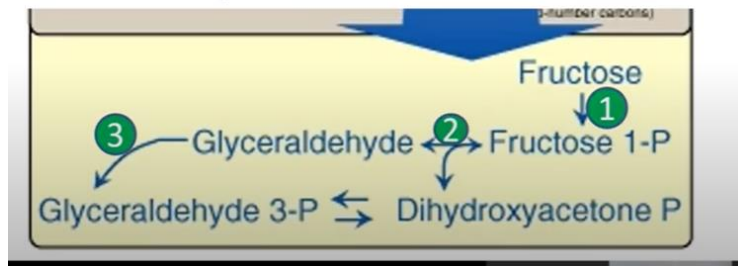


Metabolism of mono and disaccharides

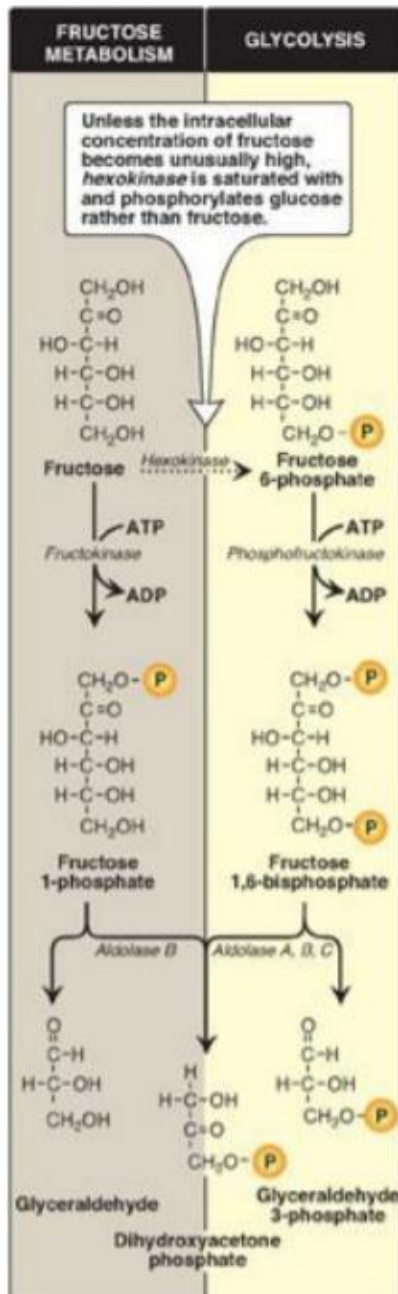
Fructose Metabolism

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



What was mentioned in the lecture:

Regarding metabolism of fructose, metabolism of fructose is important, fructose constitutes about 10% of our daily intake of calories, the most common source of fructose is sucrose, sucrose is hydrolyzed by sucrase into glucose and fructose, fructose is also abundant in honey fruits, and high-fructose corn syrup, it is extracted from corn and used in food industry, fructose is absorbed by small intestine and carried in the blood, it is not found in high concentration in the blood because it is rapidly removed from the blood into the liver, entrance of fructose into cells does not require insulin, because its entry is granted, and high concentration of fructose in the blood does not stimulate insulin secretion in contrast to glucose, fructose catabolism is depicted in the figure, firstly it is phosphorylated to fructose 1-phosphate by an enzyme called fructokinase, that prevents fructose to leak outside cells when after it enters, the second step is cleavage of glucose 1-phosphate into glyceraldehyde which is then phosphorylated to glyceraldehyde 3-phosphate and dihydroxyacetone which is then isomerized to glyceraldehyde 3-phosphate, the enzyme that catalyzes cleavage is also called aldolase because this is also an aldol cleavage, aldol cleavage is cleave of carbon-carbon bond, it cleaves between carbon #3 and carbon#4, on carbon #3 there is a hydroxyl group next to carbonyl group, after phosphorylation of glyceraldehyde and isomerization of dihydroxyacetone phosphate to glyceraldehyde 3-phosphate, glyceraldehyde 3-phosphate can enter glycolysis, therefore, there is only 3 steps that are unique to glycolysis, phosphorylation of fructose to fructose 1-phosphate, cleavage of fructose 6-phosphate and phosphorylation of glyceraldehyde to glyceraldehyde 3-phosphate, depending on cell's demands, glyceraldehyde 3-phosphate can go through glycolysis or gluconeogenesis.



What was mentioned in the lecture:

This is a comparison between phosphorylation of fructose by fructokinase into fructose 1-phosphate and phosphorylation of fructose by hexokinase into fructose 6-phosphate, fructose can be phosphorylated by hexokinase into fructose 6-phosphate than can directly enter glycolysis, but we do not depend a lot on this enzyme to catabolize fructose, because hexokinase functions intermittently in that case, this is minor reaction, because fructokinase has a much higher K_m toward fructose compared to hexokinase, therefore, hexokinase functions in fructose catabolism only if fructose concentration is high, but fructokinase can do it at very high concentrations, glucose is the favorite sugar of hexokinase.

On the down figure is a comparison between aldol cleavage of fructose 1,6-bisphosphate and fructose 1-phosphate, both can be cleaved, we have different isoforms of aldolase which are aldolase A, aldolase B and aldolase C, fructose 1-phosphate can only be cleaved by aldolase B, while fructose 1,6-bisphosphate can be cleaved by both aldolase A, B or C (it is a substrate all aldolases), therefore, deficiency of aldolase B is more dangerous, loss of A can be replaced by B but loss of B cannot be replaced by A.

Human expresses three forms of aldolase

Aldolase B

- Liver, kidney, small intestine

- Substrate

Fruc. 1 pphosphate

AND

Fruc. 1,6 bisphospate

↓activity → fructose
intolerance

Aldolase A

- In most tissues

- Substrate

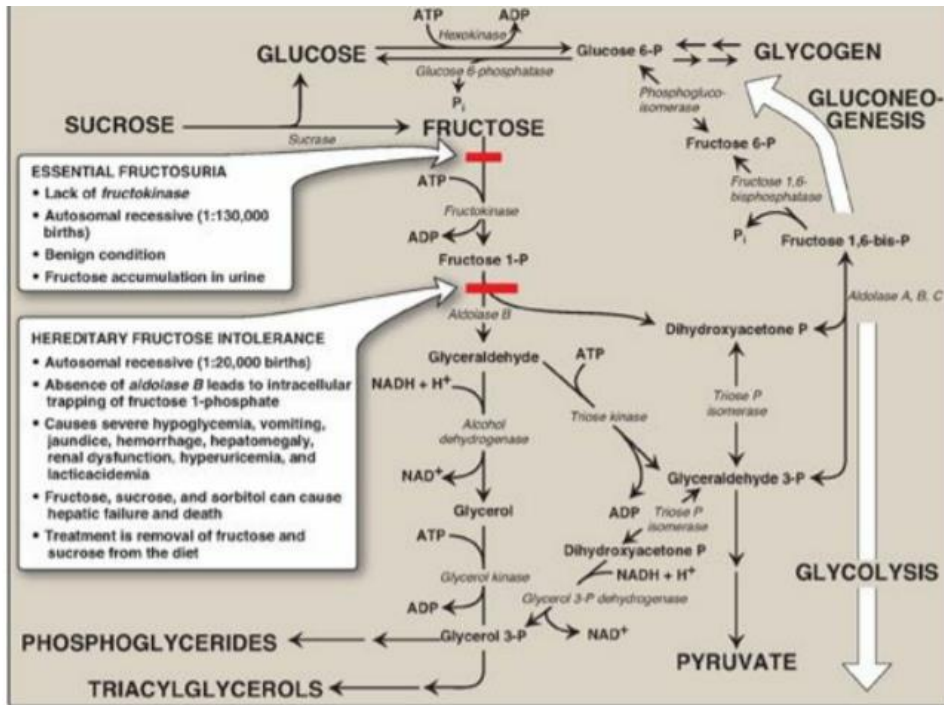
Fruc. 1,6 bisphospate

NOT

Fruc. 1 pphosphate

What was mentioned in the lecture:

This is a comparison between aldolase A and aldolase B, aldolase B is expressed in the liver, kidney and small intestine while aldolase A is expressed in almost all tissues, the liver is the main organ involved in fructose clearance from the blood, the substrates of aldolase B are fructose 1-phosphate and fructose 1,6-bisphosphate (broader specificity), while the substrate for aldolase A is only fructose 1,6-bisphosphate, there is not any other enzyme that can cleave fructose 1-phosphate other than aldolase B, therefore, decreased aldolase B means increased fructose intolerance (inability to catabolize fructose).



What was mentioned in the lecture:

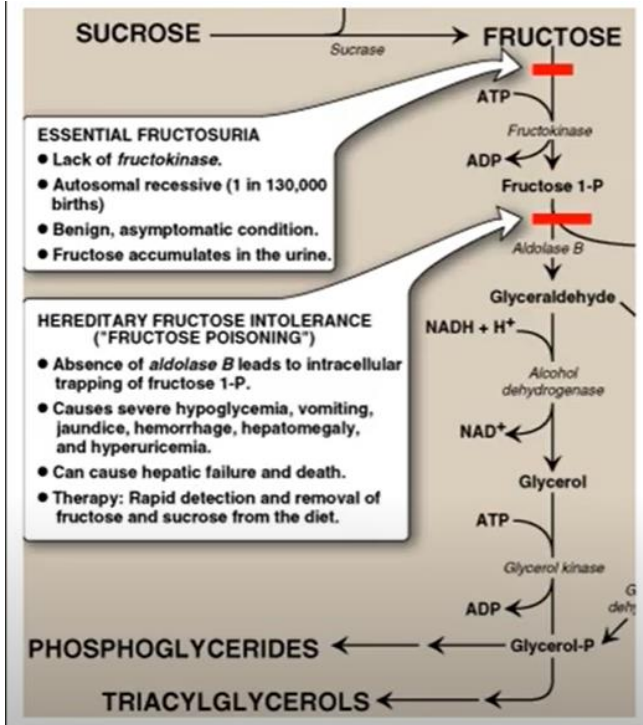
Those are the different fates of fructose.

Disorders of Fructose Metabolism

- Fructokinase Deficiency → essential fructosuria
 - Accumulation of fructose → fructosuria
 - Benign condition
- Aldolase Deficiency → hereditary fructose intolerance, (Fructose Poisoning)
 - Severe disturbance in liver and kidney metabolism
 - ↑↑↑ Fruc. 1-Phosph. → drop in P_i → drop in ATP
→ ↑↑ AMP → ↑ degradation of AMP
 - Hypoglycemia and lacticacidemia
 - Hepatic failure

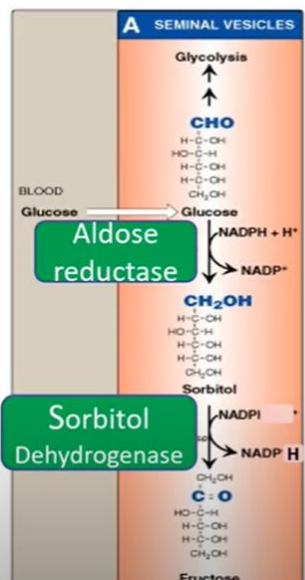
What was mentioned in the lecture:

Now we're going to talk about abnormalities of fructose metabolism, firstly, we'll talk about deficiency in fructokinase, the enzyme that catalyzes the first reaction in fructose catabolism, deficiency in this enzyme causes a condition known as fructosuria, because glucose is not phosphorylated and therefore cannot be trapped in cells, increasing its concentration in plasma, leading to presence of fructose in urine (fructosuria), it is a benign condition, actually that can be a good thing, because you are only absorbing half of the calories of sugar, and you'll worry about your weight, the worse thing is aldolase deficiency which is known as hereditary fructose intolerance or fructose poisoning, because it causes a severe disturbance in the liver and kidney's metabolism (organs involved in metabolism of fructose), because it causes accumulation of fructose 1-phosphate and therefore consuming of all inorganic phosphate causing a problem is oxidative phosphorylation and consequence ATP deficiency, which causes accumulation of AMP, less ATP in the liver means less gluconeogenesis and less inorganic phosphates means less glycogen degradation, therefore severe hypoglycemia, also drop in ATP causes lacticacidemia because lactate will be produced intensively, because many enzymes will be inhibited, that finally causes hepatic failure and death.



What was mentioned in the lecture:

this is a comparison between the two diseases, essential fructosuria (fructokinase deficiency) and hereditary fructose intolerance (aldolase B intolerance), notice that essential fructosuria is rare (1 in 130,000).



Conversion of glucose to fructose via sorbitol

Aldose Reductase:
Found in many tissues; Lens, retina, schwann cells, liver, kidney, ovaries, and seminal vesicle

Sorbitol Dehydrogenase:
Liver, ovaries and seminal vesicles

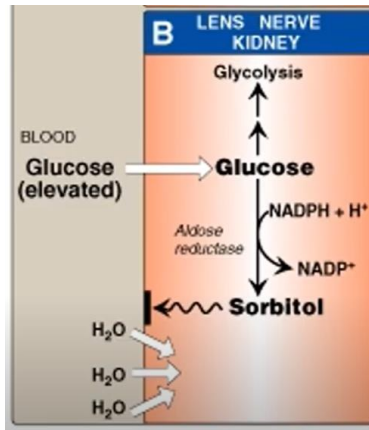
Fructose : the major energy source for sperm cells

What was mentioned in the lecture:

Glucose can be reduced into sorbitol (its aldehyde group will be converted into a hydroxyl group), which can be re-oxidized to fructose (the hydroxyl group of carbon no#2 will be oxidized into a ketone group), the intermediate between them is called sorbitol, which is 6-carbon compound each carrying a hydroxyl group only (not a sugar put polyalcohol), it is an artificial sweetener, it is used in gum production.

conversion of glucose to fructose and vice versa occur through this pathway, glucose and fructose can be reduced through aldose reductase which is

found many tissues including lens, retina, Schwann cells, liver, kidney, ovaries, and seminal vesicles, while sorbitol is oxidized through sorbitol dehydrogenase, is found only in ovaries, seminal vesicles, and the liver, why seminal vesicles? Because fructose is the major source of energy for sperms.



What was mentioned in the lecture:

Now if sorbitol dehydrogenase is deficient (like in the lens, kidney or nerve), and the glucose level is elevated, part of this glucose will be converted into sorbitol by aldose reductase, which will not be oxidized into fructose, that will cause will cause accumulation of sorbitol in the cells, and it is a high osmotic pressure small molecule, therefore, it will keep attracting water into cells, leading to tissue injury, if that happened in the lens for example, that will ultimately cause cataract, this mechanism of cataract is common among diabetic geriatrics.

Galactose Metabolism

- Epimer of glucose
- Sources: component of lactose, glycolipids and glycoproteins
- UDP Galactose; an Intermediate in Galactose Metabolism

β -Galactose Glucose

Galactose

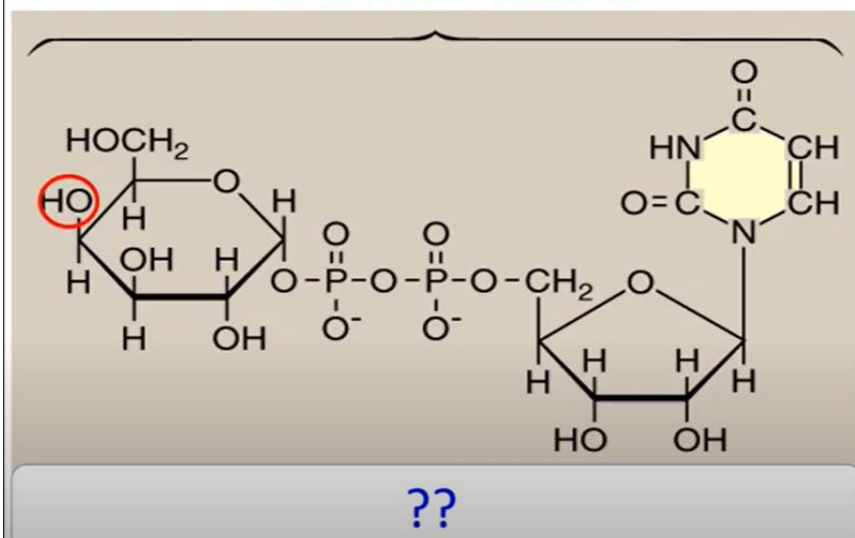
Glucose

C-4 epimer

What was mentioned in the lecture:

Galactose is an epimer for glucose, meaning that they differ only by the orientation of a hydroxyl group on carbon no#4, lactose is main source of galactose in our diet, but it also present in glycoproteins and glycolipids, to synthesize or to catabolize galactose, UDP-galactose is an important intermediate.

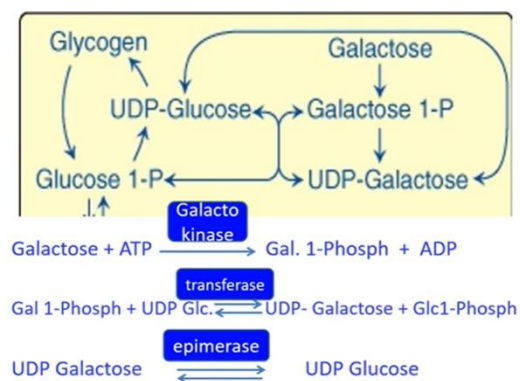
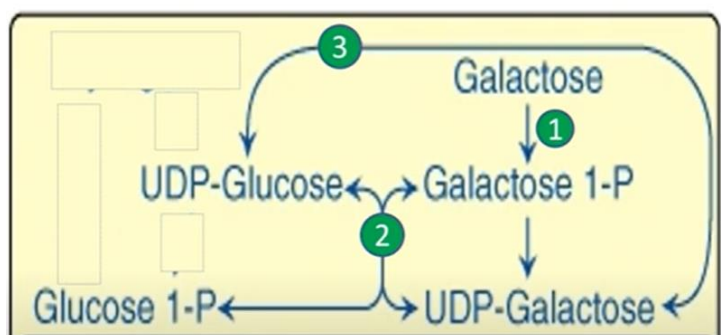
UDP Galactose; an Intermediate in Galactose Metabolism



What was mentioned in the lecture:

This is the structure of UDP-galactose, (uridine phosphate galactose), it is an important intermediate in galactose metabolism.

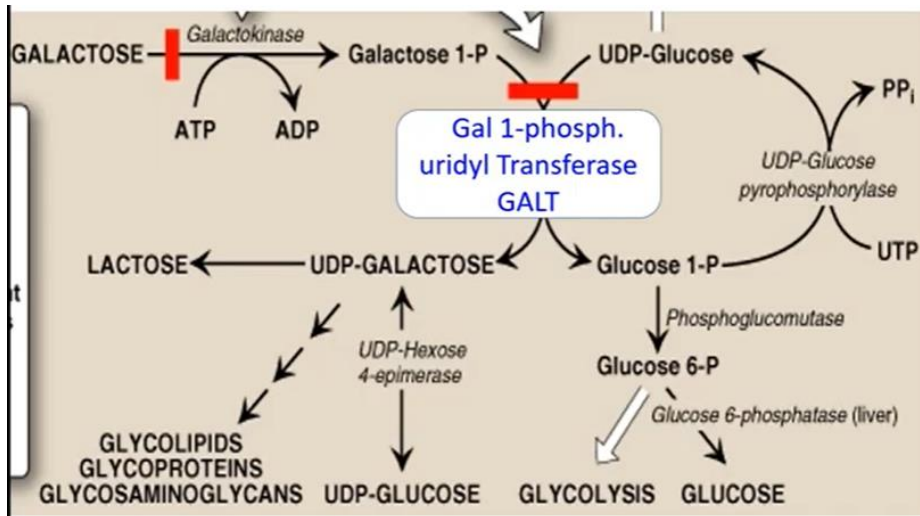
Galactose Metabolism



What was mentioned in the lecture:

This the pathway of galactose metabolism, it begins by phosphorylation of galactose to galactose 1-phosphate, this reaction is catalyzed by galactokinase, in the second reaction, Gal 1-P reacts with UDP-Glu producing UDP-Gal and Glu 1-P, this reaction is catalyzed by a transferase enzyme that glucose form UDP and put galactose in place, in the third reaction, UDP-galactose is isomerized to UDP-glucose by an

epimerase enzyme, it is a cycle that ends with glucose 1-phosphate, glucose 1-phosphate is an intermediate in glycogen synthesis, therefore, we can utilize galactose to synthesize glycogen.



What was mentioned in the lecture:

The transferase involved in galactose metabolism is called galactose 1-phosphate uridyl transferase, abbreviated as GALT.

Disorders of Galactose Metabolism

- Deficiency of GALT → classic Galactosemia
- Accumulation of Galactose 1-Phosphate and galactose
- Similar consequences to those in fructose intolerance
- Deficiency of Galaktokinase
- Galactose→ Galactitol
- Deficiency of Galactokinase →
- Accumulation of **Galactose** → → Galactitol

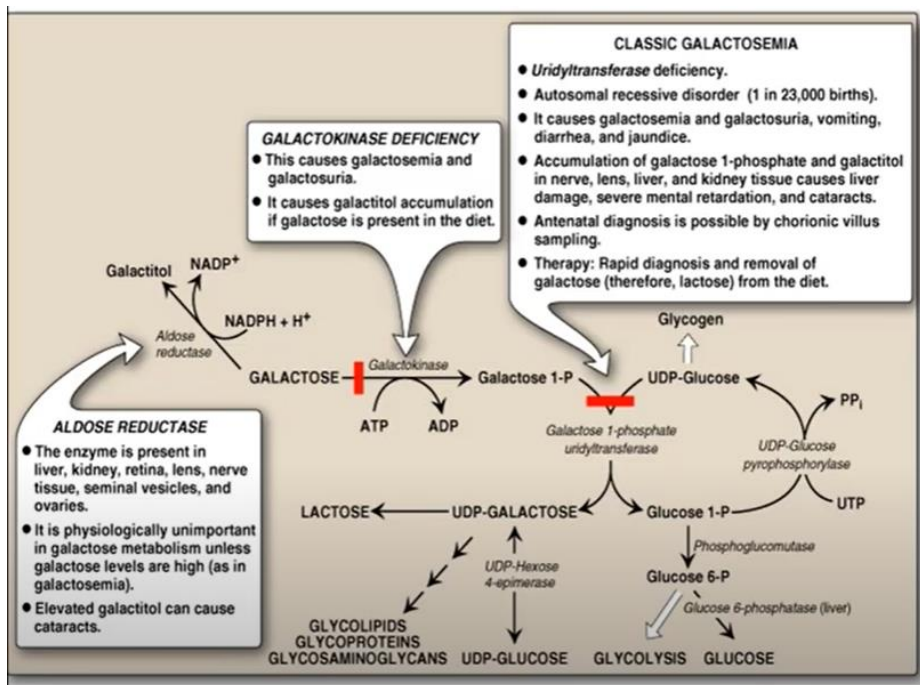
What was mentioned in the lecture:

A disorder of galactose metabolism is caused by a deficiency of GALT is called galactosemia, it causes accumulation of galactose 1-phosphate and galactose in cells, this disease have similar consequences to

those of fructose intolerance, in this disease, also inorganic phosphates are trapped causing a disruption in ATP synthesis.

there is another disease that can be caused by deficiency in galactokinase, in this case, galactose wouldn't be phosphorylated, that can cause reduction of galactose into galactitol (similar to sorbitol), and accumulation of galactitol, that can cause cataract.

How can we manage a disease in which an enzyme involved in a certain monosaccharide metabolism is deficient? By diet restriction, if -for example- a person have galactosemia, he should avoid food that contain galactose such as milk. These diseases must be diagnosed early, because they might cause an irreversible damage.



What was mentioned in the lecture:

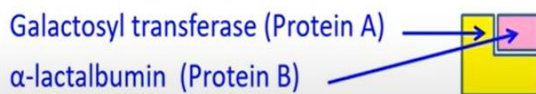
Galactosemia is an autosomal recessive disorder, it affects one from every 23,000 child, it is a recessive meaning that a person could a carrier for an affected gene but looks fine, a person needs two abnormal genes to appear (we are diploid) 50% percent of the normal amount of GLAT would be sufficient, this enzyme can be very active, actually most enzymes deficiencies are recessive.

Lactose Synthesis

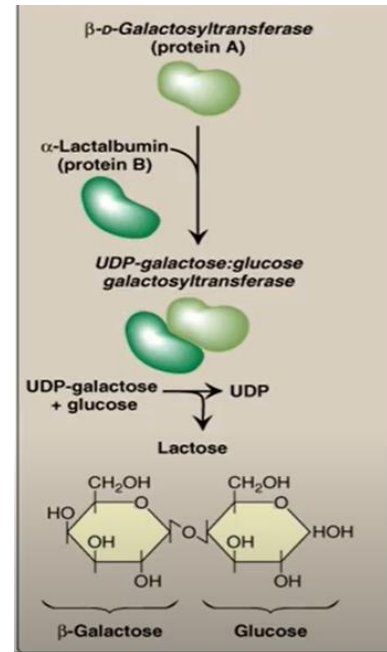
- Lactose is Galactosyl β (1 \rightarrow 4) glucose
- Galactosyl β (1 \rightarrow 4) glucose is found in glycolipids and glycoproteins



- Lactose Synthase: complex of 2 proteins



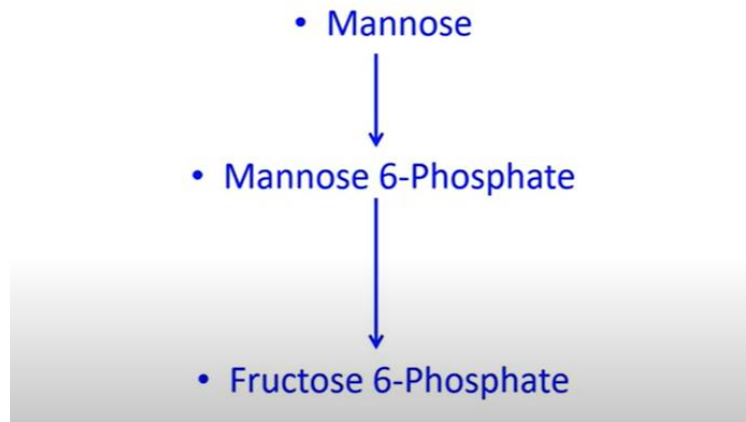
In glycolipids synthesis



What was mentioned in the lecture:

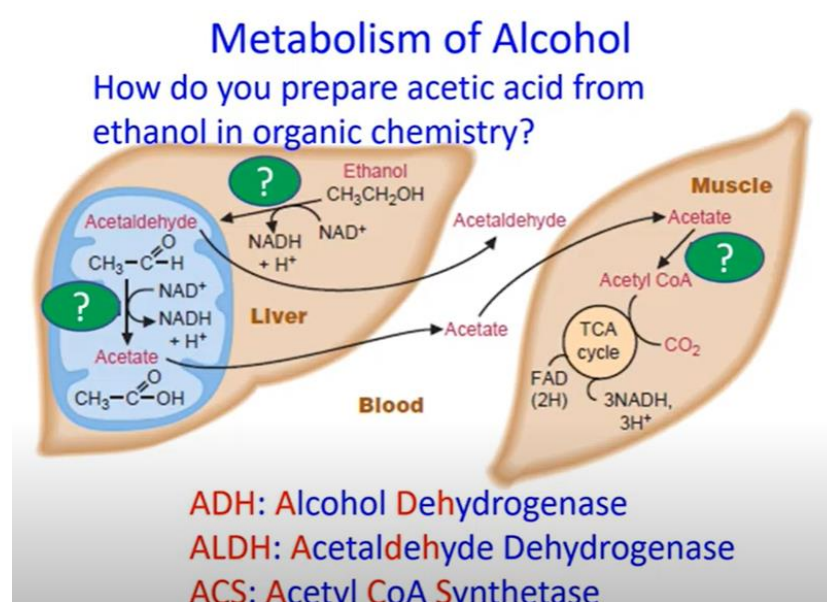
Lactose is a disaccharide formed by attaching carbon #1 of galactose to carbon #4 of glucose, the bond galactosyl β 1 \rightarrow 4 is found also in glycolipids and glycoproteins, lactose is synthesized by addition of a glucose molecule to a galactose molecule, the galactose is transferred to the glucose form a UDP-galactose, because carbon #1 of galactose should be activated, the enzyme is called lactose synthase, it has been revealed that lactose synthase is actually a complex of two proteins, one is called galactosyl transferase (protein A) and the other is called α -lactalbumin (protein B), together they are important to lactate synthesis, this enzyme is found in the mammary gland of lactating women, but that doesn't mean that it is not found in males or other organs, because most tissue require synthesis of glycolipids or glycoproteins, for this we need only protein A which adds galactose to carbohydrate chains of glycolipids and glycoproteins, lactose is produced only for milk.

Mannose conversion to Fructose 6-phosphate



What was mentioned in the lecture:

Mannose is rare in food, because it is found only on glycoproteins and glycolipids, it is metabolized as follows: firstly phosphorylated to mannose 6-phosphate then isomerized to fructose 6-phosphate which can enter glycolysis.

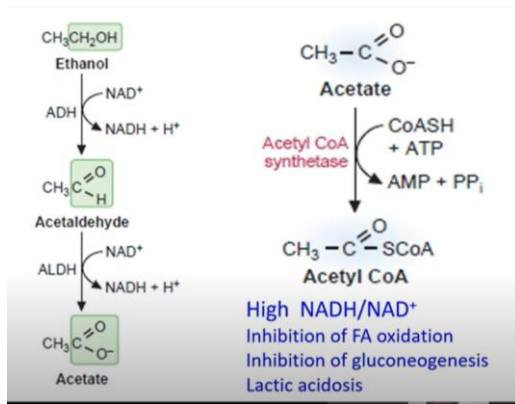


What was mentioned in the lecture:

Ethanol is converted to acetic acid through oxidation on two steps: firstly oxidation to acetaldehyde then oxidation of acetaldehyde to acetic acid, the enzyme that catalyzes oxidation of ethanol to acetaldehyde is alcohol dehydrogenase which uses NAD^+ as an electron acceptor, you cannot stop on just formation acetaldehyde because it is a toxic material, therefore, acetaldehyde is further oxidized into acetate by

acetaldehyde dehydrogenase which also uses NAD^+ , alcohol metabolism take place mainly in the liver, then acetate is carried through the blood stream into muscles, acetate must attached to Coenzyme A to be utilized, attaching acetate to CoA involves formation of a thioester bond and this reaction is carried by an enzyme called acetyl CoA synthetase. (the difference between a synthase and a synthetase is that a synthase doesn't require energy), acetyl CoA synthetase requires energy because the reaction it catalyzes involve formation of a high energy thioester bond.

Alcohol is an energy source to the cell, it is estimated that one gram of ethanol produces 7 kcals , but actually this a bad source of energy because booze is devoid of vitamins and minerals, while wheat for example have all this, that's why alcoholism is associated with vitamin deficiency.



Ingestion of ethanol causes increasing in the NADH/NAD^+ ratio, because its metabolism involves two oxidation reactions, than in turn causes inhibition of fatty acid synthesis, inhibition of gluconeogenesis, and lactic acidosis because gluconeogenesis require pyruvate, but high NADH cause it to be reduced to lactate.