Carbohydrates Metabolism

Review of Carbohydrates Digestion[1] and absorption[2] of carbohydrates

Suggested Readings:

1: Lippincott's Illustrated reviews: Biochemistry

2: Marks' Basic Medical Biochemistry

Carbohydrates Metabolism

What was mentioned in the slide:

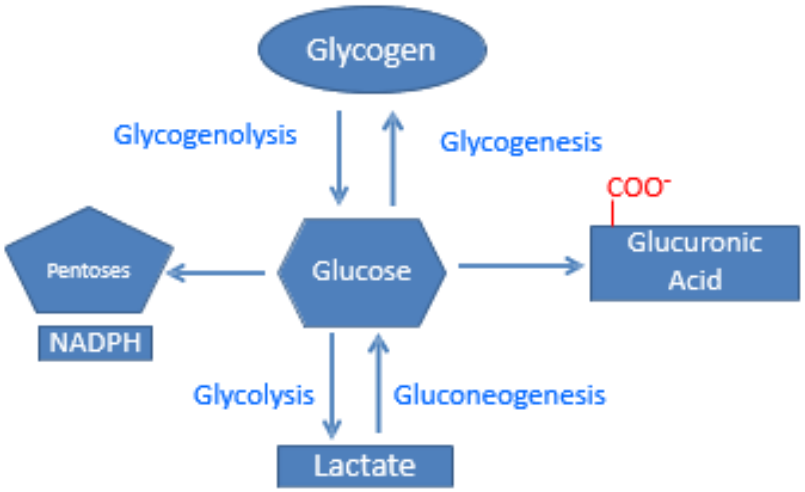
- Objectives
  - Utilization of Glucose→ Energy
  - Non-Carbohydrates→ Glucose
  - Storage of Glucose→ Glycogen
  - Release of Glucose from Glycogen
  - Reducing Power NADPH→ GSH
  - Interconversion of sugars
  - Glucuronic acid → Drug metabolism

What was mentioned in the lecture:

The major objective of carbohydrate metabolism is production of energy in the form of ATP, we know that the production of energy occurs mainly by citric acid cycle, followed by oxidative phosphorylation, but utilization of glucose for production of energy means to convert glucose into the form that can be oxidized in the citric acid cycle which is acetyl CoA, acetyl CoA is the fuel of the citric acid cycle, to convert to glucose into acetyl CoA is the major objective of the carbohydrate metabolism, and we will see this in details, the second thing is conversion of non-carbohydrates into glucose, by the way, even though glucose is the major source of energy in our body (in our cells) and It is very important molecule, yet, the glucose is not essential. and we can live without eating glucose because our cells has the ability to convert non-carbohydrate substrates like amino acids into glucose, conversion of non-carbohydrates into glucose is the second objective of carbohydrate metabolism, we can convert lactate, glycerol, amino acids, into glucose, fatty acids cannot be converted into glucose directly, we will emphasize this as we go, conversion of carbohydrates into glucose is the measure is the second major purpose objective of carbohydrate metabolism, thirdly, storage of glucose, we get the glucose from the digestion of the carbohydrates, we take the glucose intermittently, we take it with meals, So how can we manage to get the glucose in between meals? The glucose cannot be kept as it is (as a small molecule) in the plasma or in the cells, it has to be converted into a form that can be stored, and the form that can be stored is called glycogen, glycogen is a polysaccharide that is made of a large number of glucose units, when we need the glucose, we have to be able to convert the glycogen back into glucose, releasing glucose from glycogen is also a major objective of carbohydrate metabolism, regarding the reducing power,

We need reducing power to keep molecules in the reduced state, reducing power is obtained by synthesis of a reducing agent, a dinucleotide called NADPH, It is very similar to NADH that we use in oxidative phosphorylation, but NADPH is used only for the reactions which require reduction, NADPH can be used as it is, or it can be used to convert glutathione, GSH is the reduced form of glutathione, but to convert the glutathione from the oxidized form to the reduced form, that requires NADPH that is obtained from from glucose metabolism.
Regarding the interconversion of sugars, we may take in food fructose, galactose, lactose, etc. how can we convert these into glucose ? If we need to synthesize the ribonucleic acids like RNA, we need ribose, So how can we convert the glucose into Ribose? Or mannose into glucose? etcetera. So we need the ability to convert the sugars from one form to the other, And lastly, synthesis of a glucuronic acid, glucuronic acid is the carboxylic acid form for glucose, It is required for drug metabolism, So to make glucuronic acid from glucose is a major objective of carbohydrate metabolism.

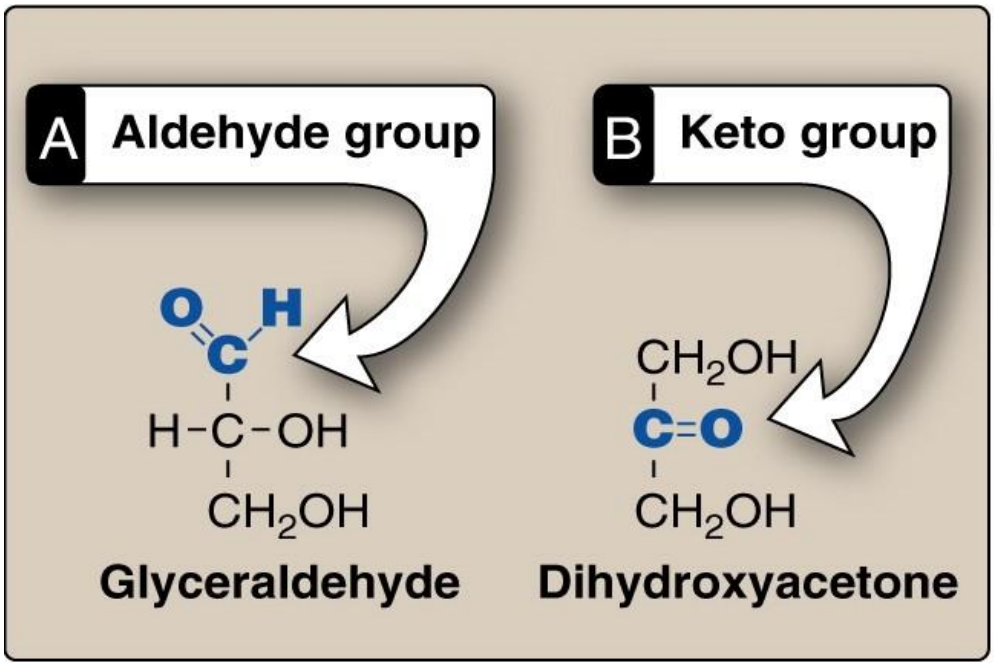
An Over-all Picture



What was mentioned in the lecture:

here we can show the overall picture, glucose is in the center, it is the major sugar in the plasma and it is major sugar in the cells, we can convert the glucose into a small molecule called pyruvate and lactate (which is the reduced form of pyruvate) by a pathway called glycolysis, glycolysis convert glucose into a smaller form with the production of some energy, conversion of glucose to lactate or pyruvate releases some energy from glucose and by this conversion we can prepare glucose for oxidation by the citric acid cycle. on the other hand, we can convert amino acids, lactate and glycerol back into glucose by a process called gluconeogenesis, gluconeogenesis is synthesis of glucose from non-carbohydrate sources.
Regarding synthesis of glucuronic acid, glucuronic acid is very similar to glucose, except that the carbon number six is oxidized to carboxylic acid group, And lastly we can use glucose to make pentoses (like ribose and deoxyribose) and NADPH by a pathway. we are going to see all these pathways: the glycolysis, gluconeogenesis, glycogen synthesis, glycogen degradation, and the production of Pentoses, reducing power (NADP) and glucuronic acid.

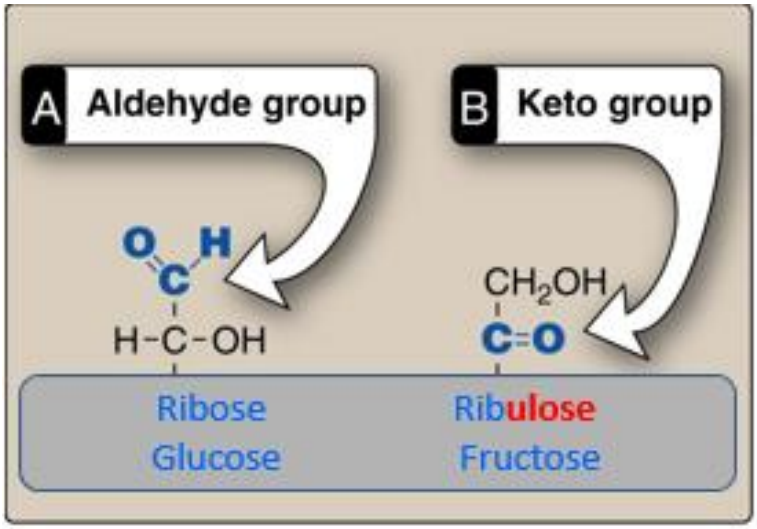
Examples of aldoses and ketoses 1



What was mentioned in the lecture:

To review the structure and chemistry of carbohydrates, the carbohydrates (sugars) must have an aldehyde or a ketone functional group, and they must have at least two carbons with hydroxyl groups, the figure depict examples of sugars that are very simple because it has only three carbons, two of them carrying -OH groups, and one carbon is forming the aldehyde or the ketone group, these two sugars are examples of the most simple sugars, we call them trioses because they contain three carbons, a triose can be either an aldose if it has an aldehyde group, or ketose if it has a ketone group.

Examples of aldoses and ketoses 2



What was mentioned in the lecture:

we have a variable number of carbons in sugars, we can have three, four, five, six, etc. they can be aldoses like glucose and ribose, or they can be ketoses like ribulose and fructose.

Examples of monosaccharides found in human

Generic names	Examples
3 carbons: trioses	Glyceraldehyde
4 carbons: tetroses	Erythrose
5 carbons: pentoses	Ribose
6 carbons: hexoses	Glucose
7 carbons: heptoses	Sedoheptulose
9 carbons: nonoses	Neuraminic acid

What was mentioned in the lecture:

Those are examples of monosaccharides found in a human, there are many sugars in nature, but in human, these are the most important ones with other two sugars, according to the number of carbons, if you have three carbons you call it triose and that includes glyceraldehyde and dihydroxyacetone , if you have four carbons it is called a tetrose and that includes erythrose, if it has five carbons, it's called pentose and that include ribose, if it has six carbons it is called hexose and that includes glucose, mannose and fructose which is a ketose, if it has seven carbons we call it heptose and that includes sedoheptulose, if it has nine carbons it is called nonoses and that includes neuraminic acid, those are some of the most important sugars found in the human.

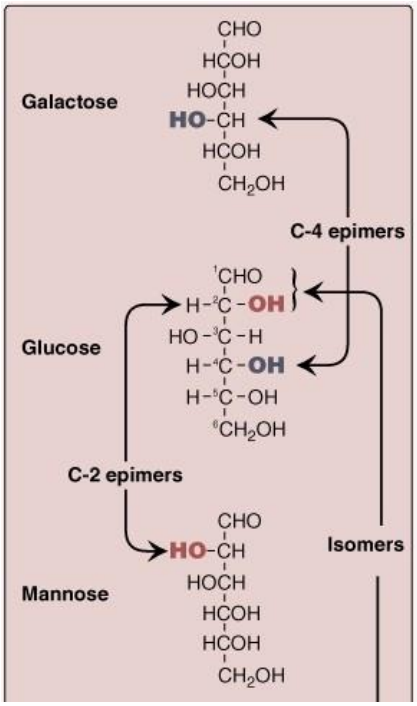
Isomers: Epimers are isomers:

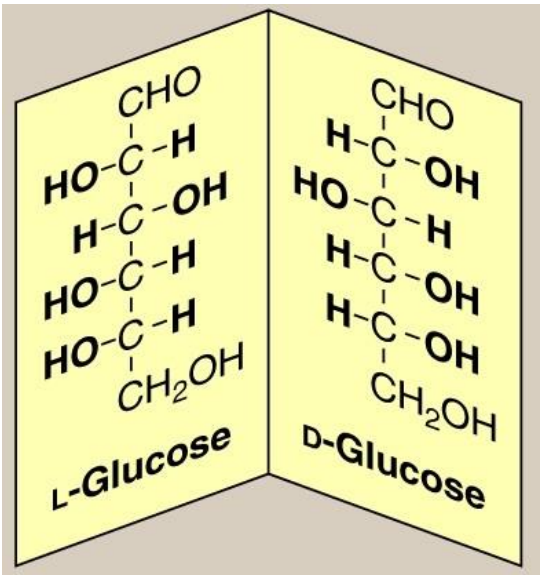
What was mentioned in the slide:

Changing the orientation of one hydroxyl group will produce a different sugar

What was mentioned in the lecture:

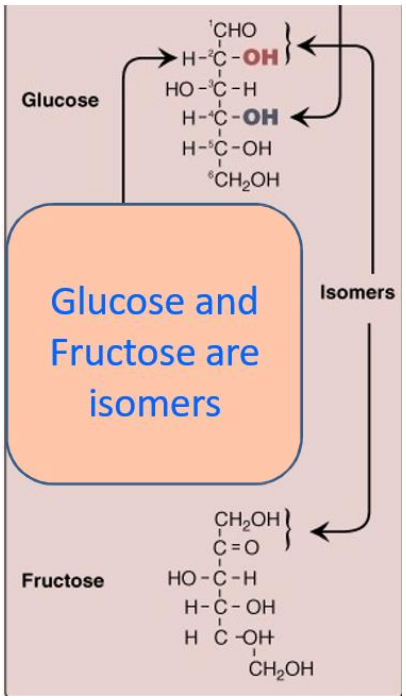
the number of carbon atoms and the different orientation of atoms around the carbons makes isomers, isomers have the same chemical formula, but they have different structures, we have many sugars that are isomers, isomers differ slightly, we have also what we call epimers, to understand epimers, Notice the difference between glucose and galactose, both of them are hexoses, both of them are aldoses, but if you noticed carbon #4, , the hydroxyl group borne by this carbon in glucose is drawn to the right, but in galactose. it is drawn out to the left, is there a difference? Yes, they have different shape in space. (different three dimensional structure), carbon #2, #3,#4, #5 are asymmetric (chiral) carbons, and it makes a difference if the hydroxyl group is drawn to the right or to the left, changing the orientation of one hydroxyl group will produce different sugar, these two sugars (glucose and galactose are epimers), regarding glucose and mannose, The difference between them is in the orientation of hydroxyl group at carbon #2 this time, glucose and mannose are epimers, but notice that galactose and mannose are not epimers, why? because they differ by the orientation of two hydroxyl groups rather than one, different orientation of hydroxyl group at one carbon will produce epimers, but different orientation at two carbons will produce just isomers.





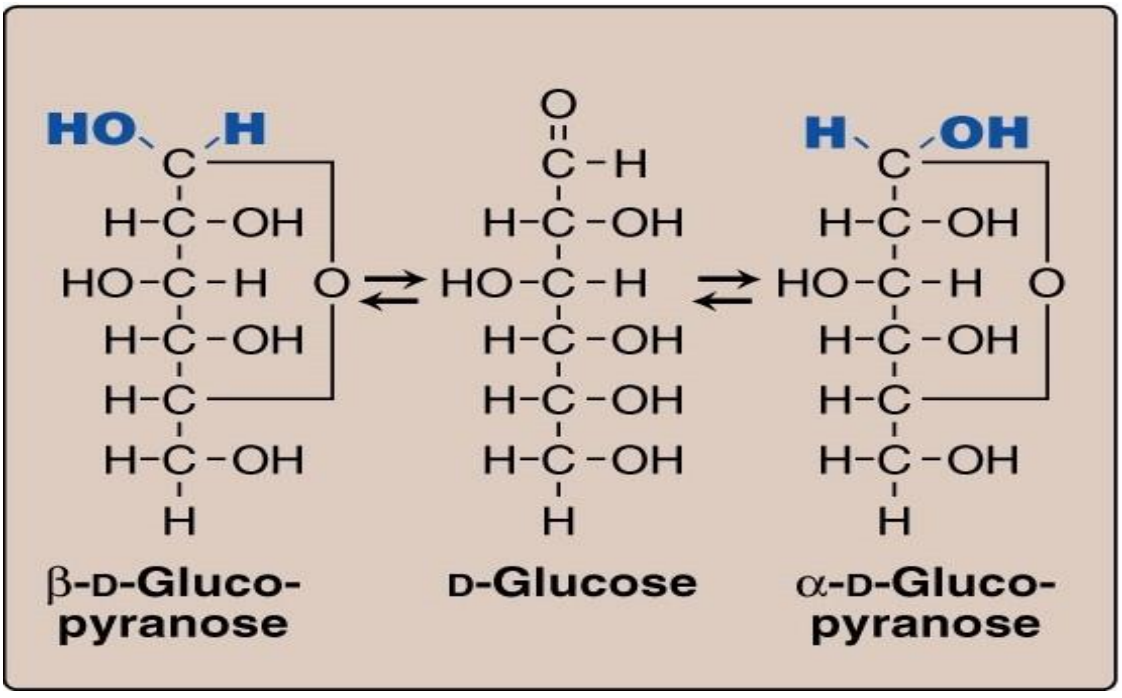
What was mentioned in the lecture:

Another type of isomerism is stereoisomerism, because carbons #2,#3, #4, #5 are asymmetric (chiral) carbons, we can change the orientation of the hydroxyl group at each one, , if you change only one hydroxyl group, you get a different sugar, for example, if you rotated the hydroxyl group of carbon #2 of glucose, it becomes mannose, If you rotated the hydroxyl group at carbon #4 of glucose. You'll get galactose, if you changed all of them (at all carbons) at D-glucose, you'll get the mirror image of the D-glucose, which is L-glucose, D-glucose and L-glucose have the same chemical properties (like oxidation-reduction), but they differ in the orientation of rotation the plane of the polarized light, the other thing is that they have different biological properties because the L-glucose and D-glucose differ in their three dimensional structure, an enzyme that recognized the D-glucose will not recognize the L-glucose (remember : an enzyme binds a substrate on at least three sites), it is like you wear your right shoe in your left foot.



What was mentioned in the lecture:

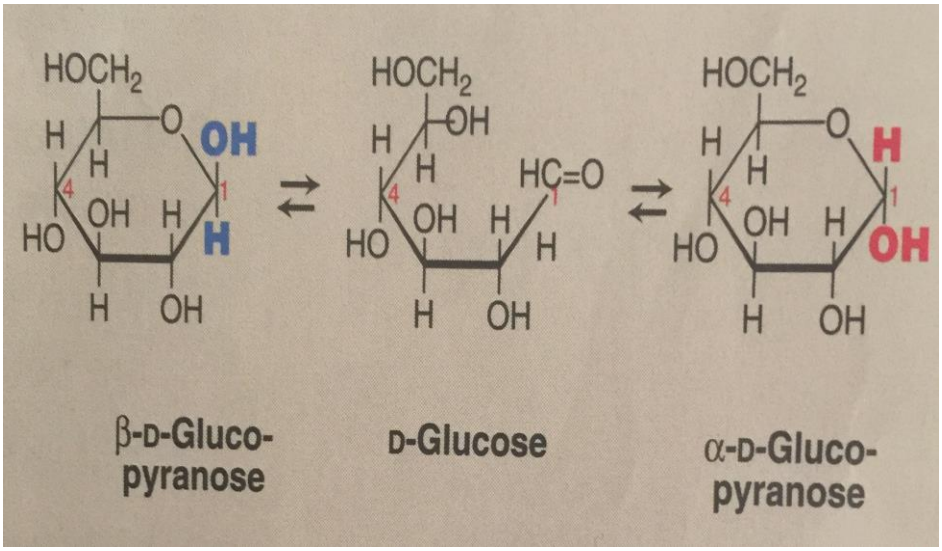
Fructose and glucose are isomers also, what is the difference between glucose and fructose? They differ only by carbons #1 and #2. In glucose, carbon#1 bears an aldehyde group while carbon #2 bears a hydroxyl group, But carbon #1 of fructose bears a hydroxyl group, while carbon #2 bears a ketone group, hydroxyl groups on carbon #3, #4, and #5 have the same orientation in both of them, we can say that they differ only in that one of them is an aldose while the other is a ketose.



What was mentioned in the lecture:

D- glucose both hydroxyl groups and an aldehyde group, usually if you mix an aldehyde with an alcohol, they can react without an enzyme, they can react, the aldehyde group can react with the hydroxyl group to produce a hemiacetal, glucose structure is usually represented as a straight chain, but glucose's structure

is not actually a straight chain, at some point, the aldehyde group of carbon #1 reacts with carbon #5' hydroxyl group to make an internal hemiacetal, forming a ring structure, this ring structure (six membered ring with one being an oxygen atom) is called pyranose, this is actually the form of glucose that is found in our body, by this reaction, carbon #1 will become bearing a hydroxyl group which have two probabilities of orientation , if it is above the ring then it is β- glucose, and if it is below the ring then it is α-glucose.

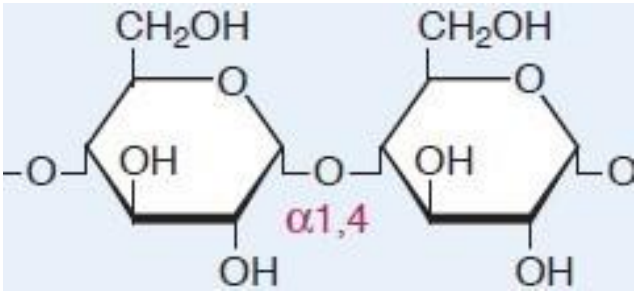


What was mentioned in the lecture:

Glucose's ring structure the structure can be drawn like this, where the ring is perpendicular to the plane of the paper, if the hydroxyl group was directed to the write in the chain conformation, we draw it below the ring. and if the hydroxyl group was directed to the left in the chain conformation, we draw it above the ring, this is the form of glucose that is found in nature, depending on the orientation of hydroxyl group of carbon #1 which exist only when glucose is in the ring conformation, we have two anomers, α-glucose if it was below the level of the ring and β-glucose if it was above the level of the ring.

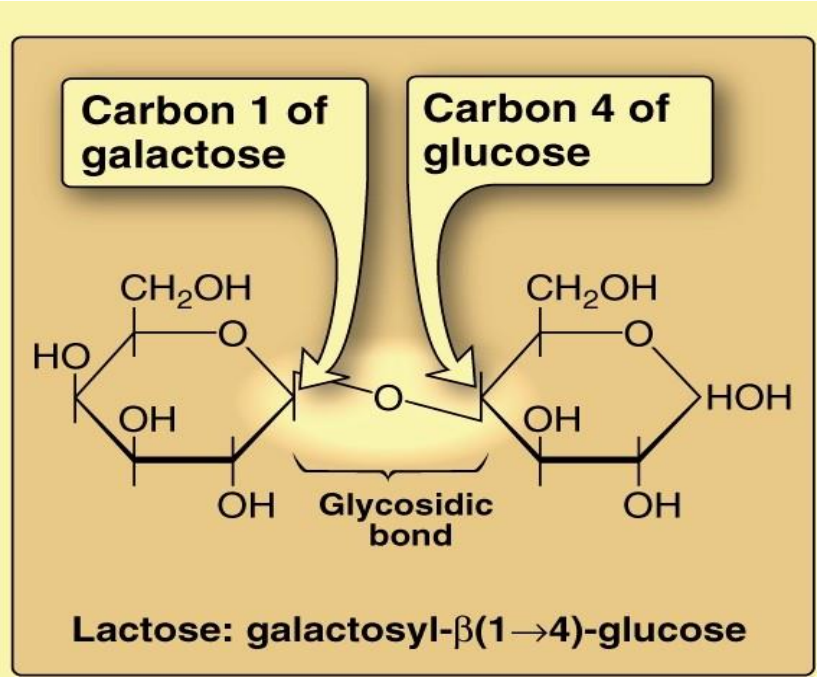
Disaccharide: A sugar made of two sugar units joined by glycosidic bond

Maltose: a disaccharide made from two glucose units



What was mentioned in the lecture:

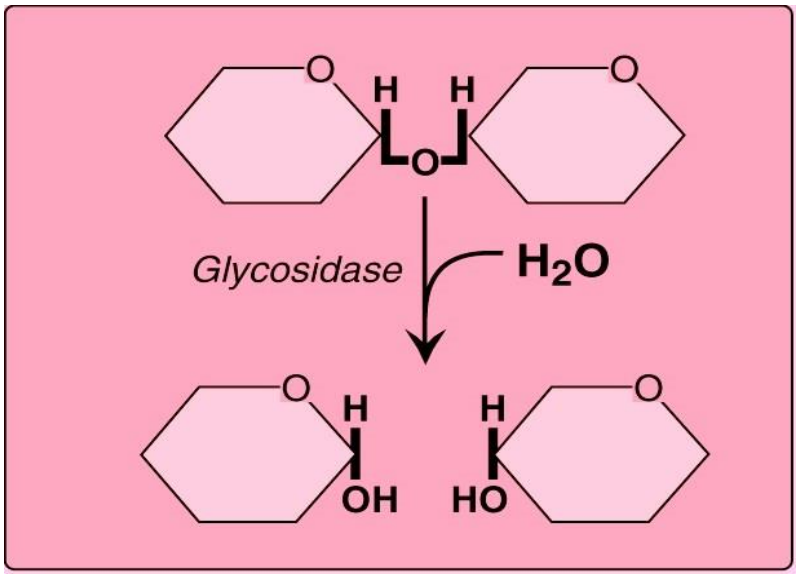
a disaccharide is a sugar made of two sugar units joined by a glycosidic bond, hydroxyl groups in ring-structures of a sugar can be joined to another hydroxyl group forming a glycosidic bond, that's how disaccharides, polysaccharides, etcetera are formed, maltose is a disaccharide made from two glucose units, the glycosidic bond of maltose occurs by condensation of hydroxyl group at carbon #1 of one glucose molecules with another hydroxyl group at carbon #4 of another glucose molecule with loss of a water molecule (-OH + -OH = -O- +H_2O), , because the Oxygen atom is below the ring, we call this bond α 1→4 glycosidic bond, notice that we have a free hydroxyl group at carbon #1 of one of the glucose molecules, making it possible for another glucose to join, forming polymers of glucose.



What was mentioned in the lecture:

lactose on the other hand is formed from galactose and glucose, They are joined by a glycosidic bond, but the here the bond is in the β orientation, because the oxygen atom is above the ring.

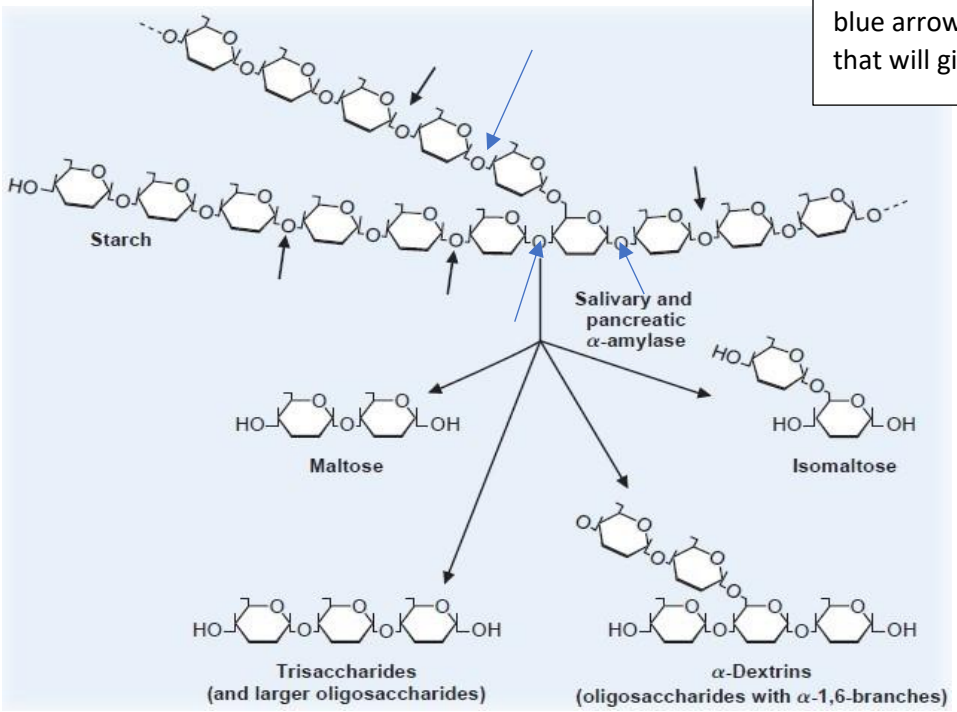
Glycosidic bond is cleaved by glycosidase



What was mentioned in the lecture:

Glycosidic bond can be cleaved by glycosidases, which are enzymes that cleave the glycosidic bonds, Glucosidases- by adding water to the disaccharide- bring back the two units of the sugar, examples on glycosidases include maltase which convert Maltose into two glucose molecules, sucrase which cleaves sucrose, and lactase which cleaves lactose.
For further information, please check this:
https://drive.google.com/file/d/1KGJhOSVpQoDBTQa5gaojwreHHeoWnlOQ/view?usp=sharing

If the bonds that have blue arrows are cleaved, that will give isomaltose

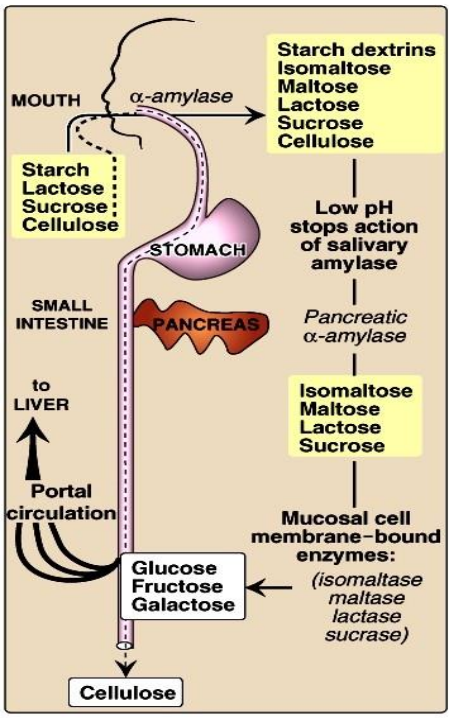


What was mentioned in the lecture:

This figure depicts the structure of starch which is the storage polysaccharide of plants, the starch is formed form polymers of glucose with α 1→4 glycosidic bonds at the main chain and the bond at branching point is between a carbon #6 of an original chain's glucose residue with a carbon #1 of a branch's glucose residue, starch is formed by millions of glucose residues, similar to starch is glycogen which is considered animal starch.
Digestion of starch starts in the mouth, it starts as soon as we start to chew food that contains carbohydrates (like bread), the saliva in the mouth which is secreted from the salivary glands (mainly the parotid gland, the amount of saliva secreted each day is normally one liter, we continuously swallow our saliva) contain an enzyme called α-amylase, amylase is a glycosidase, it can hydrolyze glycosidic bond in the starch, it is an endoglycosidase, meaning that it act within the chains, not just cleaving the terminal residues as the case of exoglycosidases, it cleaves those bonds randomly, meaning that we'll not get identical fragments, but we'll have short, very short, tall and very tall fragments, the time in which the food remains in the mouth is very short (only seconds), after that the food will move into the stomach, the α amylase is inhibited by the highest acidity of the stomach.

The products of the random cleaving of α-glycosidases are a mixture of fragments varying in length, α amylase might cleave two bonds close to each other giving maltose, it might give fragments of three sugar units, it might cleave bonds around a branching point (see the figure) giving a disaccharide which have α 1→6 glycosidic bond, this disaccharide is called isomaltose, or at might give larger oligosaccharides called α-dextrin fragments.

Digestion by α amylase lasts only for a short period of time, it is important in digestion of food debris that stick in the mouth. (not to be fermenated)



What was mentioned in the lecture:

Where does the digestion continues? The starch digestion starts in the mouth, the products of α-amylase are the dextrin fragments, maltose and isomaltose. Lactose, sucrose and cellulose, do not change in the mouth and reach the stomach as they are, cellulose is a polysaccharide of glucose, but it doesn't get digested in the mouth because it has β glycosidic bond instead of α, the low pH in the stomach acts to stop the action of salivary α amylase (as many enzymes, it gets denatured or destroyed by high acidity), the pH of the stomach is 1.5, it is very acidic, this is not suitable for the action of the amylase, after that, the contents of the stomach is released to the duodenum, in the duodenum, because the pancreas secretes bicarbonate (HCO_3^-), the pH is neutralized, along with the bicarbonate, the pancreas also secretes pancreatic α-amylase which is more potent than salivary amylase , which continues to start to continues to digest the large oligosaccharides which are α-dextrins, finally resulting in more maltose and isomaltose , while lactose, sucrose and cellulose do not change by the α-amylase, how these gonna be digested? On the outer membrane of small intestine's cells (on the brush border of them which is formed by microvilli, remember: we've taken that with Dr. Hanan in the histology course), there are enzymes that act on the disaccharides, like maltose, isomaltose, lactose and sucrose, and the oligosaccharides like dextrins, those enzymes are membrane bound (they are plasma membrane proteins), and they are not secreted into the lumen of small intestine, there are four of these, each have different specificity, so the disaccharides like maltose, isomaltose, lactose (the main sugar of milk), sucrose (beet sugar that we use it for drinks), all of these are digested by the membrane bound enzymes of the small intestine : maltase, isomaltase, sucrase and lactase. (the name indicates the specificity), the end products are glucose, galactose and fructose, those are absorbed through small intestine's cells and then they are carried into the portal circulation by the portal vein carrying them to the liver, all these sugars produced from digestion firstly go to the liver, the liver is the major organ that takes these products from the circulation, notice that cellulose hasn't been digested, cellulose is a type of dietary fibers, these cannot be digested, the most common one of these is cellulose, which exist in food derived from plants like leaves, etc. cellulose is important in our diet because it helps in the function of small intestine.

What was mentioned in the textbook:

The digestion of starch begins in the mouth .The **salivary** glands releases **α-amylase**, which converts starch to smaller polysaccharides called **α- dextrins**. Salivary α-amylase is inactivated by the acidity of the stomach (hydrochloric acid [HCl]). **Pancreatic α-amylase** and bicarbonate are secreted by the exocrine pancreas (remember form the anatomy course: the pancreas is a mixed gland, it has both endocrine (like insulin) and exocrine activity) into the lumen of the small intestine, where bicarbonate neutralizes the gastric secretions. Pancreatic α-amylase continues the digestion of α-dextrins, converting them to disaccharides (**maltose**), trisaccharides (**maltotriose**), and oligosaccharides called **limit dextrins**. Limit dextrins usually contain four to nine glucosyl residues and an **isomaltose** branch (two glucosyl residues attached through an α-1,6-glycosidic bond).
Dietary fiber, composed principally of polysaccharides, cannot be digested by enzymes in the human intestinal tract. In the colon, dietary fiber and other nondigested carbohydrates may be converted to

gases (H_2, CO_2, and methane) and short-chain fatty acids (principally acetic acid, propionic acid, and butyric acid) by bacteria in the colon.

Mucosal cell membrane-bound enzymes

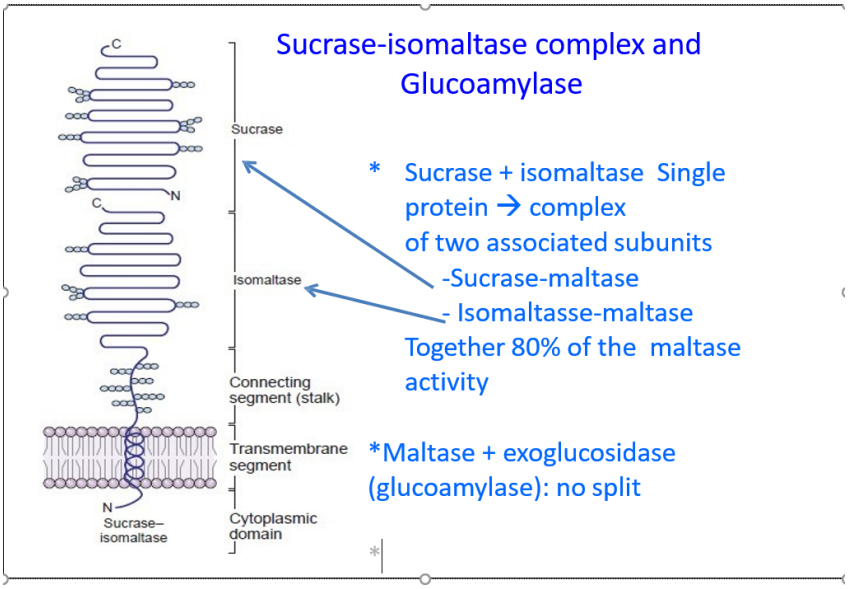
ENZYME	Bond Cleaved	Substrates
Isomaltase	α 1→ 6	Isomaltose
Maltase	α 1→ 4	Maltose
Sucrase	α 1→ 2	Sucrose
Lactase	β 1→ 4	Lactose
Trehalase	α 1→ 1	Trehalose
Exoglucosidase	α 1→ 4	Glucoamylose

What was mentioned in the lecture:

those are the cell-membrane bound enzymes of the small intestine, we have isomaltase which cleaves α 1→6 glycosidic bonds of isomaltose, maltase cleaves alpha 1-4 glycosidic bonds of maltose, sucrase cleaves the glycosidic bond which links carbon #1 of glucose with carbon #2 of fructose in sucrose, producing glucose and fructose, lactase cleaves the beta glycosidic bond that links carbon #1 of galactose with carbon #4 of glucose in lactose, trehalase acts on trehalose which is not a common sugar, we have finally the exoglucosidase which cleaves one lateral (terminal) glucose residue at a time from dextrins (glucoamylose), we have some overlapping in specificity between some of these enzymes, not all of them act on one substrate.

What was mentioned in the textbook:

The digestion of the disaccharides lactose and sucrose, as well as further digestion of maltose, maltotriose, and limit dextrins, occurs through **disaccharidases** attached to the membrane surface of the **brush border** (**microvilli**) of intestinal epithelial cells. **Glucoamylase** hydrolyzes the α-1,4- bonds of dextrins. The **sucrase–isomaltase complex** hydrolyzes sucrose, most of maltose, and almost all of the isomaltose formed by glucoamylase from limit dextrins. (limit dextrins have many 1→4 bonds and a 1→6 bond, glucoamylase cleaves 1→4 of dextrins but not 1→6, therefore, the products of glucoamylase are glucose and isomaltose which is a disaccharide of two glucose residues with an α 1→6 bond) **Lactase-glycosylceramidase** (β-glycosidase) hydrolyzes the β- glycosidic bonds in **lactose** and glycolipids (remember: glycolipids are lipid molecules attached to a carbohydrate chain, actually they are a carbohydrate chains attached to a ceramide molecule) . A fourth disaccharidase complex, **trehalase**, hydrolyzes the bond (an α-1,1-glycosidic bond) between two glucosyl units in the sugar trehalose. The monosaccharides produced by these hydrolases (glucose, fructose, and galactose) are then transported into the intestinal epithelial cells.



What was mentioned in the lecture:

We have complexes of intestinal enzymes that act on the disaccharides, the first one is sucrase-isomaltase complex, the figure the depicts the membrane of small intestine's cells, we see that this complex is extracellular, it doesn't function inside the cell, yet it is attached to membrane and therefore it doesn't move with the contents of small intestine, it doesn't move with food, but while food is moving, it becomes stuck to this enzymes, the only way of loss of this complex is through exfoliation of cells when they die, this complex has two subunits, this enzyme is synthesized as one polypeptide chain (as a single protein), then this chain is cleaved at one peptide bond to two subunits after secretion, one of them remain attached of the membrane (isomaltase-maltase) and other is peripherally attached to the first one by noncovalent interactions (sucrase-maltase), the substrates of this enzyme are sucrose, isomaltose, maltose, and dextrins, most maltose that we eat is digested (degraded) by this complex (80% of maltose).
ما يغرك الاسم الانزيم هاض برضو بكسر المالتوز
The second complex is maltase-exoglucosidase (also called maltase-glucoamylase) is very similar to sucrase-isomaltase complex but there is no splitting in its structure (it is one polypeptide chain), it is also an extracellular enzyme and has two domains, but these two domains are still connected by a peptide bond.

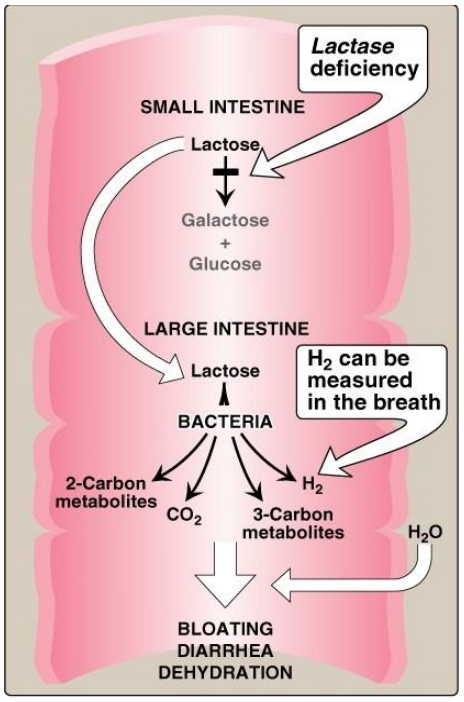
FIG. 27.5. The major portion of the sucrase–isomaltase complex, containing the catalytic sites, protrudes from the absorptive cells into the lumen of the intestine. Other domains of the protein form a connecting segment (stalk) and an anchoring segment that extends through the membrane into the cell. The complex is synthesized as a single polypeptide chain that is split into its two enzyme subunits extracellularly. Each subunit is a domain with a catalytic site (distinct sucrase–maltase and isomaltase–maltase sites). In spite of their maltase activity, these catalytic sites are often called just *sucrase* and *isomaltase*.

What was mentioned in the textbook:

Glucoamylase and the sucrase–isomaltase complex have similar structures and exhibit a great deal of sequence homogeneity (they have similar amino acids in their structure). A membrane-spanning domain near the N terminus attaches the protein to the luminal membrane. The long polypeptide chain forms two globular domains, each with a catalytic site (active site). In glucoamylase, the two catalytic sites have similar activities, with only small differences in substrate specificity. The protein is heavily glycosylated (it is a glycoprotein), with oligosaccharides that protect it from digestive proteases. (digestive proteases are enzymes that digest proteins that we eat, they include trypsin, chymotrypsin)

Glucoamylase is an *exoglycosidase* that is specific for the α-1,4-bonds between glucosyl residues . It begins at the nonreducing end (because the polysaccharide has α 1→4 glycosidic bonds, one end of the chain will have a free carbon #1's hydroxyl group, this is the reducing end, while the other end will have a free carbon #4's hydroxyl group, this is the non-reducing end) of a polysaccharide or limit dextrin, and it sequentially hydrolyzes the bonds to release glucose monosaccharides. It will digest a limit dextrin down to isomaltose, the glucosyl disaccharide with an α-1,6-branch, that is subsequently hydrolyzed principally by the isomaltase activity in the sucrase–isomaltase complex.

Abnormal Degradation of Disaccharides



What was mentioned in the slide:

- Lactase deficiency:
- ½ world's population
- Sucrase isomaltase deficiency:
- Causes:
  - Genetics
  - Variety of intestinal diseases
  - Malnutrition
  - Injury of mucosa i.e. by drugs
  - Severe diarrhea

Lactase Maximal activity is @ 1 month of age

Declines ----- >> adult level at 5 to 7 year of age

10 % of infant level

1 cup of milk (9 grams of lactose) → loss of 1 liter of extracellular fluid

What was mentioned in the lecture:

Lactase is the enzyme that acts on lactose producing glucose and galactose, lactose is the major sugar of milk, from that it has got its name (lac means milk in Latin), (fun fact: even similac and serilac have got their names from milk because they are alternatives for milk), lactase deficiency affects half of the world's population, (there are cases of sucrase-isomaltase deficiency, but it is not common), lactase deficiency have many causes, it can be genetic, meaning that it is there since birth, babies who have genetic lactase deficiency suffer from diarrhea and abdominal pain making them cry always, that be solved by using lactose-free milk, it can also be caused by a variety of intestinal diseases, like diarrhea, because in this case, cells die, so we lose the enzyme, diarrhea can be treated with oral rehydration solutions like (salt and sugar solutions or 7-up, 7-up contains glucose and salts), lactase deficiency also can be caused by malnutrition, injury of mucosa by drugs, and severe diarrhea, so people with diarrhea must avoid diary products because the enzyme is already being lost. If a baby or any person with diarrhea drinks milk, it is exaggerated more. Because diarrhea causes death of the epithelial cells of small intestine and the first enzyme we lose in that case is lactase, the lactase is at its maximal activity when

the baby is one-month-old, lactase activity decreases through life, lactase activity decline too much at the age of 5-7 (when the child's milk consumption decreases), it reaches 10% of the infant's activity at puberty, that is more apparent in certain societies, in Jordan's people, the lactase activity is weak generally.
Note: if a baby has severe diarrhea, we tell his mom to not lactate him to a week, to give a chance for the cells to rebuild themselves and produces more lactase.

What happens if a patient has lactase deficiency? (pathophysiology of lactase deficiency)

The process by which lactose is converted into galactose and glucose is broken because there is no lactase, so lactose accumulates until it reaches the large intestine which have a plenty of bacteria, this bacteria is able to utilize this lactose, the bacteria metabolizes lactose into 2-carbon metabolites like acetic acid, CO_2, 3-carbon metabolites and even molecular hydrogen (H_2), that causes diarrhea because those are small molecules which have high osmotic pressure and therefore they can prevent water to be transported form the intestine to the blood stream and they even pull water from capillaries, that watey diarrhea and dehydration, that also cause bloating الشعور بالانتفاخ .
1 cup of milk contains 90 g of lactose, therefore, undigested 250 ml of milk cause loss of one liter of ECF.
Milk was used in the past to treat peptic ulcer because it decreases stomach acidity.
Dry milk, fresh milk and even human mothers' milk all contain lactose.

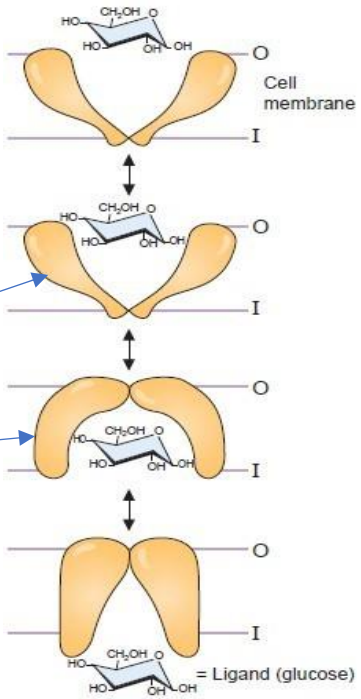
Prevalence of Late-onset Lactase Deficiency

Group	Prevalence (%)
US population	
Asians	100
American Indians (Oklahoma)	95
Black Americans	81
Mexican Americans	56
White Americans	24
Other populations	
Ibo, Yoruba (Nigeria)	89
Italians	71
Aborigines (Australia)	67
Greeks	53
Danes	3
Dutch	0

What was mentioned in the lecture:

This figure depicts the prevalence of late onset lactase deficiency (remember from community medicine course: prevalence means the ratio of number people who have the disease to the population, it measures a disease's burden عبئ), late onset lactase deficiency means lactase deficiency that is not genetic and hasn't been there since birth, the table above was made by a study made on American society (U.S. society is very multicultural), 100% of Asian Americans have lactase deficiency, while 95% of

American Indians have this diseases, the prevalence is also high in black Americans at 81% but it is low in white Americans, lactase deficiency is not very common in people of European ancestry, notice that it do not present in Dutch people, (Netherlands (Holland) is the country of cows 🐄), the prevalence of lactase deficiency in Arab people in high.



Absorption of Sugars

What was mentioned in the slide:

Polar molecules cannot diffuse

A: Na^+-independent facilitated diffusion transport

GLUT 1-----GLUT 14

Glc. Movement follows concentration gradient

Two conformation states

What was mentioned in the lecture:

Regarding absorption of sugars, digestion of polysaccharides and disaccharides will give monosaccharides like glucose, fructose and galactose, it is known that sugars are very polar (soluble) molecules and therefore cannot diffuse through membranes, therefore, they need carrier proteins, an example is the glucose carrier, this carrier is an integral membrane protein, once glucose binds to it, the carrier protein changes its conformation so as the glucose molecule that was facing the outside now will face the inside, then the glucose molecules will detach from the carrier and enter the cell, we two types of glucose's carrier proteins: the first one is Na^+-independent as the one depicted in figure, this carrier is concentration-dependent passive transporter, it moves glucose down its concentration gradient (from high concentration to low concentration), and it doesn't require energy, 14 types of this passive glucose carrier (GLUT) have been identified (GLUT1-GLUT14), GLUT1, 2, 3, 4, 5, are the most important ones, this glucose carrier has two conformational states, in one, the binding site faces the extracellular site and on the other state the binding site faces the cytosol, the state of binding depends on the concentration, if there is a high concentration of glucose, it will bind this carrier (in whatever conformation state), but glucose do not bind intensively if present with low concentration. (meaning that even if we have high concentration of glucose in the cytosol but concentration in the extracellular compartment, it will leak through this carrier to the outside of the cell) (extra info: one enters the cell, glucose is phosphorylated into glucose 6-phosphate, so that it will not bind the carrier again and leak from the cell).

Na^+-monosaccharide co-transporter system (SGLT)

What was mentioned in the slide:

* Against concentration gradient.
* Small intestine: Active uptake from lumen of intestine.
* Kidney: reabsorption of glucose in proximal tubule.

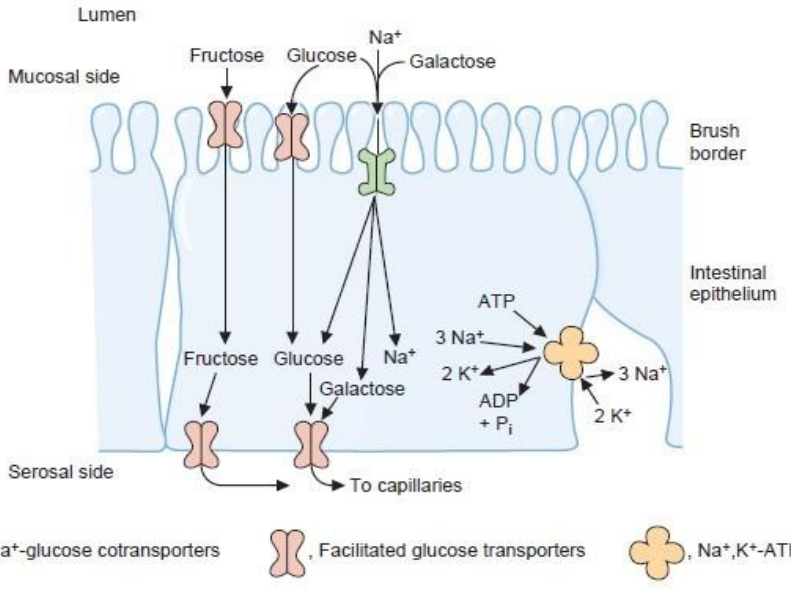
What was mentioned in the lecture:

The other type of monosaccharide transporters is Na^+- dependent, this transporter can transport glucose against its concentration gradient (form low concentration to high concentration), this type of transporters is important for the function of small intestine, it uptakes glucose from the lumen of small intestine, why do we need this? To absorb every molecule of glucose, we need glucose absorption to continue until the last molecule, we need to absorb glucose even if its concentration in the lumen of small intestine is very very low, otherwise absorption will stop at the moment when intracellular glucose's concentration is equal to that of the lumen, that would be a waste.

Na^+-glucose transporter also exist in the proximal tubule of the nephron of the kidney (الناقلة هاي موجودة بالأنبوبة الملتوية القريبة تبعت الوحدة الأنبوبية الكلوية الي أخدناها بالتوجيهي)

In the kidney, also small molecules in the blood are filtrated through the membranes of the glomeruli (glomeruli is plural of glomerulus و الي هي الكبّة الموجودة بالوحدة الأنبوبية الكلوية) , including amino acids and glucose, those substances must be reabsorbed, otherwise, glucose will leak with urine, and we need this transporter to be active transporter (able to transport against concentration), otherwise, we'll lose half of our blood glucose with urine (glucose reabsorption will stop at equal concentration).

Na^+-monosaccharide cotransporter system (SGLT)



DONE BY AHM

What was mentioned in the lecture:

This Na^+-monosaccharide transporter is specific for glucose and galactose (the facilitated transporter is specific for glucose and fructose) , it will transport monosaccharide only if there were sodium, sodium will bind the transporter among with monosaccharide and both of them will transported to the inside of the cell (remember form the physiology course: this type of transport is called secondary active co-transport, here we use energy, but not in the from of ATP, rather, in the form of sodium gradient), the intracellular sodium concentration is very small, therefore it moves down its concentration gradient from the lumen of small intestine into the cells carrying glucose with it, once inside the cell, sodium is pumped again outside the cell by Na^+-K^+ pump which uses ATP.

We had said that diarrhea can be treated with oral rehydration solutions (like 7-up and salt & sugar solution), that helps in glucose absorption, because absorption of glucose requires sodium which is lost with water in the case diarrhea, but if we want to compensate the lost sodium using oral rehydration solutions we must give glucose with it, because sodium doesn't enter the cells without glucose and vice versa.

Table 27.5 Properties of the GLUT 1 to GLUT 5 Isoforms of the Glucose Transport Proteins

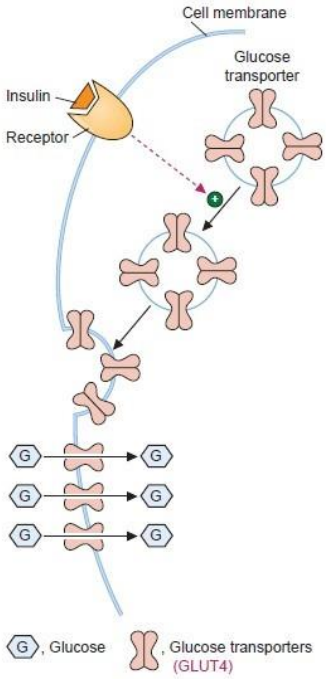
Transporter	*Tissue Distribution*	*Comments*
GLUT 1	Human erythrocyte Blood–brain barrier Blood–retinal barrier Blood–placental barrier Blood–testis barrier	Expressed in cell types with barrier functions; a high-affinity glucose transport system
GLUT 2	Liver Kidney Pancreatic β-cell Serosal surface of intestinal mucosa cells	A high-capacity, low-affinity transporter May be used as the glucose sensor in the pancreas
GLUT 3	Brain (neurons)	Major transporter in the central nervous system; a high-affinity system
GLUT 4	Adipose tissue Skeletal muscle Heart muscle	Insulin-sensitive transporter. In the presence of insulin, the number of GLUT 4 transporters increases on the cell surface; a high-affinity system
GLUT 5	Intestinal epithelium Spermatozoa	This is actually a fructose transporter
GLUT 7	Glucogenic tissues	at endoplasmic reticulum membrane

What was mentioned in the lecture:

This is a comparison between the various isoforms of GLUT (glucose passive carrier protein), GLUT1 has high affinity to glucose, it binds glucose even at if its concentrations in the surroundings are low, (do not be confused, what we mean by " low concentration" is that glucose is deficient is all the body like in starving condition, not that they transport glucose against a concentration gradient), GLUT1 exist in erythrocytes (red blood cells), blood-brain barrier, blood-retinal barrier, blood-placental barrier, and blood-testis barrier, these tissues is highly dependent on glucose, so they should take glucose even when it present at low concentrations (for example: RBCs do not possess mitochondria, therefore they depend completely on glycolysis for energy (no TCA or OXPHOS) that's why they are highly dependent on glucose).

(have fun with these extra info: one of the functions of blood-placental barrier (placenta = المشيمة ، الكيس الموجود داخل الرحم و بكون جواه الجنين) is that it prevents the blood of the mother and the embryo's blood to get mixed, if that happen when the mother and embryo have different blood types, that might be dangerous,

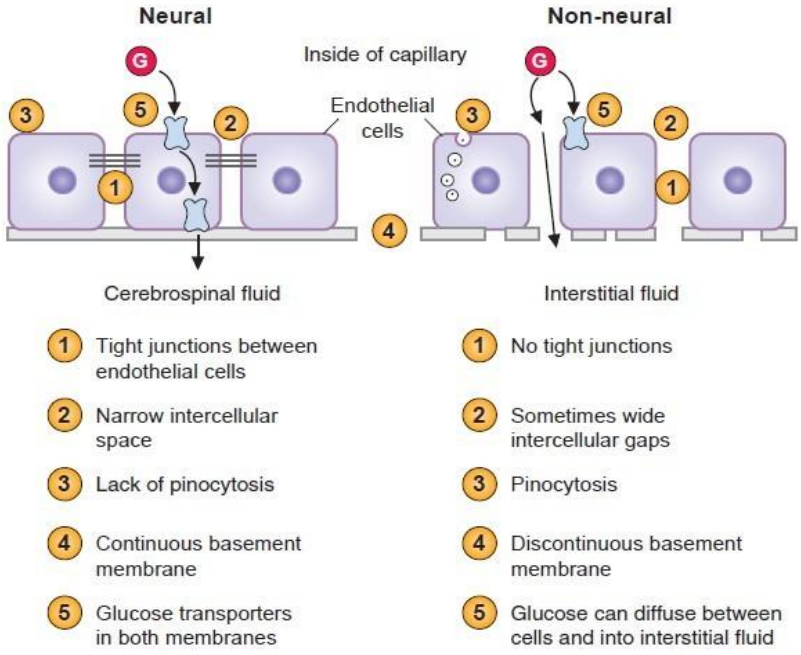
one of the functions of the blood-testis barrier is to prevent sperms to contact with blood, blood contains leukocytes which might initiate an immune response against sperms because their genetic makeup is somehow different from the father) (blood retinal barrier is in the retina, شبكيّة العين).
GLUT2 isoform has low affinity to glucose yet high capacity (high capacity means higher Vmax, it can transport more glucose molecules in a unit of time, faster) meaning that it doesn't function very well in low glucose concentrations, this isoform presents in liver, kidney and pancreatic β cells (insulin-synthesizing pancreatic cells), to understand the function of GLU2, let's review the liver as an example, the liver functions to store excess glucose, so it does make sense that it doesn't absorb glucose unless we have high concentrations of it, that's why the liver has GLUT2 isoform which has low affinity.
GLUT4 is insulin-sensitive, meaning that it is upregulated by the cell through a signaling cascade that starts with insulin, GLUT4 is found in adipose tissue, skeletal muscle and cardiac muscle, to understand its function, let's review the skeletal muscles and adipose as examples, in skeletal muscles, the glucose in not absolutely required, skeletal muscles can use fatty acids as a source of energy, while adipose tissue stores glucose, if blood glucose is low, insulin level is low and therefore GLUT4 is down regulated, but if GLUT4 synthesis is induced by insulin, that means high blood glucose, so some glucose will be taken from the blood toward the adipose tissue and skeletal & cardiac tissues, to be stored in the adipose tissue or utilized as a source of energy in muscles.
GLUT5 has more affinity to fructose that glucose, GLUT5 is found in the intestinal epithelium for absorption of glucose and it is also found in spermatozoa, sperms use fructose as a source of energy.



Insulin stimulates transport of glucose into muscle and adipose tissues

What was mentioned in the textbook:

In muscle and adipose tissue, the transport of glucose is greatly stimulated by insulin. The mechanism involves the recruitment of glucose transporters (specifically, GLUT 4) from intracellular vesicles into the plasma membrane (remember from the cytology course: membrane proteins are synthesized by bound ribosomes on the rough endoplasmic reticulum than transported through vesicles to Golgi apparatus and then to the plasma membrane, transport of these vesicles into the plasma membrane requires stimulation by insulin) . In adipose tissue, the stimulation of glucose transport across the plasma membrane by insulin increases its availability for the synthesis of fatty acids and glycerol from the glycolytic pathway. In skeletal muscle, the stimulation of glucose transport by insulin increases its availability for energy generation (glycolysis) and glycogen synthesis.



What was mentioned in the textbook:

A hypoglycemic response is elicited by a decrease of blood glucose concentration to some point between 18 and 54 mg/dL (1 and 3 mM). The hypoglycemic response is a result of a decreased supply of glucose to the brain and starts with light-headedness دُوار and dizziness دوخة and may progress to coma غيبوبة. The slow rate of transport of glucose through the blood–brain barrier (from the blood into the cerebrospinal fluid) at low levels of glucose is thought to be responsible for this neuroglycopenic response. Glucose transport from the cerebrospinal fluid across the plasma membranes of neurons is rapid and is not rate-limiting for ATP generation from glycolysis. In the brain, the endothelial cells of the capillaries have extremely tight junctions, and glucose must pass from the blood into the extracellular cerebrospinal fluid by GLUT 1 transporters in the endothelial cell membranes and then through the basement membrane (glucose is transported from brain's capillaries to the brain through the transcellular route and not the paracellular route as in other organs, in other organs glucose can use many routes to leave the capillaries, such as pinocytosis.). Measurements of the overall process of glucose transport from the blood into the brain (mediated by GLUT 3 on neural cells) show a *K*m,app of 7 to 11 mM and a maximal velocity not much greater than the rate of glucose use by the brain. Thus, decreases of blood glucose below the fasting level of 80 to 90 mg/dL (~5 mM) are likely to significantly affect the rate of glucose metabolism in the brain because of reduced glucose transport into the brain.
Notice that glucose absorption in the brain does not require insulin because it is mediated by GLUT1 and GLUT3 but not GLUT4, and brain is highly dependent on glucose in contrast to muscles which can use fatty acids as a source of energy, so glucose must be able to pass to brain even if it present at very very low concentration that's why glucose passage to brain is not insulin mediated,