METABOLISM

بسم الله الرحمن الرحيم



MID - Lecture 10

carbohydrate * Metabolism (pt.1)

﴿ وَإِن تَتَوَلَّوْاْ يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُواْ أَمْثَلَكُم ﴾

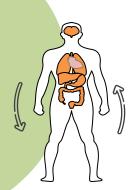
اللهم استعملنا ولا تستبدلنا

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بسم الله الذي لا يضرُّ مع اسمه شيءٌ في الأرض ولا في السماءِ وهوَ السميعُ العليم اللهم إنّي أسألك علمًا نافعا يقرّبني إليكَ

Carbohydrates Metabolism

Review of Carbohydrates

Digestion and absorption of carbohydrates

Dr. Diala Abu-Hassan

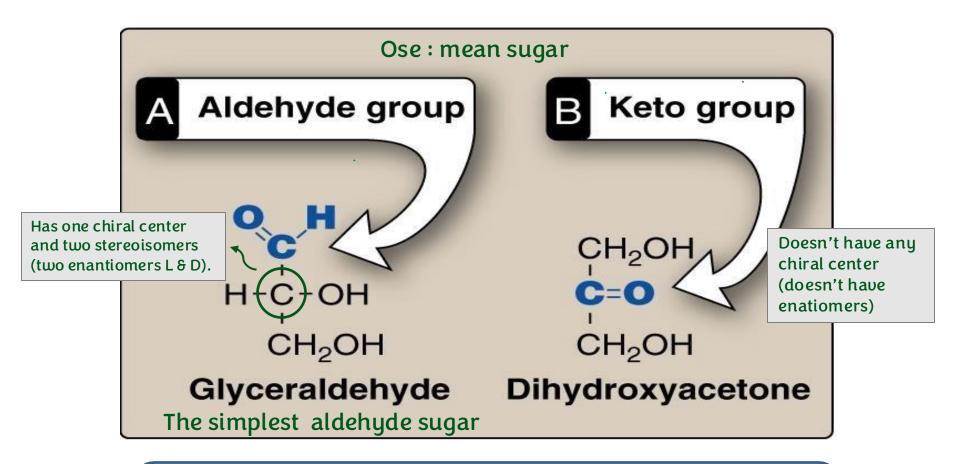
Quiz for the previous lecture —> https://forms.gle/CsWx7NV1GydLGwxH9



Sugars are either

Carbohydrates are classified into polyhydroxy aldehydes and ketones.

aldoses or ketoses



⁵ Ribose

Glucose

Ribulose Ulose means: ketose

Fructose

Recall from Biochemistry course:

- Different classifications of carbohydrates:
- Based on their functional group (Aldoses/Ketoses).
- · Based on their the number of carbons they contain.
- o The number of chiral centers in:
- Aldoses = n-2
- Ketoses = n-3

Where n is the number of carbons.

Examples of monosaccharides found in humans

Generic names Examples

3 carbons: trioses Glyceraldehyde

4 carbons: tetroses Erythrose Threose and Erythrulose.

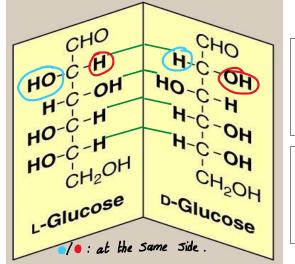
5 carbons: pentoses Ribose

6 carbons: hexoses Glucose Galactose, Fructose, and Mannose.

7 carbons: heptoses Sedoheptulose

9 carbons: nonoses Neuraminic acid

Each group or atom surrounding the chiral center is reverted in the opposite direction in its mirror image.



The most common

ones are:

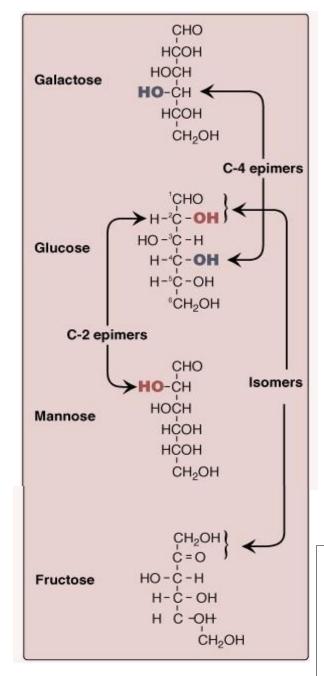
Enantiomers

Chiral center: A carbon atom that is bonded to four different groups.

Enantiomers: Stereoisomers that are non-superimposable <u>mirror images</u> of each other.

To determine whether a sugar is classified as L or D, look at the orientation of the hydroxyl (-OH) group on the last chiral center. If the -OH group is on the left, it is L-glucose; if it is on the right, it is D-glucose.

We utilize D sugars in metabolic pathways.



Sugars have Isomers

Epimers are isomers:

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

Glucose and Fructose are isomers

Why we study these details?

- These minor differences between sugar molecules are important to expect the function of the enzyme that can interconvert them.
- Most of the metabolic pathways are designed from glucose.
- Our metabolic pathways recognize only glucose, so we must convert other sugars into glucose through isomerization reactions.

1. Diastereomers and Epimers:

Diastereomers: they are compounds that have similar configuration at some carbons and different configuration at some carbons.

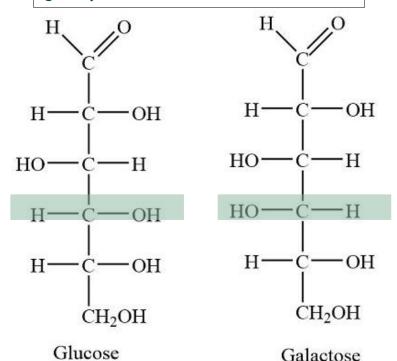
Epimers: compounds that differ in configuration at only one chiral

carbon.

They differ in orientation of OH group at carbon number four.

In glucose, the hydroxyl group on the right of the fourth carbon in the open-chain form.

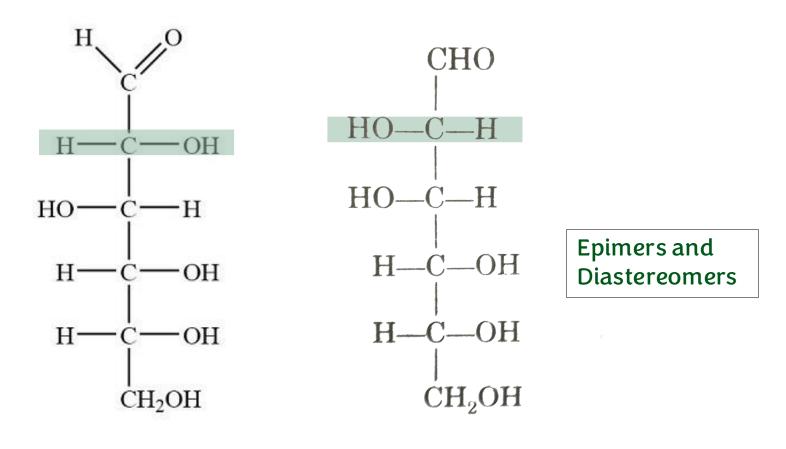
And it is oriented downward in the ring structure.



In galactose, the hydroxyl group on the left of the fourth carbon in the open-chain form.

And it is oriented upward in the ring structure.

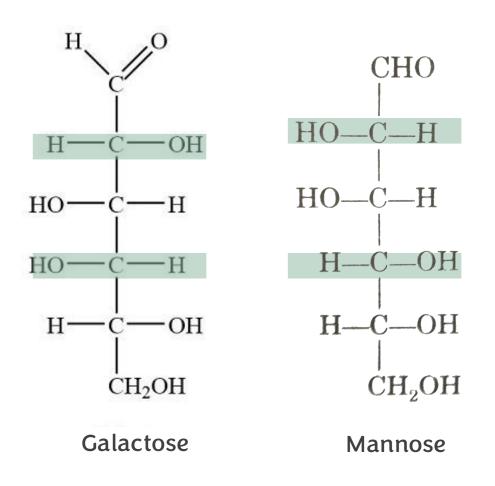
They differ in orientation of OH group at carbon number two.



Glucose

Mannose

They differ in orientation of OH group at carbon number two and four.

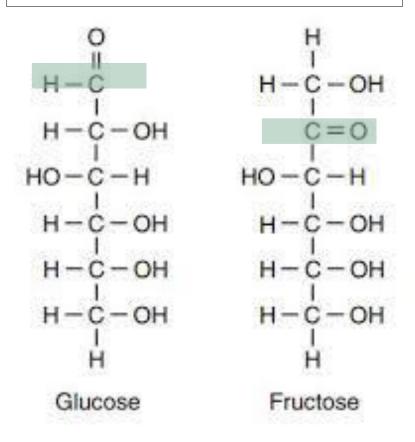


Diastereomers but not Epimers

2. Constitutional Isomers:

Constitutional isomers: they are compounds that have the same molecular formulas, but they have different connectivities.

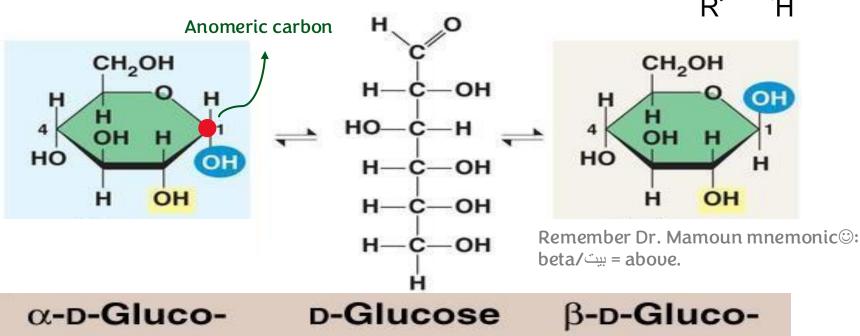
They differ in their functional groups.



Constitutional but not stereoisomer

Alpha and Beta Sugars (Anomers)

This occurs when the open-chain structure forms a ring structure. RO When an aldehyde sugar forms a ring, it becomes a hemiacetal



pyranose

pyranose

Each glucose molecule can alternate between three states (liner structure "open chain form", α -D-Glucopyranose, β-D-Gluco-pyranose).

The interconversion between α and β anomers occurs spontaneously, unlike the conversions between L and D forms.

- The β anomer is the most stable form, so the molecule will predominantly exist in this form. It may then convert to the α form by breaking the ring into an open-chain form (during reactions).
- The arrangement of glucose anomer structures based on stability is as follows: $\beta > \alpha >$ open-chain form.
- ✓ The ring structure is more stable than the open-chain form.
- ✓ The position of the hydroxyl group at the anomeric carbon affects stability: if it is above the ring, it is in the equatorial position, which is more stable; if it is below the ring, it is in the axial position, which is less stable (Look at the picture below).

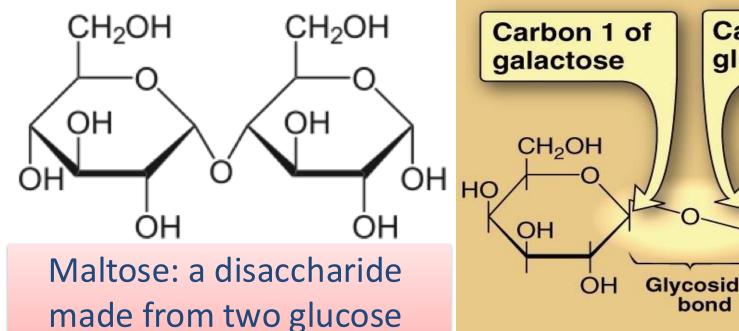
Additionally, the doctor mentioned that the OH groups on carbons 1 and 2 in the β anomer are farther apart and have more space.

 Your body's enzymes are capable of distinguishing anomers depending on the reaction.

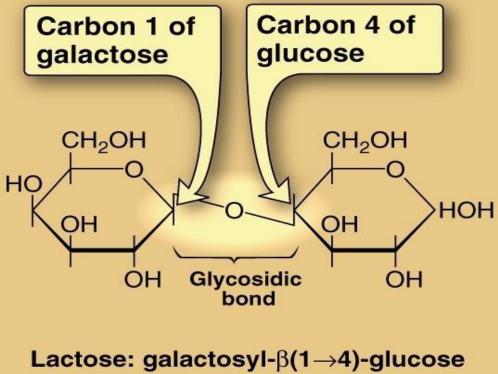
$$\alpha$$
-glucose β -glucose

Disaccharides

Sugars made of two monosaccharide units joined by a glycosidic bond



units



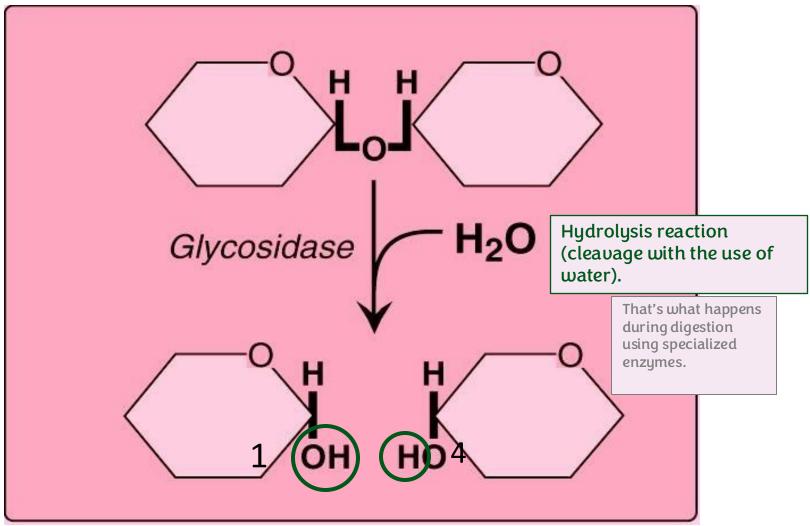
Let's talk about the formation of disaccharides:

- Linking sugar monomers together produces water via a <u>dehydration reaction</u>, which is responsible for forming a glycosidic bond.
- Different disaccharides can be formed either from two of the same type of monosaccharide (such as maltose, which is made from two glucose residues linked by a α -1,4 glycosidic linkage) or from two different monosaccharides (such as lactose, which is made from glucose and galactose linked by a β -1,4 glycosidic linkage). Sucrose is another disaccharide, composed of glucose and fructose linked by an α -1,2 glycosidic linkage.

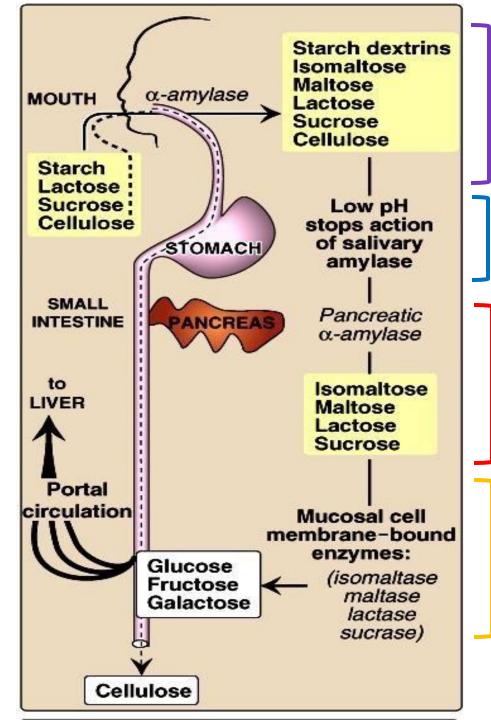
Glycosidic bond is cleaved by

glycosidase enzyme

A group of enzymes (since there are many types of glycosidic bonds).



Bond formation requires removing the hydroxyl group from carbon 1 and the hydrogen atom from carbon 4.







Stomach

Digestion of Carbohydrates

Go to the next slides for explanation...
Page (18+19)



Pancreatic enzymes 2

Of course, these enzymes perform their function in the intestines, but here we have organized the information based on enzyme groups rather than their site of action.



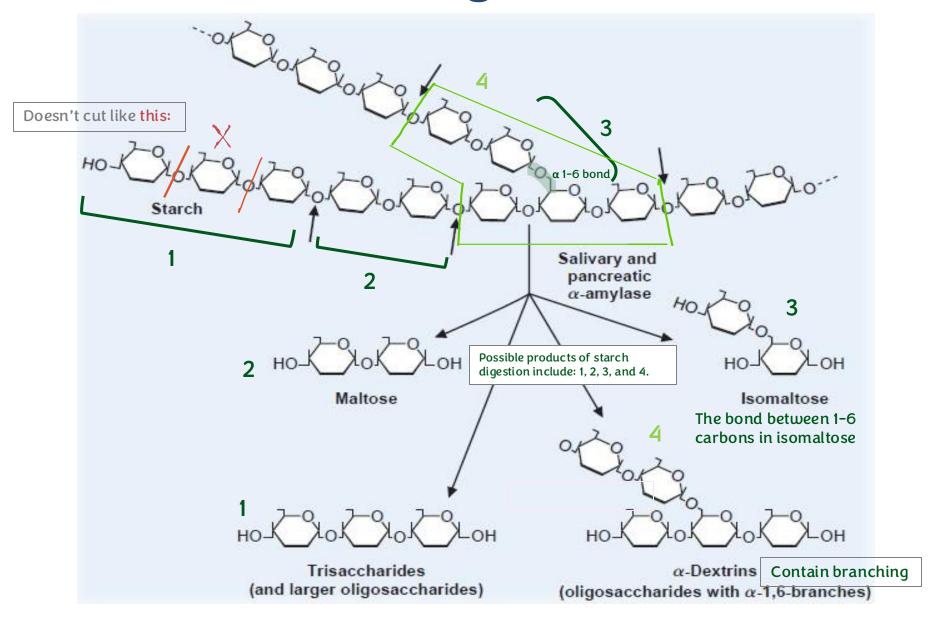
Intestinal enzymes

How does digestion occur, and where does it take place?

- Digestion of carbohydrates starts very early on the oral cavity.
- Salivary glands secrete salivary α amylase, this enzyme can recognize the α -1,4 linkages of starch (amylose and amylopectin).
- No things happen to lactose, sucrose, cellulose.
- It will randomly start hydrolysis different bonds, resulting in fragmentation of starch. (The doctor then began explaining page 20).
- Chewing typically lasts about 10 to 15 seconds. However, because time is a crucial factor for enzyme activity, this brief period often limits the complete digestion of starch molecules, resulting in only partial digestion.
- If a person loses consciousness, there are several diagnostic options, including fasting or diabetes (we assume it is hypoglycemia rather than hyperglycemia). Treatment involves administering sugar dissolved in water (such as juice). This sugar will be digested orally, absorbed sublingually (thin mucosa), enter the bloodstream, and assist the patient in regaining consciousness.
- Hypoglycemia is more dangerous than hyperglycemia because it can result in brain death due to the lack of essential nutrients.
- The dietary components move to the stomach (no things happen to the Carbs in the stomach, because there is no carbs digestion enzymes in the stomach). It involves the digestion of proteins by pepsin in a low pH environment.

How does digestion occur, and where does it take place?

- Then they continue to the small intestine (especially duodenum).
- The pancreatic duct delivers digestive enzymes (for lipids, proteins, and carbohydrates) into the duodenum.
- Regarding the carbs digestive enzyme, it is pancreatic α -amylase. It digests the α -1,4 linkages in starch but does not affect the branching (α -1,6 linkages). Digestion is more efficient because dietary components remain in the small intestine for a longer duration, allowing for complete digestion into disaccharides such as maltose and isomaltose.
 - Small intestinal cells protrude some digestive enzymes (membrane-bound enzymes). These enzymes are specific in targeting different types of disaccharides (e.g, lactase, maltase, isomaltase, and sucrase). They digest disaccharides into monosaccharides, which can be absorbed.



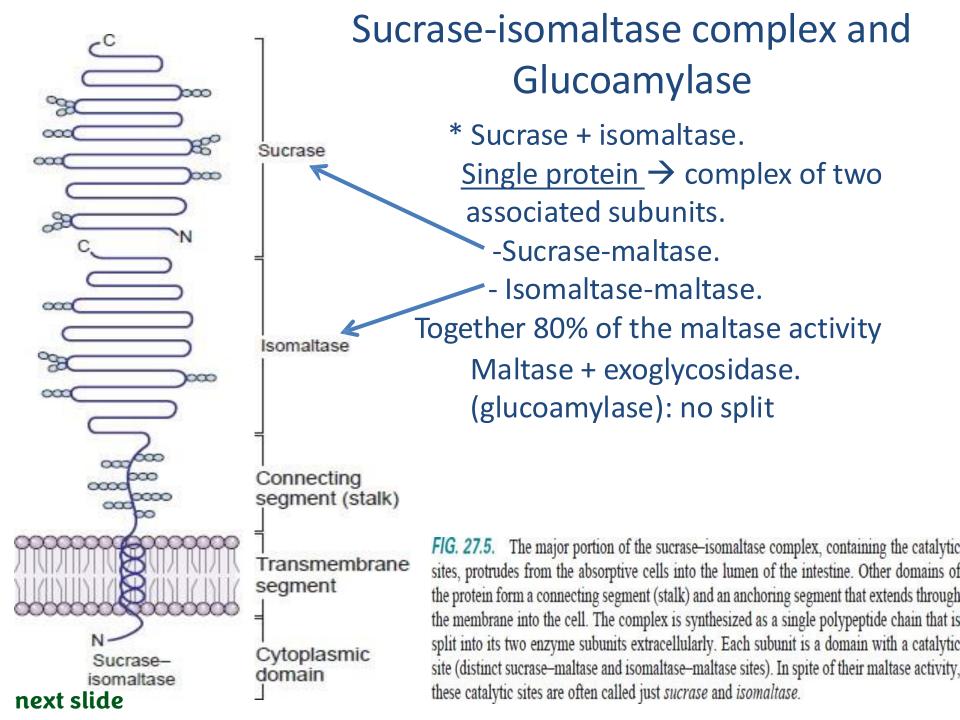
Explaining of the previous slide:

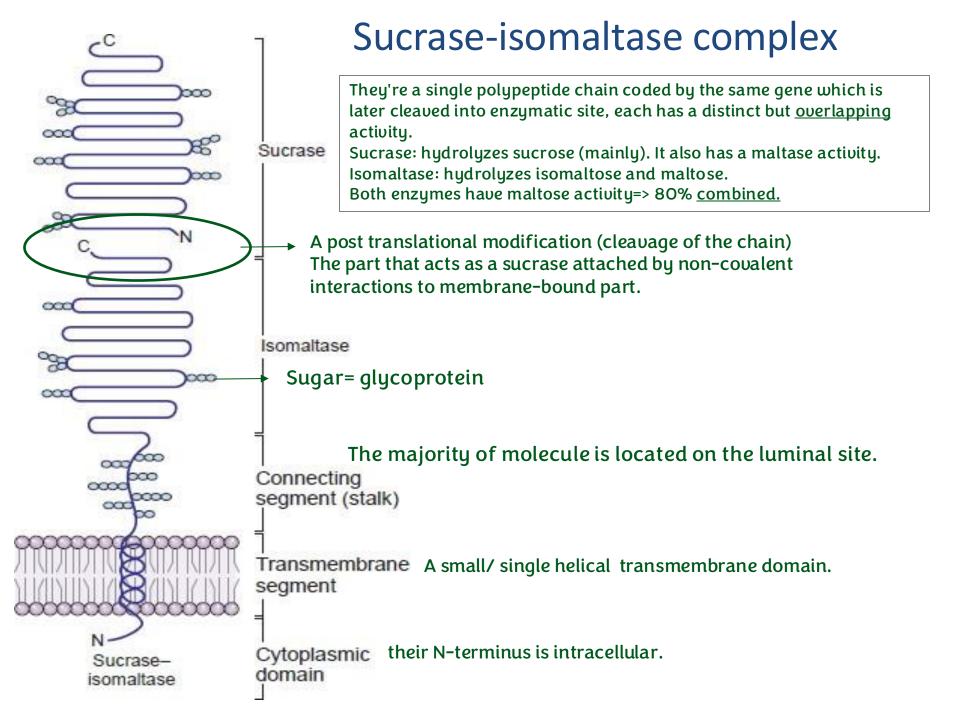
- Before we begin, here is some basic information:
- Starch can exist as either **amylose** (an unbranched polymer of glucose) or **amylopectin** (a branched polymer, with branches occurring at carbon number 6 via **alpha-1,6 bonds**).
- The digestion of starch is carried out by the enzyme amylase (either pancreatic amylase or salivary amylase). Amylase can only hydrolyze alpha-1,4 glycosidic bonds.
- Now, let's discuss the possible products of starch digestion:
- 1. Trisaccharides or Larger Oligosaccharides: unbalanced products that contain only glucose residues linked by alpha-1,4 bonds.
- 2. Maltose: A disaccharide made up of two glucose residues connected by an alpha-1,4 bond.
- 3. **Isomaltose**: A disaccharide composed of two glucose residues linked by an **alpha-1,6 bond**.
- 4. **Dextrins**: A broad category of molecules produced from the partial degradation of starch. Dextrins contain both **alpha-1,4** and **alpha-1,6 linkages** and often retain branch points.
- It doesn't break the ends monomer by monomer (it is not as meticulous as that).
- It is a random process.

Mucosal cell membrane-bound enzymes

ENZYME	Bond Cleaved	Substrates
Isomaltase	$\alpha 1 \rightarrow 6$	Isomaltose
Maltase	$\alpha 1 \rightarrow 4$	Maltose
Sucrase	$\alpha 1 \rightarrow 2$ Anomeric	Sucrose
Lactase	$\beta 1 \rightarrow 4$	Lactose
Trehalase	$\alpha 1 \rightarrow 1$	Trehalose 2 glucose residues connected to each other by α 1-1.
Exoglycosidase (Glucoamylase) Acts on the termini	$\alpha 1 \rightarrow 4$ and $\alpha 1 \rightarrow 6$	Starch Found in mushroom, honey, and sea food.

اللهم أصلح أحوال المسلمين، وأنج المستضعفين منهم برحمتك، اللهمَّ عليك باليهود وأوليائهم، دمرهم اللهمَّ واطمس على أموالهم وعدتهم وأرنا بهم يومًا أسود كيوم عادٍ وثمود





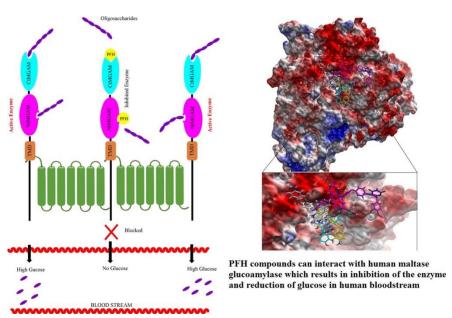
Maltase-exoglycoidase (Glucoamylase) complex

It's a single membrane protein that doesn't get cleaved.

This complex is also embedded in the intestinal cell membrane by a helical transmembrane domain with the majority of the chain in the intestinal lumen

it has 2 enzymatic activities (Maltase activity & Glucoamylase activity). It's responsible for 20% of the maltase activity.

Quick comparison: Sucrase-isomaltase (SI) complex is a single protein that is cleaved into two functional subunits, which remain associated in the cell membrane and perform two enzymatic activities. In contrast, maltase-exoglycosidase complex (MGA) is a single membrane protein that doesn't get cleaved. It has two enzymatic activities, first one is maltose digestion, and the second one is (glucoamylase) so it cleaves a(1->4) glycosidic bond in dextrins.

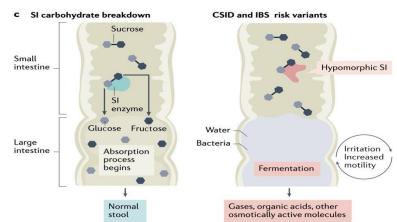


The pic's link

Clinical Hint: Abnormal Degradation of disaccharides

Some applications on the digestion of disaccharides:

Normally, sugars must be digested until they become monosaccharides, allowing for absorption to occur. If there is a deficiency in disaccharide-digesting enzymes, disaccharides will accumulate in the intestinal lumen, resulting in increased osmotic pressure and pulling water molecules into the intestine, which can lead to diarrhea. The normal bacteria present in the small intestine use this accumulated sugar, producing side products like CO2 and CH4, leading to bloating.



1. Sucrase-isomaltase deficiency:

☐ Causes: directly or indirectly

Genetics: genetic mutations in a single gene can lead to different diseases, and the severity of a single disease can also vary.

The degree of deficiency plays a role in the severity-> mutation that causes a 50% deficiency is less severe than an 80% deficient, and how it affects the protein structure.

Variety of intestinal diseases: certain chemicals produced during inflammatory reactions lead to cell distraction, which affects the quality of intestine function (digestion & absorption).

When we lose intestinal surface area due to excessive cellular death, normal intestinal function is expected to be affected.

Crhon's disease and ulcerative colitis are inflammatory bowel diseases.

اللهم أمِّن أهل غزةً من كل خوف **Malnutrition:** although the enzymes and transporters are hale ,but there's no substrate to work on. أطعمهم الله وآواهم

Injury of mucosa i.e by drugs: side effects of the drug.

Severe diarrhea: diarrhea could be a cause or result (symptom).

more contractions of small intestinal smooth muscles (the components are pushed outside too quickly, so the time is not enough for full digestion and good absorption to occur).

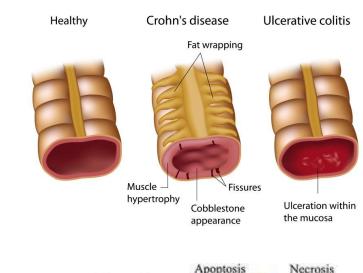
Clinical Hint: Abnormal Degradation of disaccharides

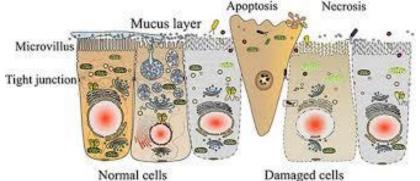
1. Sucrase-isomaltase deficiency:

Further explanation:

- 1. The genetic mutation leads to the accumulation of undigested sucrose and isomaltose in the intestinal lumen. These are soluble molecules that affect the intestinal osmotic pressure, drawing H2O into the lumen and causing diarrhea.
- 2. In inflammatory bowel diseases, chemical mediators of inflammation decrease cell quality, leading to rapid cell death and impaired cell regeneration (which normally occurs every few days in a healthy person). As a result, the intestinal surface area decreases. This surface is normally wave-like to accommodate more cells, allowing for higher concentrations of enzymes and transporters necessary for digestion and absorption. The reduced surface area leads to the metabolic suspension of not only sucrose and isomaltose but also various types of sugars, lipids, and proteins, increasing osmotic pressure and causing diarrhea.

Inflammatory Bowel Disease





Damaged intestinal mucosa

On the sidelines:

- What is the difference between infection and inflammation?
- Infection: refers to the invasion and multiplication of microorganisms within the body.
- Inflammation: normal response from your body to till you that there is something wrong somewhere.
- > The intestine renews its cells every three days.

Clinical Hint: Abnormal Degradation of disaccharides

2. Lactase deficiency (lactose intolerance): ½ world's population normal state

2 possible reasons:

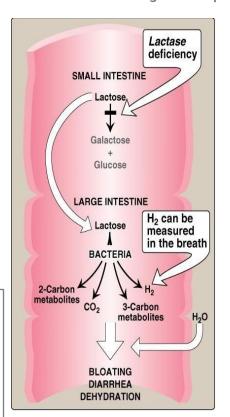
- 1. The amount of lactase decreases. Or:
- 2. The enzyme activity declines.
- ✓ Lactase reached maximal activity
- @ 1 month old
- ✓ Declines----> <u>adult level</u> 5 to 7 year of age
- √ 10% of infant level
- 1 cup of milk (9 grams of lactose) -> loss of 1 liter of extracellular fluid when the lactose reaches the small intestine, the osmotic pressure π changes, causing a lose of water in order to restore π to its normal level.

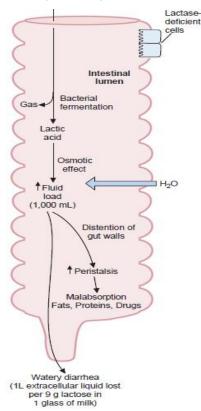
Osmotic Diarrhea:

The intestinal bacteria (normal flora) takes advantage of excess accumulated lactose to metabolize it and produce byproducts (CH4 and CO2).

it's very common half of the population is affected by it . Solutions for this condition include lactose-free products or lactase supplements or avoiding milk consumption (We can substitute some nutrients by taking supplements, such as calcium (Ca^{2+}) and vitamin D supplements "or by increasing exposure to sunlight").

Milk contains fatty acids, proteins (casein), and lactose.





UV light acts as a catalyst that initiates Vit. D synthesis in the skin.

Absorption of Sugars

(monosaccharides)

Polar molecules can not diffuse

A: Na⁺-independent facilitated

diffusion transport

Some features:

- · Independent of sodium.
- Down the concentration gradient.
- Doesn't need energy.
- Require a transporting protein.

1. GLUT 1----GLUT 14 different type

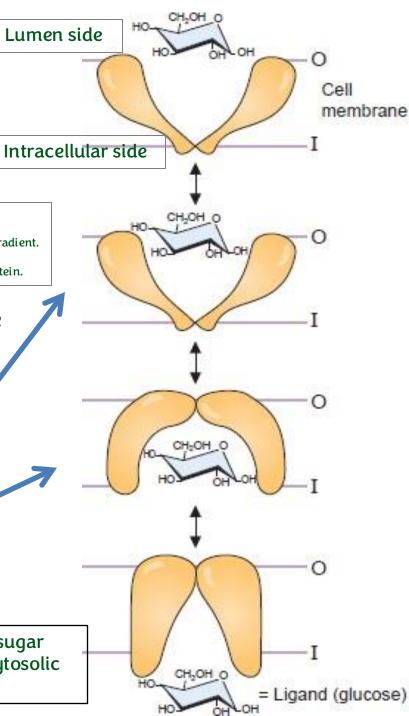
Glut: glucose transporters but it can also transport other monosaccharides.

2. Glc. Movement follows concentration gradient

Two conformational states

After binding to the ligand "glucose"

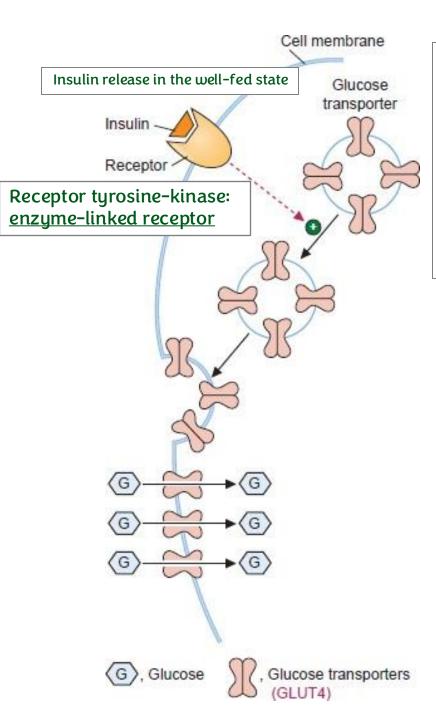
Increases the sugar levels in the cytosolic end.



Glut 7: In glucose synthesis a step takes place in the ER and this transporter is needed/will be discussed later on through the course

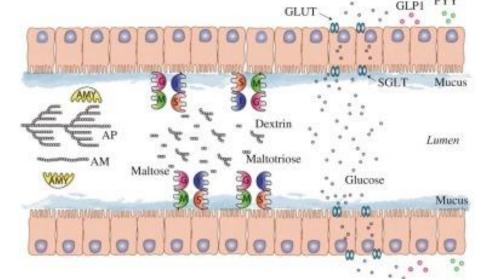
Table 27.5 Properties of the GLUT 1 to GLUT 5 Isoforms of the Glucose Transport Proteins

Transport Frote	Transport Froteins				
Transporter	Tissue Distribution	Comments			
GLUT 1	Human erythrocyte	Expressed in cell types with barrier			
Highly expressed in barriers. Barriers are made of tight junctions between endothelium cells.	Blood-brain barrier Blood-retinal barrier Blood-placental barrier Blood-testis barrier	functions; <u>a high-affinity glucose</u> transport system Non- specific			
GLUT 2	Liver	A high-capacity, low-affinity transporter			
Glucose,	Kidney	May be used as the glucose sensor in			
galactose	Pancreatic β -cell	the pancreas			
and fructose	Serosal surface of intestir mucosa cells	nal (Basolateral surface)			
GLUT 3	Brain (neurons)	Major transporter in the central nervous system; a high-affinity system			
GLUT 4	Adipose tissue Skeletal muscle Heart muscle After eating, levels rise an the synthesis protein.	insulin-sensitive transporter. In the			
GLUT 5 Fructose	Intestinal epithelium Spermatozoa	This is actually a fructose transporter Na independent			
GLUT 7	Glucogenic tissues	at endoplasmic reticulum membrane			



After the activation of kinases, a transcription factor is activated, which promotes certain target genes, including the gene responsible for synthesizing GLUT4. GLUT4 is a membrane protein that is initially inserted into the vesicle membrane and then transported to the cell membrane through vesicle fusion. This process increases the concentration of GLUT4 on the cell surface, allowing for greater glucose uptake from the blood. As a result, insulin lowers blood sugar levels after meals

Insulin stimulates transport of glucose into muscle and adipose tissues

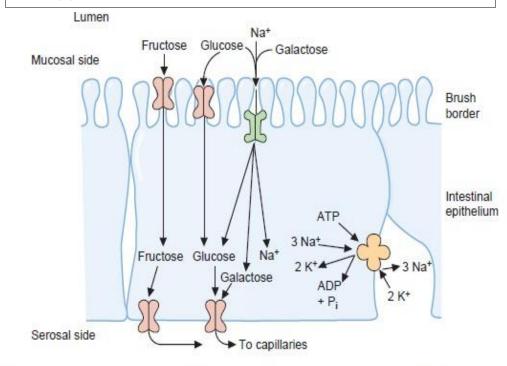


Na+ monosaccharide cotranspoerter system (SGLT)

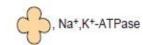
- Against concentration gradient(requires energy)
- Small intestine: Active uptake from lumen of intestine.
- Kidney: Sugar in urine= diabetes
 Reabsorption of glucose in
 proximal tubules.
- For glucose and galactose absorption.

It enters the glucose with Na⁺ ion.

This process facilitated by sodium-glucose cotranspter and it is coupled with Na⁺/K⁺pump that requires energy.







Why is against the gradient?
Because most of the glucose is intracellular
(transported by glut 4) and to ensure that the
absorption process is more efficient

Test yourself ©

- 1) Is sucrase-isomaltase complex a membrane-bound enzyme?
- 2) The sugar/ monosaccharide needed by the sperm is?
- 3) The percentage of lactase in adults is_____% of infant levels.
- 4) What type of reaction does glycosidase catalyze?
- 5) The incorrect statement is:
- A. Glucose and mannose are epimers.
- B. Glucose and fructose are diastereomers.
- C. Galactose and mannose are not epimers.

- 6) Trehalose consists of one of the following:
- A. Glucose with glucose connected by a α -1,6 linkage.
- B. Glucose with Galactose connected by an α -1,1 linkage.
- C. Glucose with glucose connected by a β -1,1 linkage.
- D. Glucose with glucose connected by an α -1,1 linkage.
- 7) What type of glycosidic bond can our amylase enzymes digest?
- **A**. α-1,6
- B. α-1,2
- **C.** β-1,4
- D. α-1,4

ربِّ اجعلني لكَ شكَّارًا، لك ذكَّارًا، لك رَهَّابًا، مطواعًا لك، مخبتًا إليكَ منيبًا.

The intestinal epithelial cells are polarized, meaning they have two distinct surfaces:

Apical surface (brush border): This side faces the intestinal lumen, where nutrients are absorbed.

Basolateral surface: This side faces the bloodstream and other underlying tissues, where absorbed nutrients are transported.

Glucose Transport:

1- Apical Surface Transport:

Sodium-Glucose Linked Transporters (SGLTs):

These are active transporters that use the sodium gradient (high outside the cell, low inside the cell) to co-transport sodium (Na $^+$) and glucose into the cell. This occurs against the glucose concentration gradient , requiring energy indirectly from the sodium gradient.

Na⁺/K⁺ Pump:

The activity of the SGLTs increases intracellular Na^+ . To maintain the sodium gradient, the Na^+/K^+ ATPase pump on the basolateral surface actively pumps Na^+ out of the cell and K^+ into the cell. This pump uses ATP to function and ensures the sodium gradient remains intact.

The influx of Na⁺ disrupts the charge distribution, necessitating the Na⁺/K⁺ pump's activity to restore balance.

2-Basolateral Surface Transport:

Glucose Transporters (GLUTs):

On this surface, facilitated diffusion is used to move glucose into the bloodstream. GLUTs allow glucose to flow down its concentration gradient (from high inside the cell to low in the bloodstream). This process does not require energy.

No SGLTs on the Basolateral Surface:

Since glucose is moving down its gradient, there's no need for active transport (like SGLTs) on this side.

3- Intracellular Glucose Function:

Some glucose is retained within the intestinal cells to provide energy for cellular processes and maintain cell function.

Polarized Transport:

Apical Surface (lumen-facing) : Uses SGLTs for active glucose uptake (with Na $^+$) and depends on the Na $^+$ /K $^+$ pump to expel excess Na $^+$

Basolateral Surface (blood-facing): Uses GLUTs for passive glucose transport into the bloodstream, driven by the concentration gradient.

For any feedback, scan the code or click on



Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	تم اعتماد محاضرة سكشن آخر وإعادة صياغة الكثير من المعلومات		
V1 → V2	Page 29 Page 33	9 grams of lactase Na ⁺ /k ⁺ pump releases energy	9 grams of lactose Na ⁺ /k ⁺ pump requires energy
V2 → V3	تم إضافة صفحتين التوضيح فكرة شُرحت في بداية محاضرة ١١ Page 35 & 36		

Additional Resources:

رسالة من الفريق العلمي:

Reference Used:

Chapter 7: Lippincott illustrated reviews 7th edition.

https://youtu.be/jI7GnBKGx3c?si=whisvHh_cRUHsQdH

https://youtu.be/Lc6UikgCCh0?si=e5IY 12LxdS MBvi

اللهم اغفر لي خطيئتي و جهلي و إسرافي في أمري و ما أنت أعلم به مني اللهم اغفر جدي و هزلي و خطأي و عمدي و كل ذلك عندي.

اللهم اغفر لي ما قدمت و ما أخرت و ما أسررت و ما أعلنت و ما أنت أعلم به مني أنت المقدم و المؤخر و أنت على كل شيء قدسر