



SHEET NO.

7

العلم



METABOLISM

DOCTOR 2019 | MEDICINE | JU

DONE BY : Doctor 2018

SCIENTIFIC CORRECTION : Omar Rashdan

GRAMMATICAL CORRECTION :

DOCTOR : Faisal Al-Khatib

Carbohydrate Metabolism

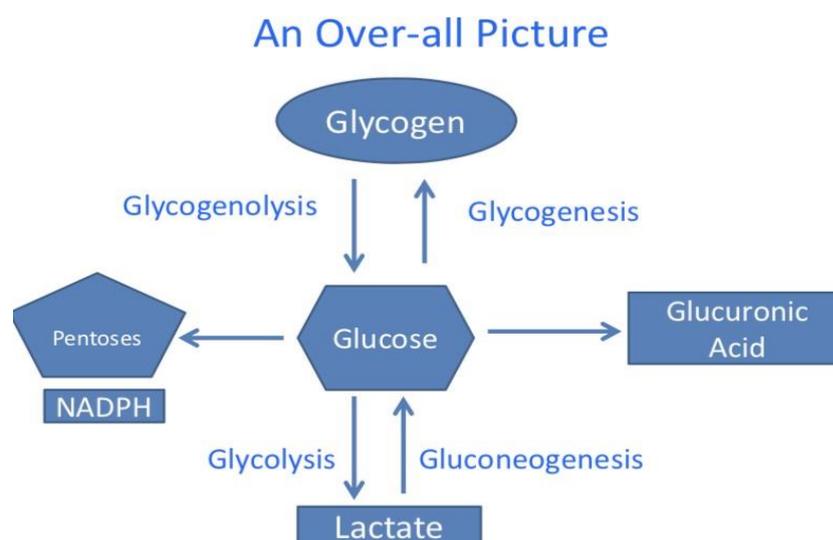
Carbohydrates, also known as Saccharides, are the most abundant organic molecules in nature. In the next couple of lectures, we'll be discussing topics related to carbohydrates and their metabolism. Some of the objectives we are aiming to cover are:

- 1) Glucose, which is a monosaccharide, is a source of energy. (Major purpose)
 - Glucose degradation produces Acetyl CoA, which is a molecule that enters the TCA cycle, followed by the oxidative phosphorylation, and produces energy.
- 2) Ways to transfer non-carbohydrate sources (i.e. Amino Acids) to Glucose
- 3) The process of storing Glucose in the form of Glycogen (Glycogenesis).
- 4) The process of breaking down Glycogen to form (releasing) Glucose (Glycogenolysis).
- 5) The production of NADPH and GSH (Glutathione).
 - The conversion of Glutathione from the oxidized form to the reduced form requires NADPH (which is obtained from glucose metabolism)
 - NADPH is very similar to NADH, however, NADPH is used in anabolic reactions meanwhile NADH which is used in catabolic reactions
- 6) Interconversion of sugars, which is the process of turning one sugar to another (i.e. Galactose to Glucose).
 - Happens upon need (i.e. the conversion of glucose into ribose when ribonucleic acid is needed)
- 7) The production of Glucuronic Acid, which is used in drug metabolism to convert hydrophobic molecules to hydrophilic ones.

An Over-All Picture

Glucose out of the many molecules we are about to discuss, seems to be the most important carbohydrate for humans. It's the form of sugar that runs in our blood and is used mainly as the source of energy in humans.

Glucose is involved in several reactions that happen on a daily basis. The picture below shows an over-all chart of the reactions that glucose takes part of:



1) **Glycolysis:** Glycolysis is the process of turning Glucose to Pyruvate or Lactate to obtain energy. (Glyco: Glucose, lysis: break-down)

2) **Gluconeogenesis:** The conversion of Lactate or Pyruvate to Glucose. This is the opposite of Glycolysis. (Gluco: glucose, neo: new, genesis: production of.)

Altogether, it's the production of a new glucose molecule (from non-carbohydrate sources)

3) **Glycogenesis:** The production of Glycogen from Glucose. (Glyco: Glycogen, genesis: Production of)

4) **Glycogenolysis:** breaking down Glycogen to Glucose.(Glycogen: self-explanatory, lysis: break-down)

5) **Glucuronic Acid:** an acid used to convert hydrophobic drugs to hydrophilic ones.

6) **Pentoses and NADPH:** NADPH is a molecule used in anabolism, unlike NADH which is used in catabolism.

Distinguishing Sugars: Classification and Structure

Monosaccharides can be classified according to:

1) Number of carbons:

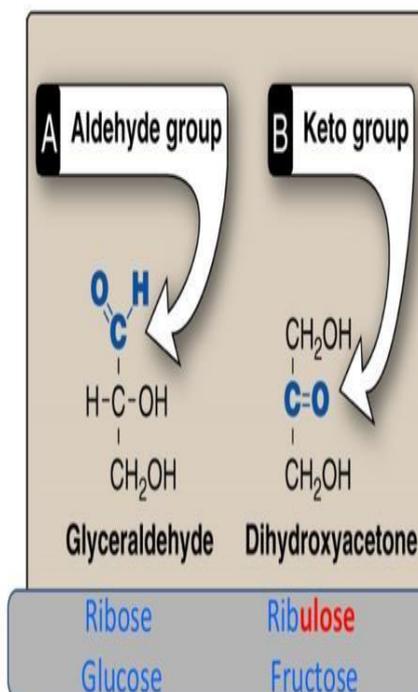
Monosaccharides can be categorized into different classes based on the number of carbons they have. We have trioses, pentoses, hexoses ...etc. The table on the right shows different classes of sugars found in humans depending on the number of carbons they have.

<u>Generic names</u>	<u>Examples</u>
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

2) Carbonyl Group:

This classification gives us two types of sugars: Aldoses and Ketoses.

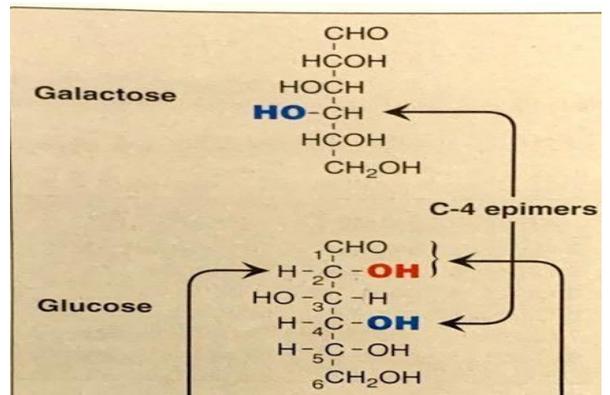
- Aldoses are sugars with an **Aldehyde group** on carbon number 1. The simplest Aldose is **Glyceraldehyde**, which contains 3 carbons.
- Ketoses are sugars with a **Ketone group** on carbon number 2. The simplest Ketose is **Dihydroxyacetone**, and this sugar also has 3 carbons.
- In the simplest Aldoses & Ketoses (trioses), we have three carbon units, two of which are associated with hydroxyl groups, and a carbonyl group which can be an aldehyde or a ketone group.
- Ribose & glucose are Aldoses
- Ribulose & fructose are ketoses



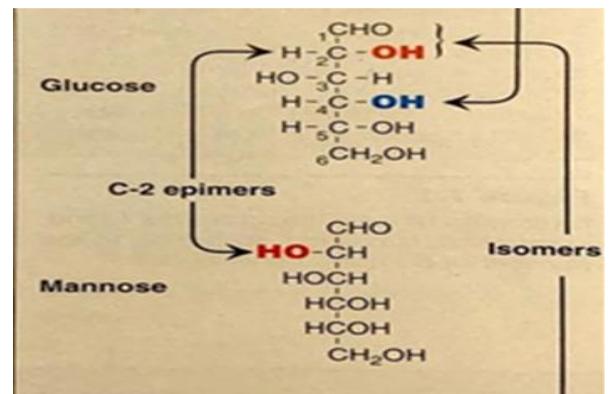
3) Isomers and Epimers:

- Isomers are compounds that have the same chemical formula, but different structures.
 - For example, Fructose, Glucose, Mannose and Galactose are all isomers of each other, with the chemical formula $C_6H_{12}O_6$.
- Isomers that differ in the configuration around only one carbon atom, with the exception of the carbonyl carbon, are called epimers of each other.

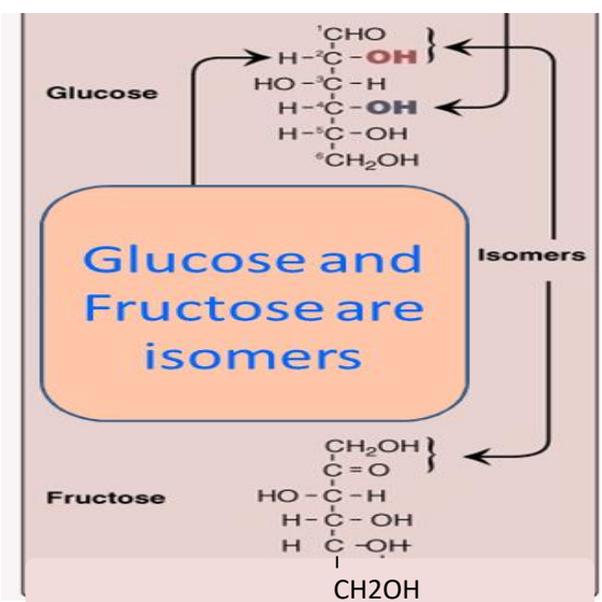
- Glucose and Galactose are C4 Epimers because their structure differs only in the position of the Hydroxyl (-OH) group at Carbon 4.



- Glucose and Mannose are C2 Epimers because their structure differs only in the position of the Hydroxyl (-OH) group at Carbon 2.

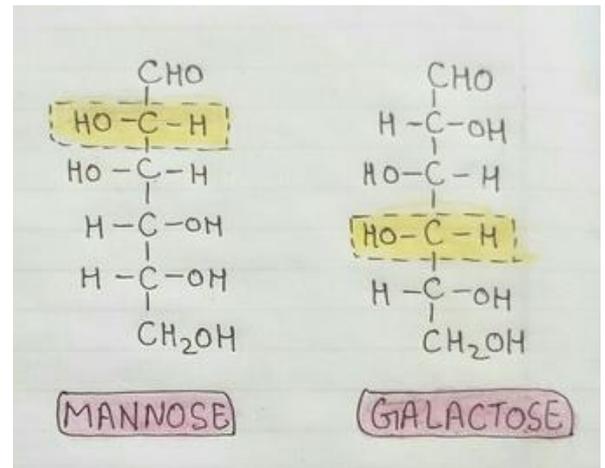


- Glucose and Fructose are isomers
 Glucose has an Aldehyde group on carbon number one and a hydroxyl group on carbon number two.
 Fructose has a ketone group on carbon number two and a hydroxyl group on carbon number one.



- Galactose and Mannose are only isomers, because they differ in the orientation of two hydroxyl groups rather than one.

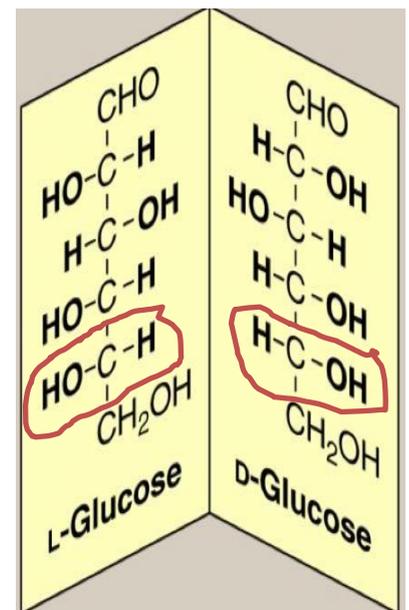
(You have to note that isomers or epimers are two different sugars with different characteristics, even if the change is as slight as a hydroxyl group on one carbon).



4) Enantiomers: (stereoisomerism)

A special type of isomerism is found in pairs of sugars that are mirror images of each other (not just one carbon is different). These mirror images are called Enantiomers. Enantiomers are described as D-Enantiomers, and L-Enantiomers. The D-Enantiomer has the Hydroxyl Group (-OH) on the chiral carbon that is furthest from the carbonyl carbon to the right, while the L-Enantiomer is to the left.

- Most sugars in the body are in the D-Isomers
- They have different biological properties.
- An enzyme that works on D-Glucose cannot work on L-Glucose.



5) Cyclic Forms:

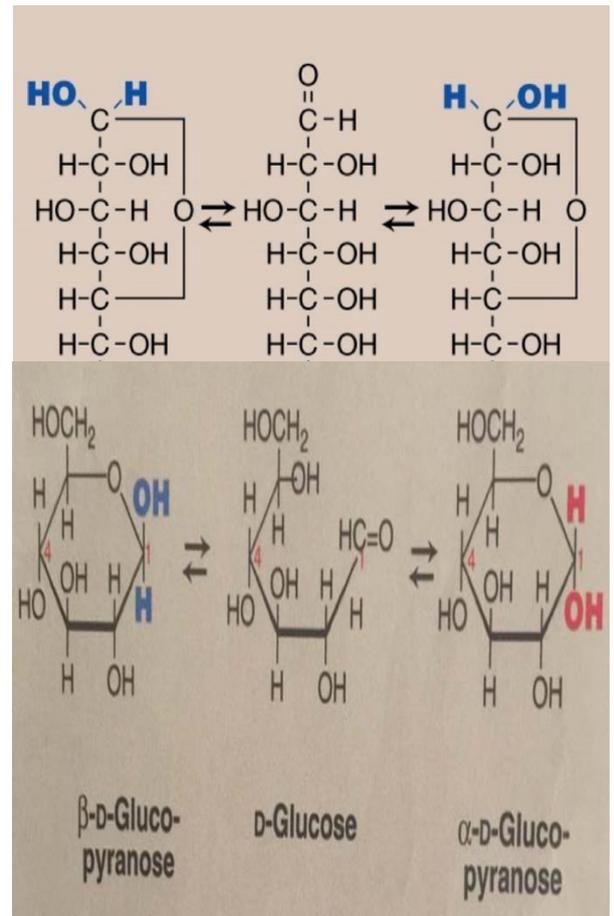
The Carbonyl Group (Aldehyde or Ketone) reacts with a hydroxyl group on the same sugar, making the Carbonyl group asymmetric. This asymmetric carbon is referred to as the anomeric carbon.

This generates a new pair of isomers, Alpha (α) and Beta (β).

Alpha configuration is when the Hydroxyl group on the anomeric carbon is downwards (originally **right** in the chain form), while Beta configuration is when it's upwards (originally **left** in the chain form).

Notes:

- When carbon number one in glucose (aldehyde group) reacts with the hydroxyl group on carbon number five a hemiacetal is formed.
- The ring is perpendicular to the plain of the paper
- Less than 1% of Monosaccharides with 5 or more carbons exist in the chain form.



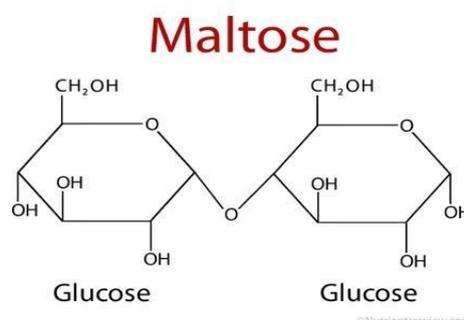
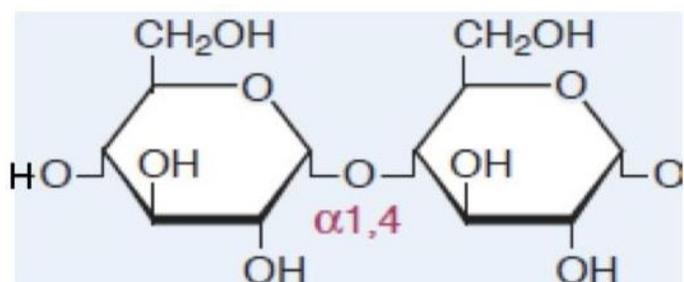
Monosaccharide Joining

- ❖ Monosaccharides are joined to form a 2-unit sugar called a Disaccharide
- ❖ Or an Oligosaccharide, which contains 3-10 monosaccharides
- ❖ Or a Polysaccharide which has more than 10 monosaccharide units.
- ❖ This process removes one water molecule per 2 sugars joined, meaning the total number of water molecules removed (= number of sugars - 1).
- ❖ The linkage between two monosaccharides is referred to as a Glycosidic Bond.
- ❖ Glycosidic Bonds are named according to the carbons participating the bond.

We will mainly discuss two Disaccharides here:

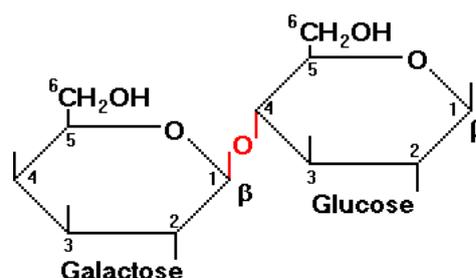
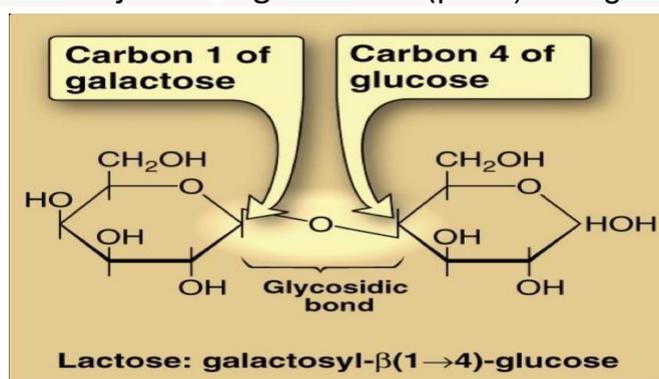
1) Maltose:

Also known as the malt sugar, maltose is a Disaccharide made of 2 Glucose molecules, linked together in a glycosidic (α 1-4) linkage. The right glucose molecule in the picture has a free hydroxyl group on the anomeric carbon, meaning that Maltose is a reducing sugar, and can be oxidized (by adding more glucose subunits).



2) Lactose:

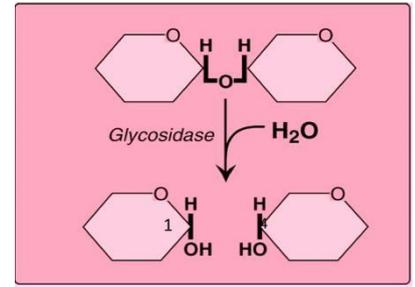
Also known as the milk sugar, Lactose is a Disaccharide made of a Glucose and a Galactose molecule joined together in a (β 1-4) linkage.



Breakdown of Sugars: Glycosidic Bond Cleavage

This is the exact opposite of monosaccharide joining. It requires the same number of water molecules removed to get the sugar broken down because it's a hydrolysis process.

Enzymes responsible for the cleavage are called **Glycosidases**, which, as the name implies, hydrolyses, and breaks down Glycosidic bonds.



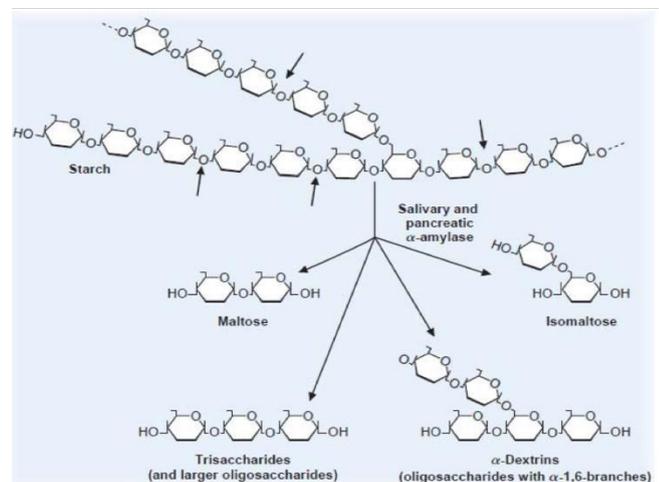
Example: Maltase is an enzyme that works on (hydrolyses) maltose and produces two glucose subunits.

- Here's an example to see how they work:

This picture on the right has part of a starch chain.

The monosaccharides in the chain are connected by α 1-4 linkage except at the branches it an α 1-6 linkage.

If starch was exposed to Glycosidases (i.e. α - Amylase, which is an endoglycosidase that acts anywhere within the chain), it will result in 4 types of sugars:

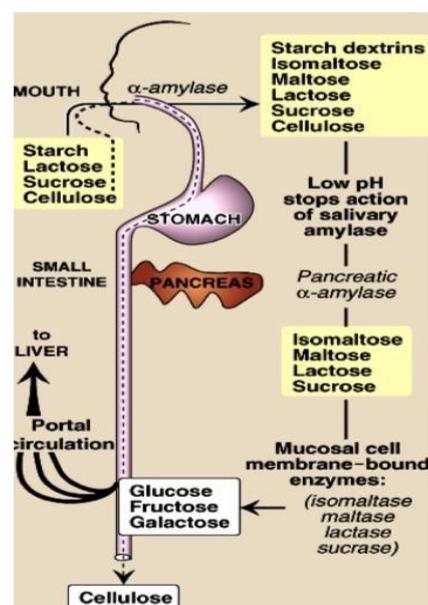


- 1) **Maltose:** If the cleavage happened in a linear way (no branch included) at the sides of 2 glucose molecules (α 1-4 linkage).
- 2) **Trisaccharides:** Same concept as Maltose, but at the sides of 3 adjacent Glucose molecules.
- 3) **Isomaltose:** if the cleavage made a cut around the Glucose that is branched (remember that the α 1-4 is broken and not the α 1-6 at the branch).
- 4) **α -Dextrins:** Oligosaccharides with (α 1-6) branches. (smaller than starch).

Dietary Carbohydrate Metabolism

Since we take very little Monosaccharides in our diet, as the majority is Polysaccharides, the body uses breakdown methods to convert these Polysaccharides to Monosaccharides. This happens mainly in the mouth (using salivary α -Amylase secreted by the salivary glands) or in the intestinal lumen (using pancreatic α -Amylase and other specific enzymes, such as Maltase). α -Amylase in all its kinds works on hydrolyzing (α 1-4) bonds only, and that's how it gets its name. The process is summarized as follows:

- The food enters the mouth as Polysaccharides and the break-down starts by **Salivary α -Amylase**. Examples on sugars that enter are starch, lactose, sucrose, and cellulose.
- α -Amylase breaks down starch to the parts in the previous page but can't break down the other sugars mentioned because they don't have (α 1-4) Glycosidic bonds.
- Salivary α -Amylase gets inactivated in the stomach, because of the high acidity.
- The Pancreas then releases **pancreatic α -Amylase (which is more potent)** that works just the salivary α -Amylase, and the break down continues.
- **Note: When the acidic stomach contents reach the small intestine, they are neutralized by bicarbonate secreted by the pancreas**
- Remember the other sugars that don't have (α 1-4) linkages? The mucosal membrane of the intestines has a specific bound set of proteins for breaking down specific sugars, such as Lactose, Sucrose and etc.
- **Cellulose can't be broken down since humans don't have the enzymes to do so.**
- Then we end up with the basic units (Glucose, Fructose and Galactose) which get absorbed and enter the circulation and into the liver.



Mucosal cell membrane-bound enzymes

Important

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

Sucrase- Isomaltase Complex and Glucoamylase

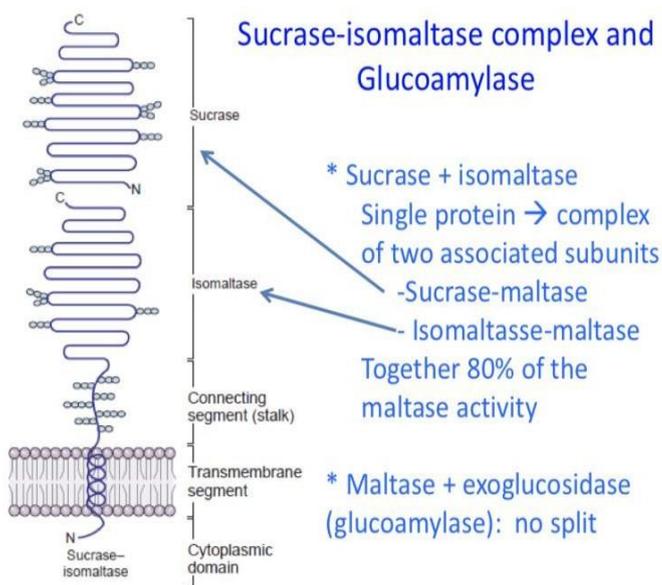
Sucrase-Isomaltase complex is inserted into the membrane of the small intestinal cells , the enzyme is extracellular and is fixed.

Sucrase-Isomaltase is formed from two domains (initially formed as a single polypeptide chain which then gets cleaved forming two domains).

Sucrase- Isomaltase is a transmembrane protein, that is formed from 2 subunits (2 Polypeptides). After synthesis, these 2 Polypeptides go through modifications and get cleaved giving 2 enzymes:

- Sucrase-Maltase: Breaks-down Sucrose and Maltose.
- Isomaltase-Maltase: Breaks-down Isomaltose and Maltose.

Together, they form 80% of the total maltase activity.



Glucoamylase is a specific type of Amylase that is produced when these 2 subunits don't break.

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*.

Abnormal Degradation of Disaccharides

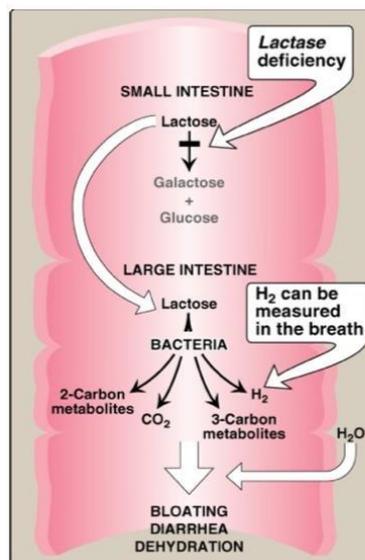
A lot of people have problems in digesting Disaccharides, such as Lactose. Here we discuss some problems that are related to the degradation of Disaccharides and their causes:

1) Lactose Intolerance (Lactase deficiency):

- Over 50% of the world's population suffers from this problem.
- Causes include:
 - Genetics
 - Variety of intestinal diseases
 - Malnutrition
 - Injury of mucosa i.e. by drugs
 - Severe diarrhea
- The maximum activity of Lactase is at one month of age, and it starts to decline afterwards.

- When someone is 5-7 years old, the level of activity reaches its adult or normal level, which is around 10% of the maximum level.

- If someone is intolerant to Lactose, and they end up ingesting it in some way, their bodies wouldn't be able to handle the Lactose ingested. Instead, it will be metabolized



Maximal activity @ 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 lactoses) → loss of 1 liter of extracellular fluid

by intestinal bacteria, giving off 2 and 3 carbon metabolites, which stay in the stomach until the extracellular fluid comes and washes them out from the intestines. Each cup of milk (9 g of lactose) needs 1 liter of extracellular fluid to wash it out. This causes watery diarrhea.

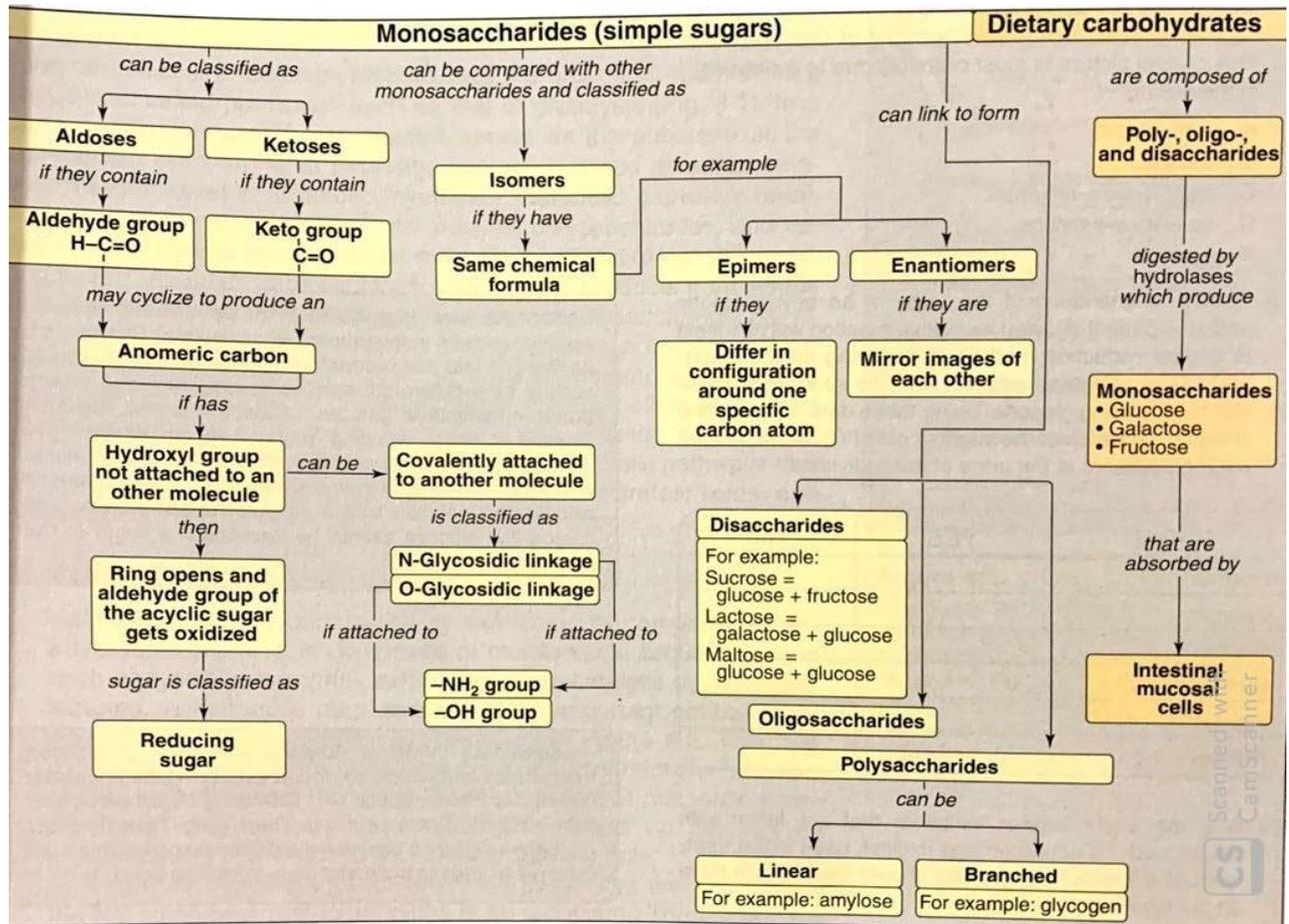
- Another metabolite that comes out gases, such as CO₂ and H₂. These cause bloating.
- The net result is bloating, diarrhea and loss of fluids.

2) Sucrase-Isomaltase deficiency: not very common

Prevalence of Late-onset Lactase Deficiency

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

To summarize



Carbohydrate absorption by the Intestinal Epithelium

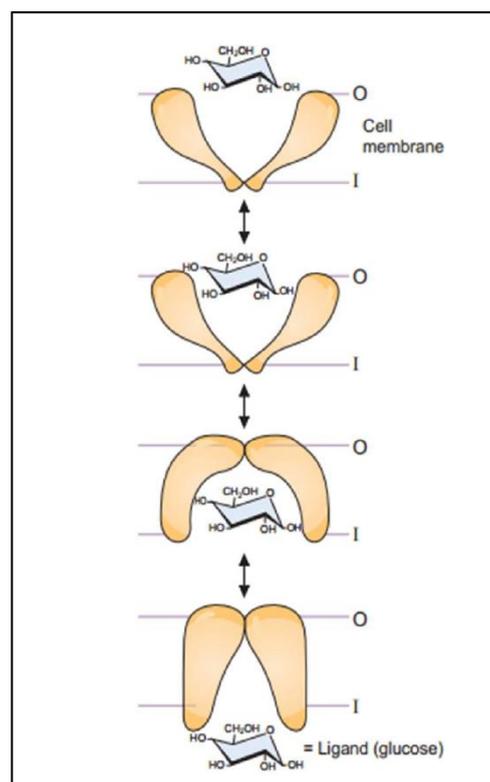
-The glucose molecule is extremely polar and cannot diffuse through the hydrophobic phospholipid bilayer of the cell membrane. Therefore, it enters the absorptive cells by binding to transport proteins, membrane-spanning proteins that bind the glucose molecule on one side of the membrane and release it on the opposite side. There are two methods of glucose transport:

1. Na⁺ Independent facilitated diffusion transport.
2. Na⁺ _ monosaccharide co-transporter system (SGLT).

* Na⁺ Independent facilitated diffusion transport.

GLUTs (glucose transporters) are integral membrane proteins that **transport glucose down its concentration gradient** according to a model of alternate **conformation**, which predicts that the transporter uncovers a single substrate **binding** site toward areas of **high** glucose concentration (either the outside or the inside of the cell) and induces a conformational change associated with transport that **releases** glucose to the other side of the membrane (**lower** concentration).

-This figure shows the **two** conformational states of GLUT transporters. →



-Recall that facilitated transport **does not** require chemical energy from ATP hydrolysis; rather, molecules and ions move **down** their concentration gradient reflecting its diffusive nature.

* **Na⁺ _ monosaccharide co-transporter system (SGLT).**

-Sodium **G**lucose **L**inked **T**ransporters or Na⁺ dependent glucose co-transporters are a family of glucose transporters that transport glucose against its concentration gradient and are found in:

1)The **intestinal mucosa** of the **small intestine** in order to **actively** transport **glucose from lumen of intestines into the epithelial absorptive cells.**

2) Also, they are found in the **proximal tubule in the kidney** to **reabsorb glucose from the lumen back into the blood.**

-Glucose should be **completely** and **continuously** absorbed from the lumen into the absorptive cells in the small intestines. For that reason, when glucose concentration in the lumen is **very low** – before a meal for example- the **level** and intrinsic **activity** of facilitative diffusion decreases and the absorption of glucose **against** its concentration gradient occurs through (**SGLT**) system.

-The glomeruli filter **glucose** from the **plasma, all of which** should be reabsorbed through glucose transporter proteins that are present in cell membranes within the proximal tubules in order to prevent it from disappearing from the body through the urine.

-A **low intracellular Na⁺** concentration is maintained by Na⁺/k⁺ ATPase pump that uses the energy from adenosine triphosphate (**ATP hydrolysis**) to pump Na⁺ out of the cell.

-The SGLT proteins use the energy from the **downhill sodium ion gradient** created by the **ATPase** pump to transport glucose across the apical membrane, **against** an **uphill glucose gradient** (from a **low** to a **high** glucose concentration).

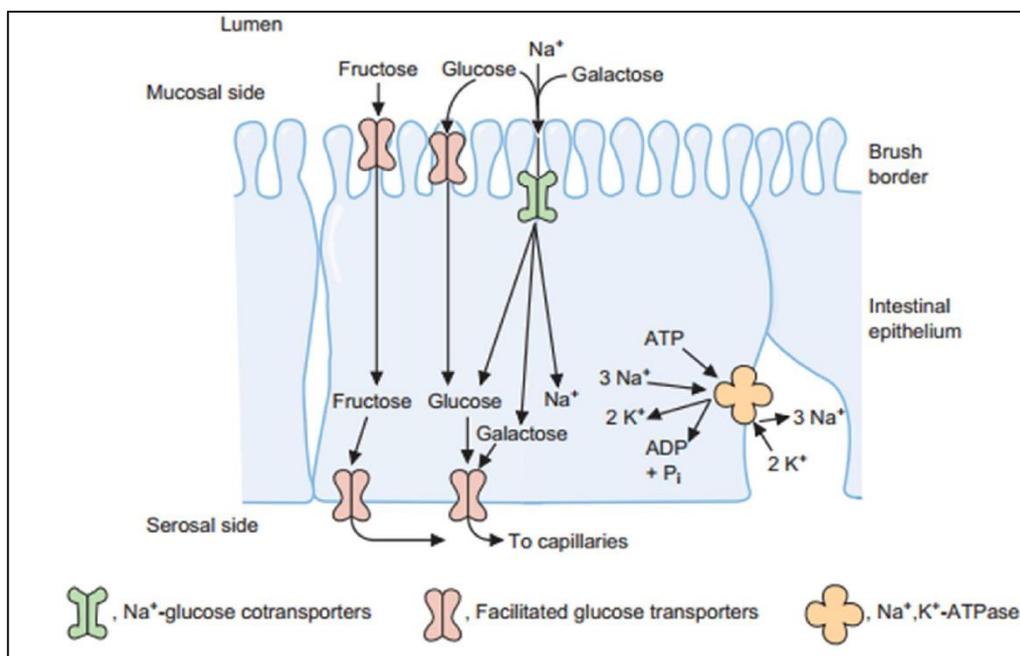


-Glucose is absorbed by this **secondary active transport** system, in which co-transport carriers on the luminal border transport **both** the monosaccharide and Na^+ from the lumen into the interior of the intestinal cell.

The operation of these co-transport carriers, which **do not directly** use energy themselves, depends on the **Na^+ concentration gradient** established by the energy-consuming Na^+/K^+ pump.

Glucose having been **concentrated in the cell** by the co-transport carriers leaves the cell **down** its concentration gradient, by means of a passive carrier (GLUT2), to enter the **blood** (a lower concentration).

Fructose is absorbed from the lumen to the blood through the intestinal cell **solely** by facilitated diffusion (GLUT5) **down** its concentration gradient.



Note:

Oral rehydration therapy (ORT) : is a type of fluid replacement used to treat dehydration, especially that due to diarrhea. It involves drinking water with modest amounts of sugar and salts, specifically sodium. The co-transport of glucose into epithelial cells via the SGLT protein requires sodium. Also, without glucose, intestinal sodium is not absorbed. This is **why oral rehydration salts include both sodium and glucose**. For each cycle of the transport, hundreds of **water** molecules move into the epithelial cell to **maintain osmotic equilibrium**. The resultant absorption of sodium and water can achieve **rehydration**.

-Now please read these points carefully and try to **understand** them, and then memorize the following table:

❖ **GLUT1 glucose transporter:**

- It is expressed in mature **erythrocytes** and epithelial **barriers**
- It has very high affinity for glucose , to ensure adequate supply of glucose to cells who have absolute dependence on glucose.

❖ **GLUT2 glucose transporter:**

- It is expressed in the liver , kidney , pancreatic β -cell.
- It has low affinity for glucose, and this is in keeping with the liver's role as the organ that maintains **blood glucose levels**. Thus, the liver will convert glucose into other energy **storage** molecules **only** when blood glucose levels are **high**; to ensure that there is an adequate supply of glucose to the brain and RBCs.

❖ **GLUT3 glucose transporter:**

- It is expressed in the neurons.
- It has **high** affinity for glucose since the brain needs constant supply of glucose.

❖ **GLUT4 glucose transporter:**

- It is found in skeletal muscle, heart muscle and adipose tissues.
- **It is the insulin-sensitive glucose transporter** (in the presence of insulin the number of GLUT4 transporters increase on the cell surface)
- High insulin levels indicate high levels of glucose , therefore , glucose can be uptaken by the skeletal muscles and adipose tissues.

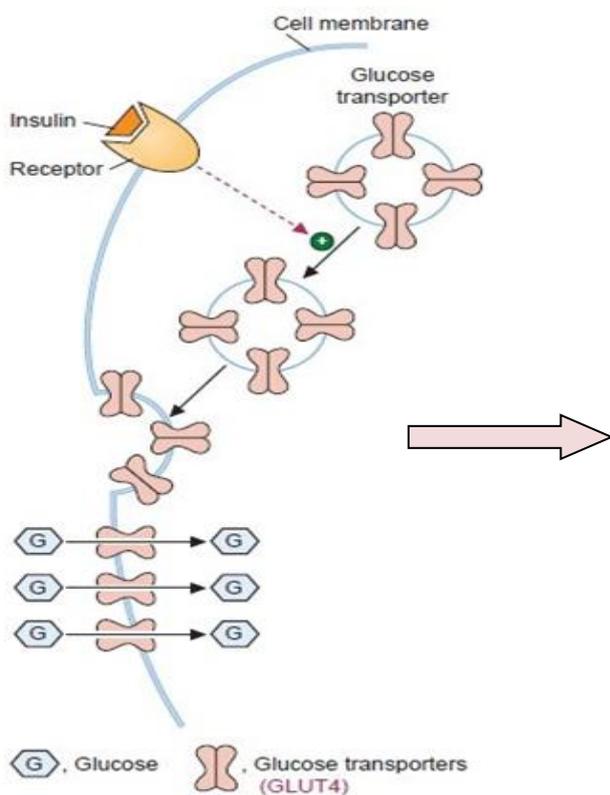
❖ **GLUT5 transporter:**

- It is expressed in the intestinal epithelial cells and spermatozoa (fructose is the main energy source for the sperm.)
- Its main function is binding and transporting **fructose** although it can transport glucose.

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



GLUT4 glucose transporter is found in intracellular vesicles in muscle and adipose tissues. **It is the insulin-regulated glucose transporter**; because when insulin binds to its proper cell membrane receptors, these vesicles are mobilized to the cell membrane and **recruit** GLUT4 transporters into the membrane.

⌘ Glucose transport through the blood-brain barrier and into neurons.

!!) You only need to know the characteristics of transport through the **capillary endothelium** in neural and non-neural tissues.

