, the ratio of NADH to NAD+ increase. This reduction in coenzyme availability can decrease the activity of the TCA cycle, particularly in liver cells. As a result, the body compensates by relying more on anaerobic respiration, which can lead to an increase in lactic acid production. This increase in lactic acid may contribute to a condition known as lactic acidosis.

- **The complement in this slide:** In the muscles, acetate is available and used to produce acetyl CoA, which enters the TCA cycle and provides energy. However, when we're in a fasting state or relying on fatty acid breakdown for energy, the oxidation of fatty acids decreases. This reduction in fatty acid oxidation leads to a decrease in the breakdown of stored fats in adipocytes, resulting in lower levels of free glycerol, which is an important precursor for gluconeogenesis. This inhibition of gluconeogenesis can be problematic for individuals who consume alcoholic beverages.

- **The complement in this slide:** Acetaldehyde has a strong odor, similar to the smell of dead bodies, cinnamon, and vanilla. When people drink alcohol, they may have a lingering smell of acetaldehyde.

Metabolism of Alcohol

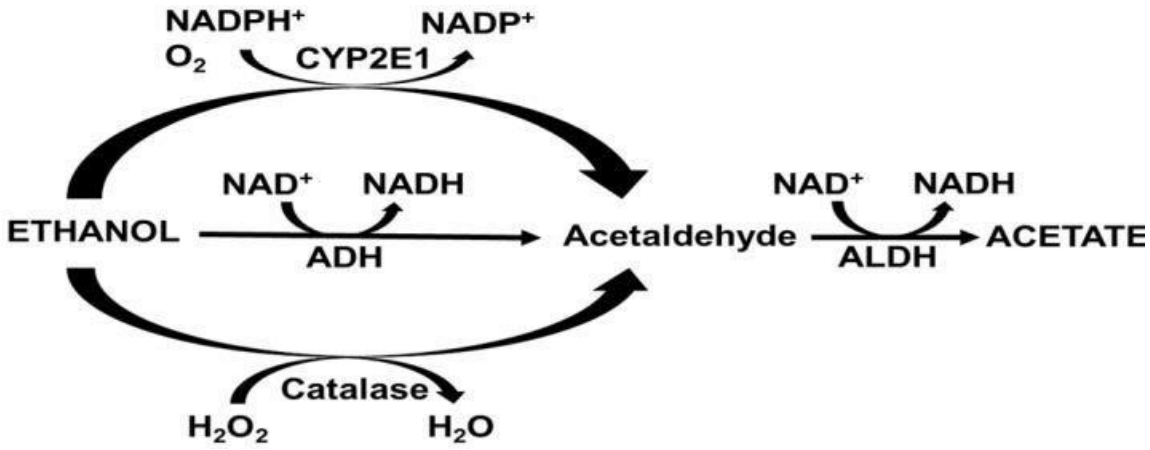
MEOS: Microsomal Ethanol Oxidizing System



- ✓ 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
- ✓ 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^-)

- **The complement in this slide:** the MEOS is a mechanism in our body that helps break down ethanol, which is found in alcoholic beverages. This process involves enzymes in our liver called cytochrome P450 2E1 enzymes. These enzymes convert ethanol into acetaldehyde by oxidation , which is then further metabolized into acetate. This process helps our body eliminate ethanol and prevent it from causing harm.
- cytochrome P450 enzymes, responsible for detoxifying substances, mainly in the liver.
- But this process is not limited to ethanol, but rather to all toxic substances that enter our GIT, such as toxins and drugs.
- NADPH acts as a coenzyme, helping to transfer hydrogen ions during the process. It transfers 4H+ to O2 to produce two water molecules (NADPH gets oxidised to form NADP+ and reducing O2)
- this pathway has a low affinity (high km), which means it doesn't kick into action until there's a high amount of ethanol present. So, it's like the pathway waits for a big party of ethanol before getting to work ☺
- It is true that this process eliminates ethanol, but it also generates a large amount of various ROS. This is one of the main risks associated with drinking alcohol.

Metabolism of Alcohol-Catalase



- 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

- **The complement in this slide:** The metabolism of alcohol through catalase (peroxisomal enzyme) is a minor pathway that aims to eliminate reactive oxygen species (ROS) rather than directly removing ethanol. In this process, catalase oxidizes ethanol to acetaldehyde and also breaks down hydrogen peroxide (H2O2) into water. So, while dealing with ROS, ethanol itself undergoes oxidation(بالمعيّة).
- After ethanol is oxidized to acetaldehyde, it is further oxidized by the enzyme ALDH into acetate.
- The primary function of peroxisome is to decrease oxidative stress in cells caused by ROS.
- ROS is a natural byproduct in our bodies and not inherently harmful. However Eating unhealthy food and not having enough antioxidants can cause more of those ROS to build up. And when that happens, it can increase the risk of developing cancer.

The complement in this slide: NADH is the electron carrier that is most abundant and needed as NAD+ during reactions when we want to oxidize something (it will be reduced). On the other hand, NADPH is the electron carrier that is most abundant as NADPH and gets oxidized during reactions when we want to reduce something. In simpler terms, NADH is like a superhero that helps with oxidation, while NADPH is like a superhero that helps with reduction.

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

- **NOTE:** **African Americans don't get drunk easily**
- **Unlike people in Southeast Asia, they have a mutation in this enzyme and get drunk very easily**

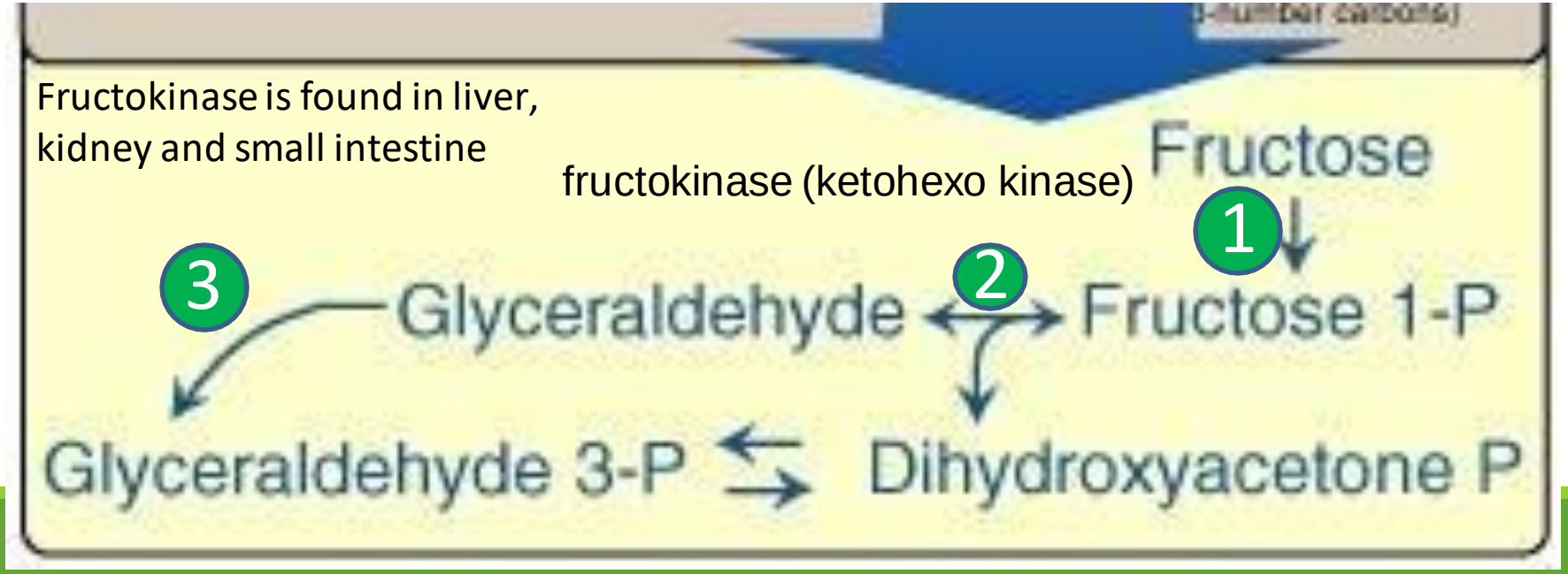
- **NOTE:** **ADH is the primary enzyme responsible for alcohol metabolism, and it catalyzes the oxidation process in hepatocytes.**

Metabolism of Monosaccharides and Disaccharides

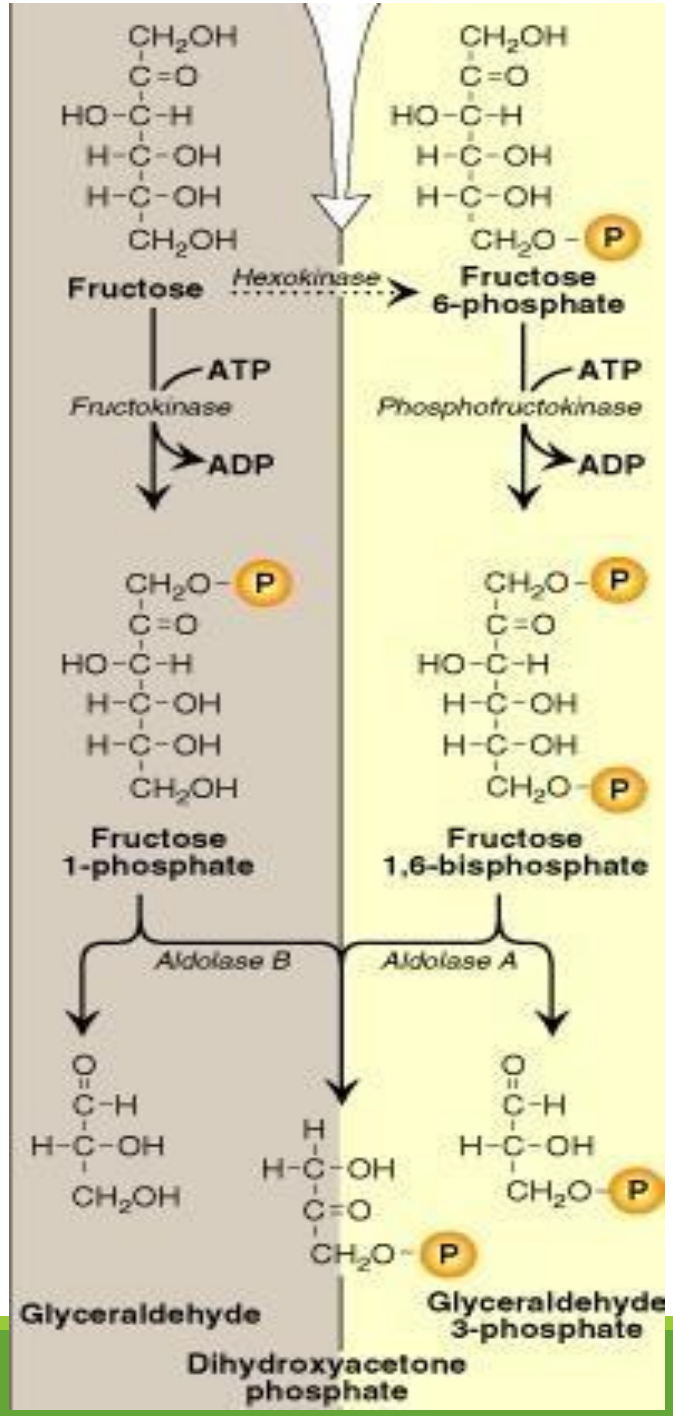
Dr. Diala Abu-Hassan, DDS, PhD

Fructose Metabolism

- 10% of the daily calorie intake
- Sources: sucrose, Fruits, honey, high-fructose corn syrup
- Entry into cells is not insulin dependent.
- Does NOT promote the secretion of insulin



- **The complement in this slide:**
- Previously we talked about the metabolism of glucose specifically, in the next lectures we will be discussing the metabolism of monosaccharides like fructose and galactose, and the metabolism of some disaccharides like lactose.
- We will start in this lecture with fructose.
- Sucrose metabolism yields fructose (remember it's a disaccharide made of glucose + fructose).
- High-fructose corn syrup is a cheap and widely used sweetener made from corn starch.
- In general, fructose doesn't raise the blood sugar levels as much as glucose.
- In terms of metabolism, fructose can enter the glycolytic pathway through phosphorylation by hexokinase (on C6) producing fructose-6-phosphate then continuing the normal glycolytic pathway.
- Or it can use its own pathway through phosphorylation by fructokinase (on C1) producing fructose-1-phosphate which is cleaved directly by Aldolase B unlike in glycolysis.
- The results of this cleavage are two familiar molecules, Glyceraldehyde (without a phosphate) and Dihydroxyacetone phosphate.

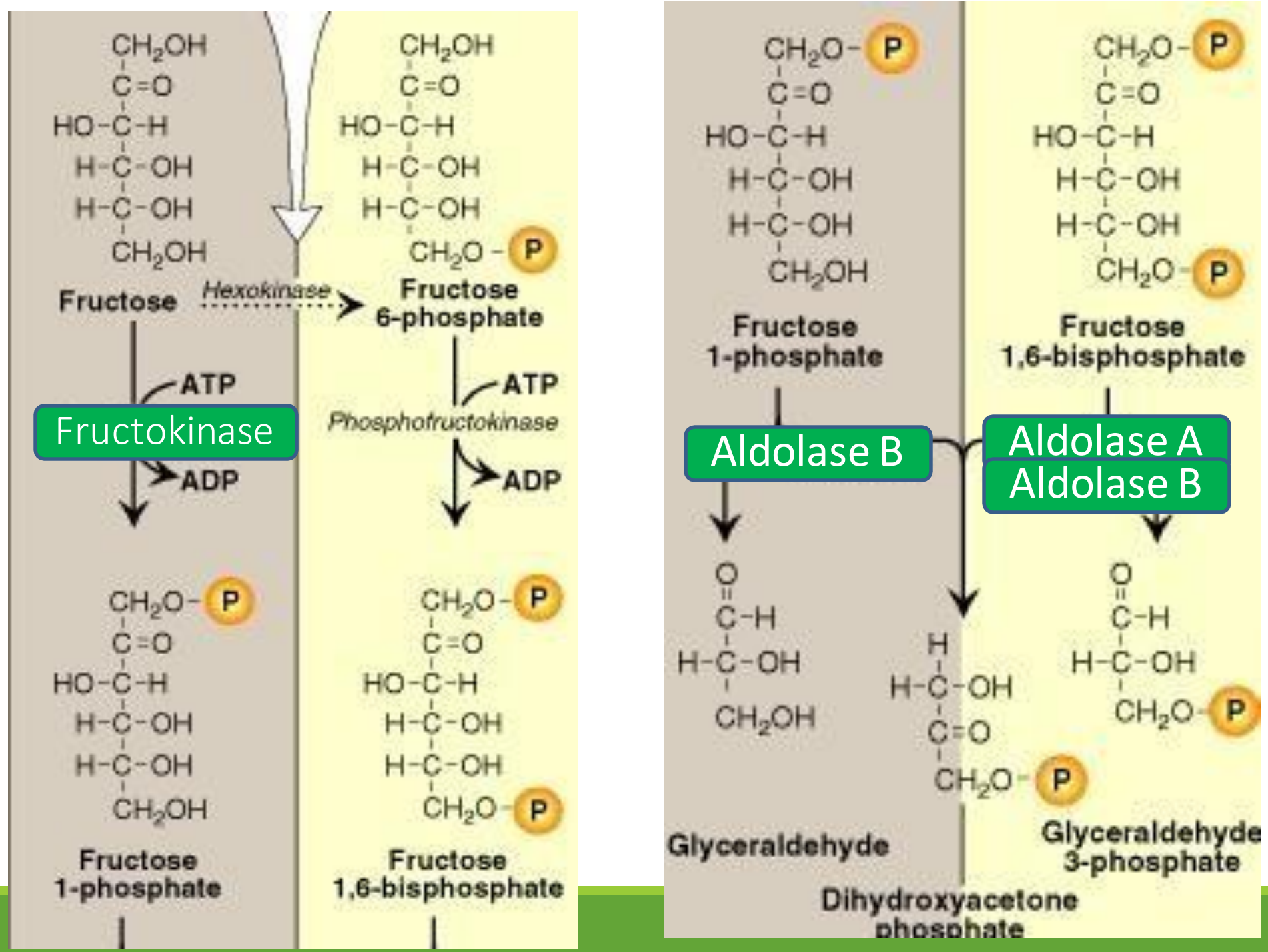


Fructose Metabolism

Hexokinase affinity to fructose is low

- The rate of fructose metabolism is more rapid than that of glucose because the trioses formed from fructose 1-phosphate bypass *phosphor fructokinase-1-P* the major rate-limiting step in glycolysis

- **The complement in this slide:**
- Dihydroxyacetone phosphate can be isomerized by triose phosphate isomerase (the same enzyme in glycolysis) to G3P and then enters glycolysis.
- Glyceraldehyde (without a phosphate) now must be phosphorylated to G3P and then enters glycolysis.
- This pathway is favored over the general pathway (the one using hexokinase) because it skips phosphofructokinase, which is the slowest step in glycolysis (rate limiting step).


Fructose
Hexokinase
Fructose 6-phosphate
ATP
Fructokinase
ADP
ATP
Phosphofructokinase
ADP
Fructose 1-phosphate
Fructose 1,6-bisphosphate
Fructose 1-phosphate
Fructose 1,6-bisphosphate
Aldolase B
Aldolase A
Aldolase B
Glyceraldehyde
Dihydroxyacetone phosphate
Glyceraldehyde 3-phosphate

- **The complement in this slide:**
- **The cleavage in the general pathway (the glycolytic pathway) can happen by the two isoforms of the enzyme aldolase, Aldolase A and Aldolase B.**
- **But in the specific pathway only Aldolase B can perform the cleavage.**
- **In summary:**
- **When fructose enters our body, it undergoes degradation through two main pathways: the general pathway and the specific pathway.**
- **The general pathway is less preferred as it has a low affinity for fructose. It initiates with the phosphorylation of C6 of fructose, resulting in the production of F6P. This compound is then further phosphorylated, continuing through the glycolytic pathway.**
- **On the other hand, the specific pathway, which is more favored, begins with the phosphorylation of C1 of fructose, producing F1P. Aldolase B then directly cleaves F1P, generating Glyceraldehyde and Dihydroxyacetone. Glyceraldehyde is phosphorylated and continues the glycolytic pathway, while Dihydroxyacetone is isomerized to G3P, also continuing the glycolytic pathway.**
- **It's worth noting that the general pathway can utilize both Aldolase A and B, while the specific pathway exclusively relies on Aldolase B**


فلسطين
اللهم كُن لفلسطين عونًا
اللهم إنّا لا نملك إلا الدعاء
لهم فيارب لا ترد لنا دعاء ولا تخيب لنا رجاء
اللهم أنصر ضعفهم فإن ليس لهم سواك

V2: slide no. 11:

This paragraph has been added:

NADH is the electron carrier that is most abundant and needed as NAD+ during reactions when we want to oxidize something (it will be reduced). On the other hand, NADPH is the electron carrier that is most abundant as NADPH and gets oxidized during reactions when we want to reduce something. In simpler terms, NADH is like a superhero that helps with oxidation, while NADPH is like a superhero that helps with reduction.

Slide no. 6:

reduction of NAD+ to NADH.

Slide no. 9:

(NADPH gets oxidised to form NADP+ and reducing O2)

Slide no. 7:

the ratio of NADH to NAD+ increase

Slide no. 3: **Ethanol can function as both a hydrophobic and hydrophilic molecule. Its hydrophobic nature enables it to easily pass through membranes.**

Slide no. 11:

by the enzyme ALDH into acetate.