فريق طوفان الأقصى

METABOLISM

Modifide No.10

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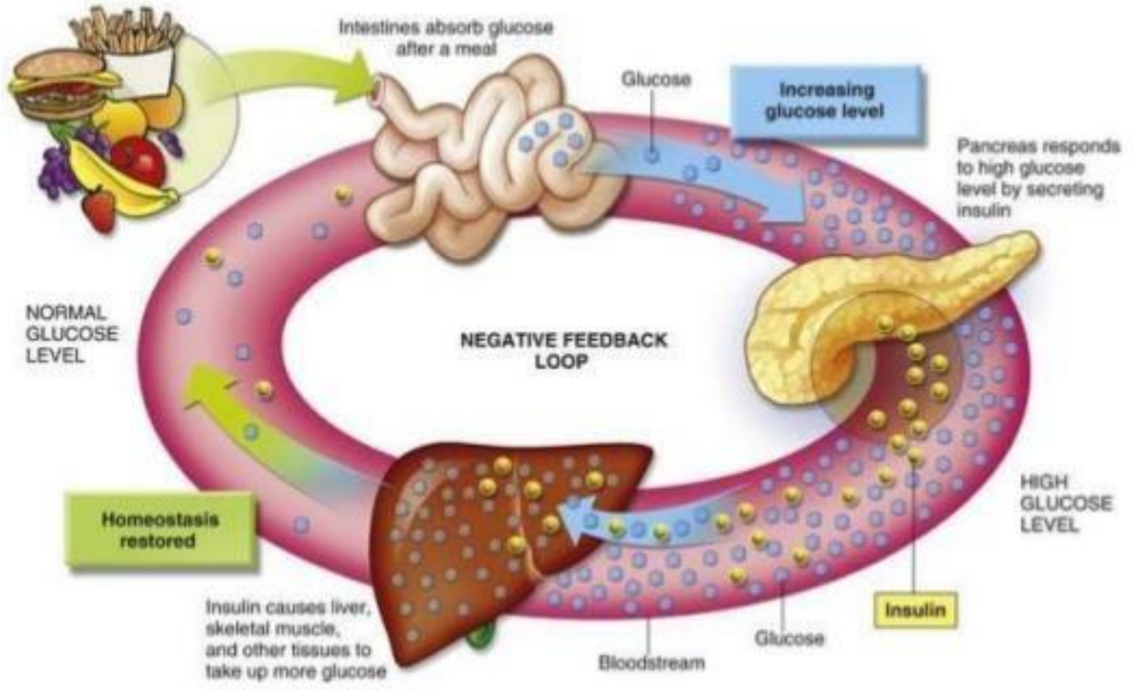


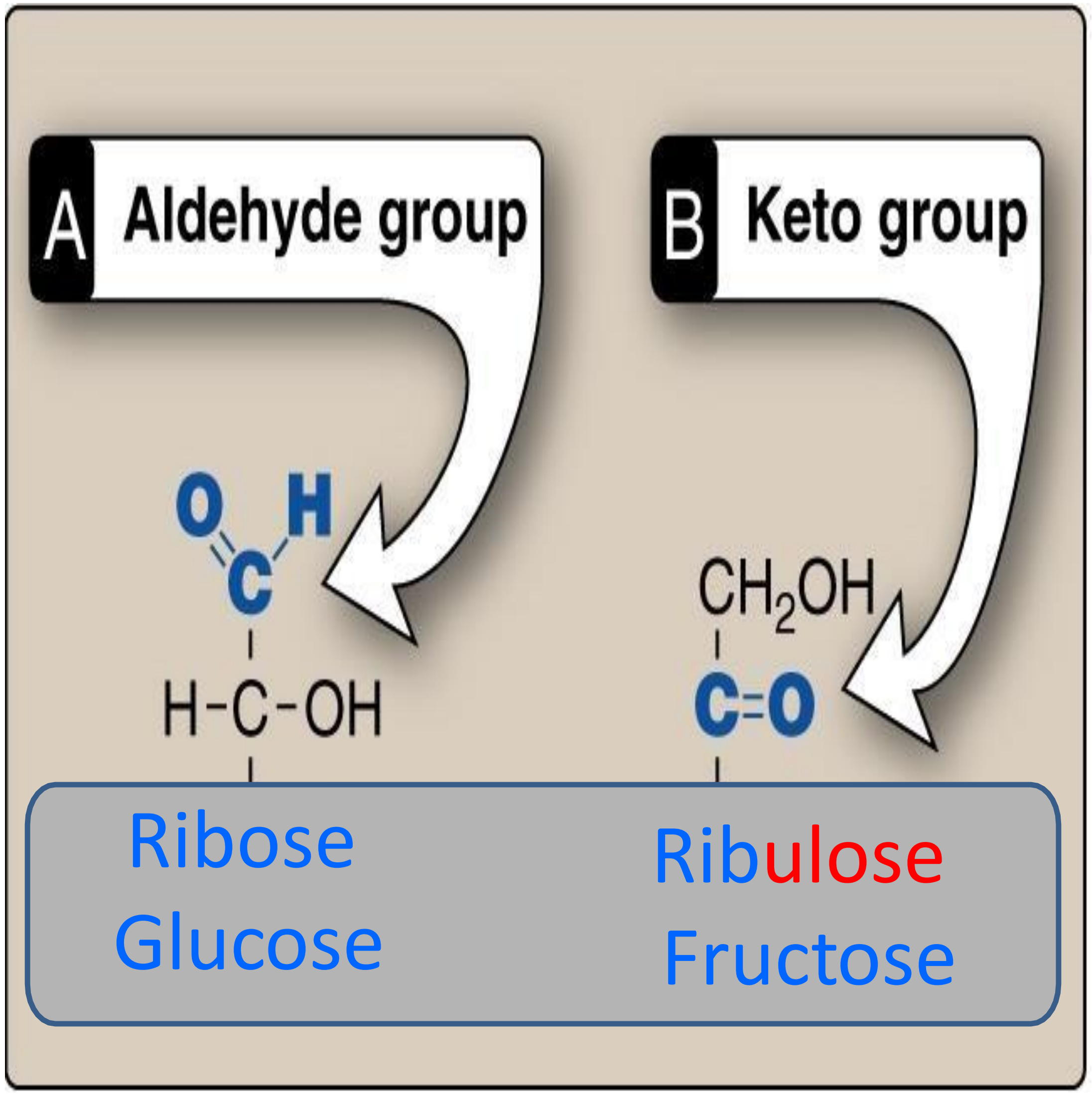
Carbohydrates Metabolism

Dr. Diala Abu-Hassan

Review of Carbohydrates
Digestion and absorption of carbohydrates

Suggested Readings:
1: Lippincott's Illustrated reviews: Biochemistry 2: Marks' Basic Medical Biochemistry

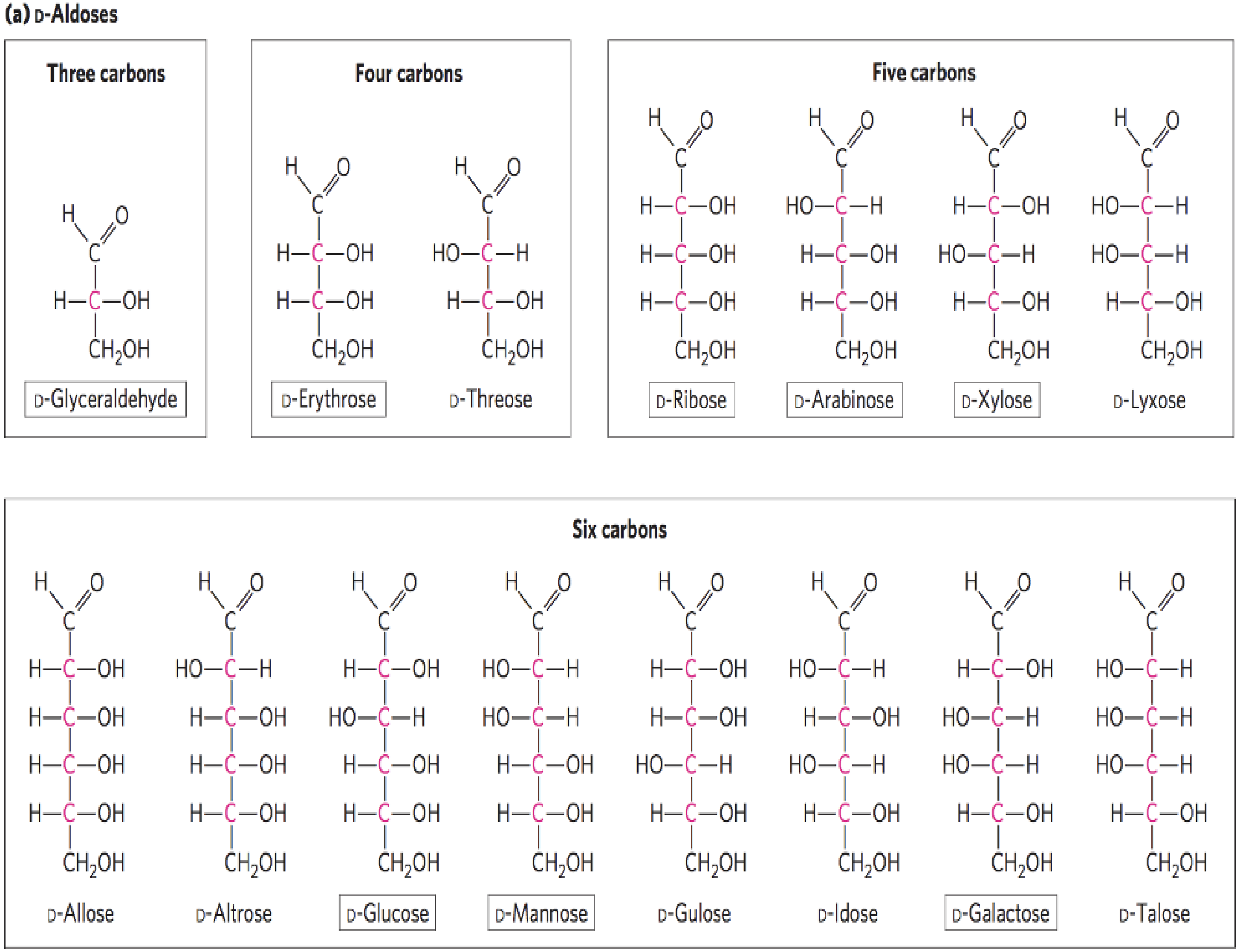
Sugars are either ketoses or aldoses

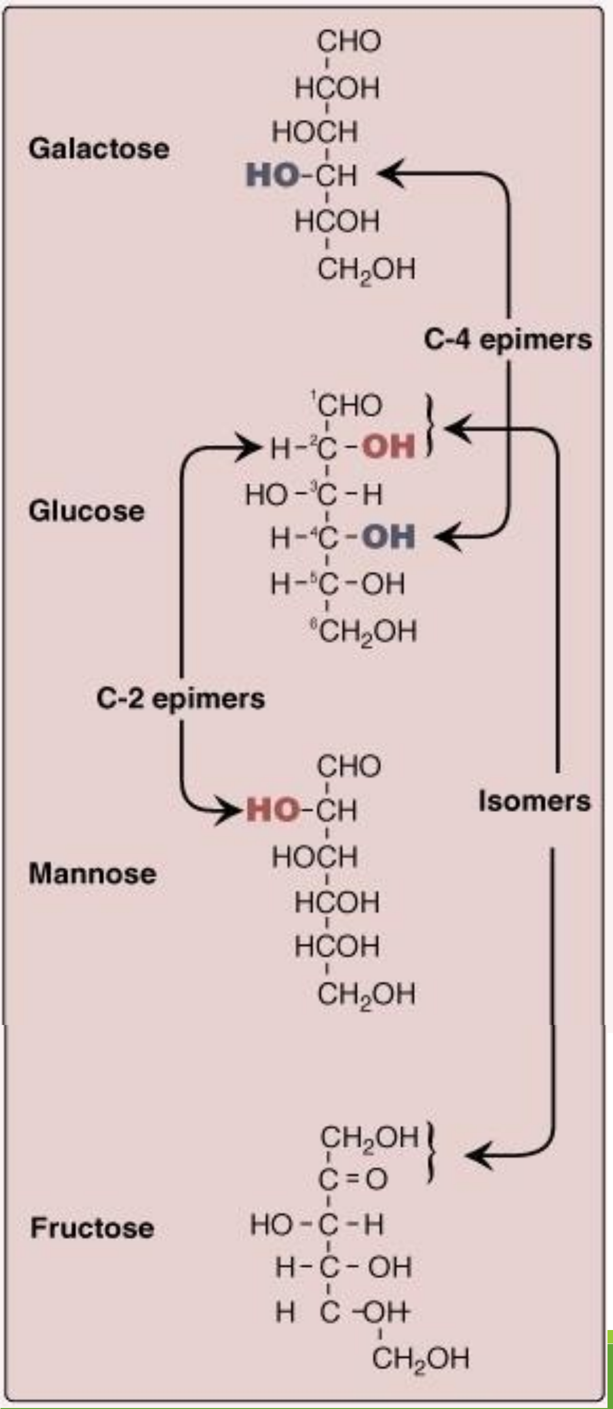


- NOTE: You should remember that sugars are either **Aldoses** or **ketoses** , and the majority are **aldoses** .
- The simplest aldose is Glyceraldehyde(3carbons) and the simplest ketose is Dihydroxyacetone(3 carbons) .
- Glyceraldehyde has one chiral center , but Dihydroxyacetone doesn't have any chiral center .
- There are a lot of sugars and they differ mainly in the number of carbon atoms, but most commonly you find pentoses and hexoses.
- The suffix (–ulose) is a hint of ketoses, but not necessarily found in all ketoses names.

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





Sugars have Isomers:

Because of the chiral centers in aldoses, and especially stereoisomers , they maintain the same functional group but have different orientations in the 3D shape .

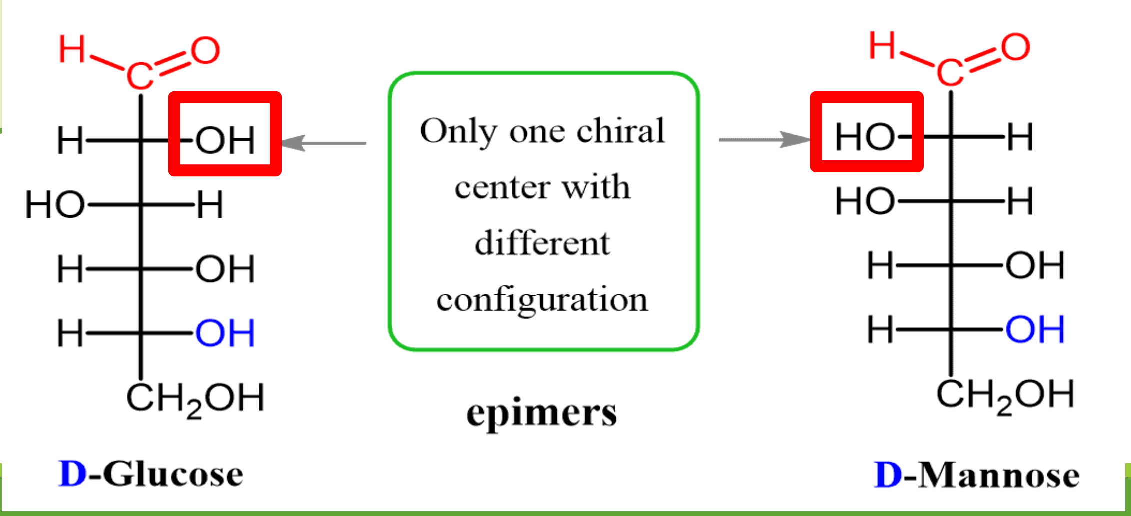
- **Diastereomers : two compounds having different (OH) orientation on multiple carbons but not all of them .**
- **If the two compounds are mirror images , we call them enantiomers .**

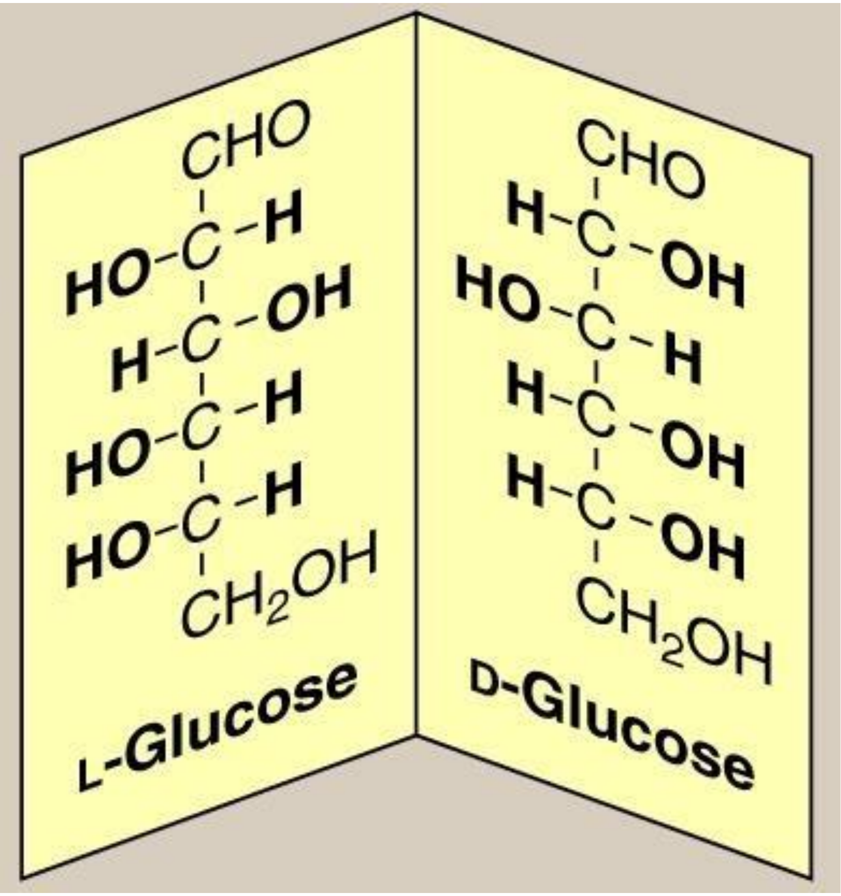
Epimers are isomers:

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

- Glucose and Fructose are isomers

- **Galactose and Mannose are only diastereomers .**
- **Glucose and Fructose are Constitutional isomers .**

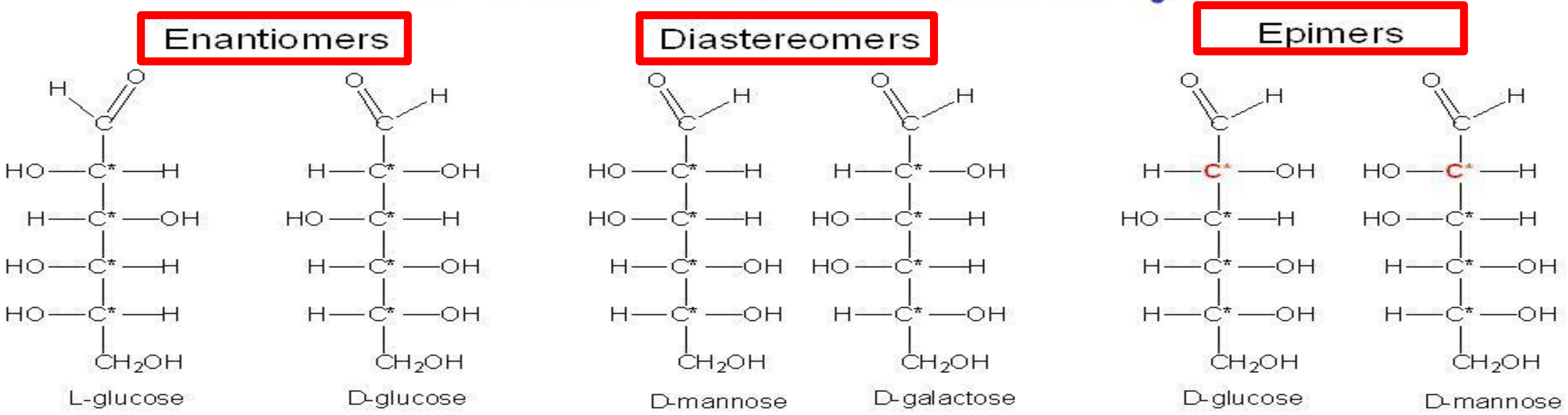




Enantiomers

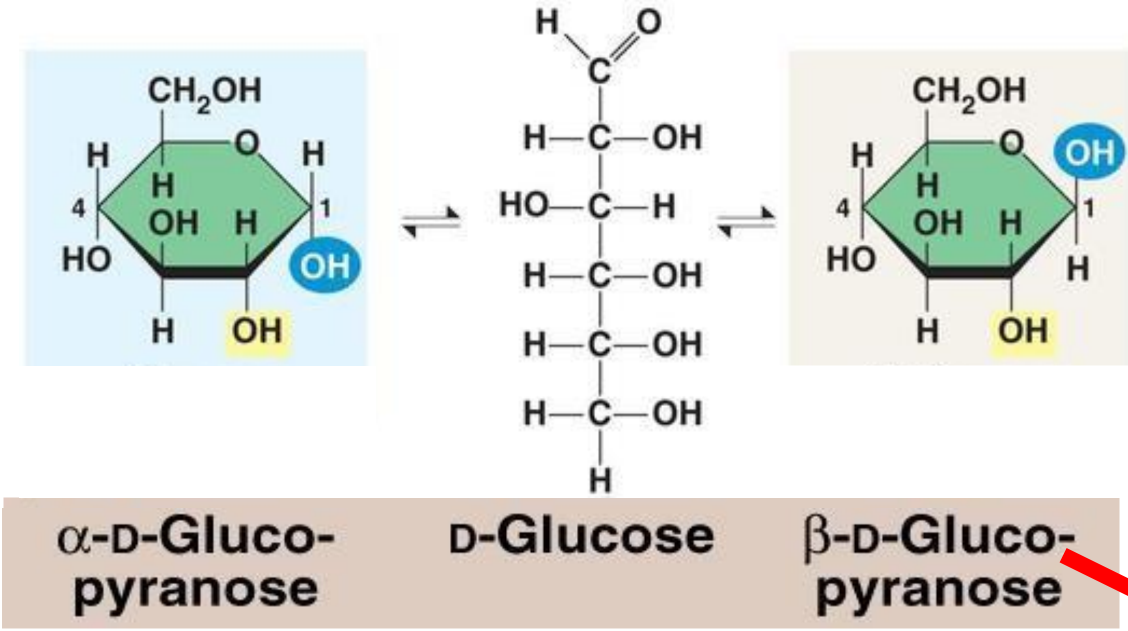
- **NOTE: The predominant form of sugars in our body is <u>(D conformation)</u>**

Stereochemistry



- **Enantiomers** = mirror images
- Pairs of isomers that have opposite configurations at one or more chiral centers but are NOT mirror images are **diastereomers**
- **Epimers** = Two sugars that differ in configuration at only one chiral center

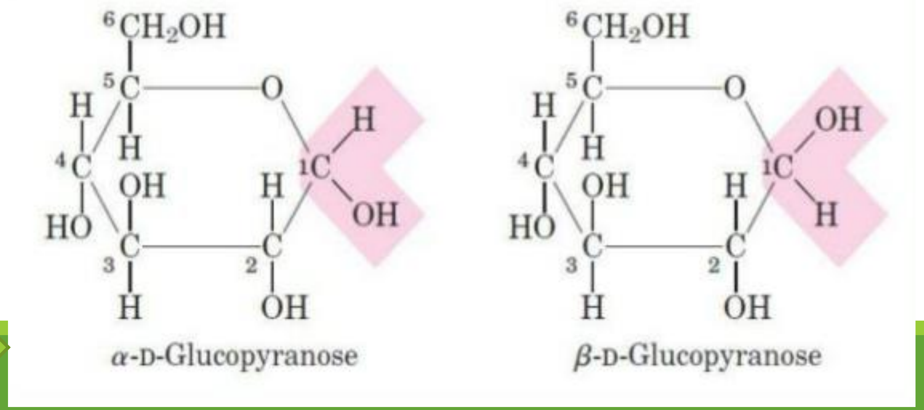
Alpha and Beta Sugars (Anomers)



- NOTE: Sugars are mostly present in a cyclic form (ring structure) rather than a linear structure. The ring structure is more stable because there are **less active functional groups** that interact with each other → **more stability.**

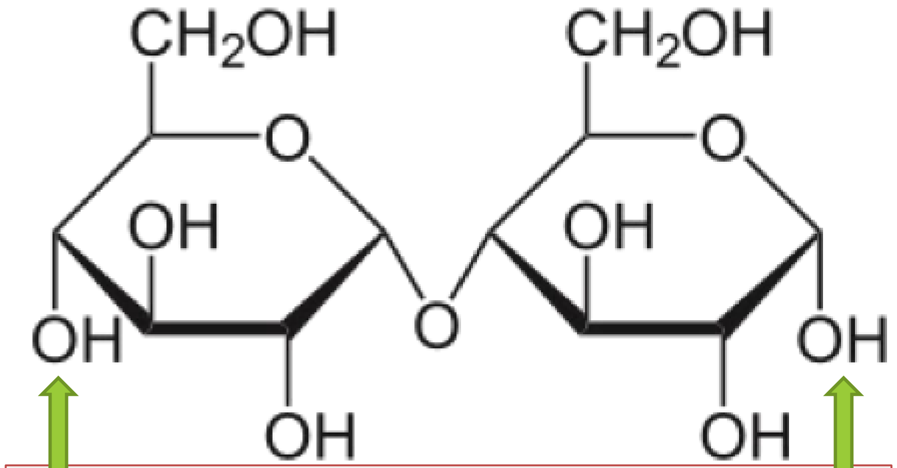
- NOTE: carbon #1 in aldoses and carbon #2 in ketoses have OH group in the ring structure while in the open chain it doesn't , it's a **carbonyl group** .
- These OH groups can be oriented downwards**(alpha)** or upwards**(beta)** of the ring , it can be either alpha or beta , so in aldose for example, the OH group may be upwards and downwards →that's what we call **(ANOMERS)** .

- The most stable form of glucose sugar .

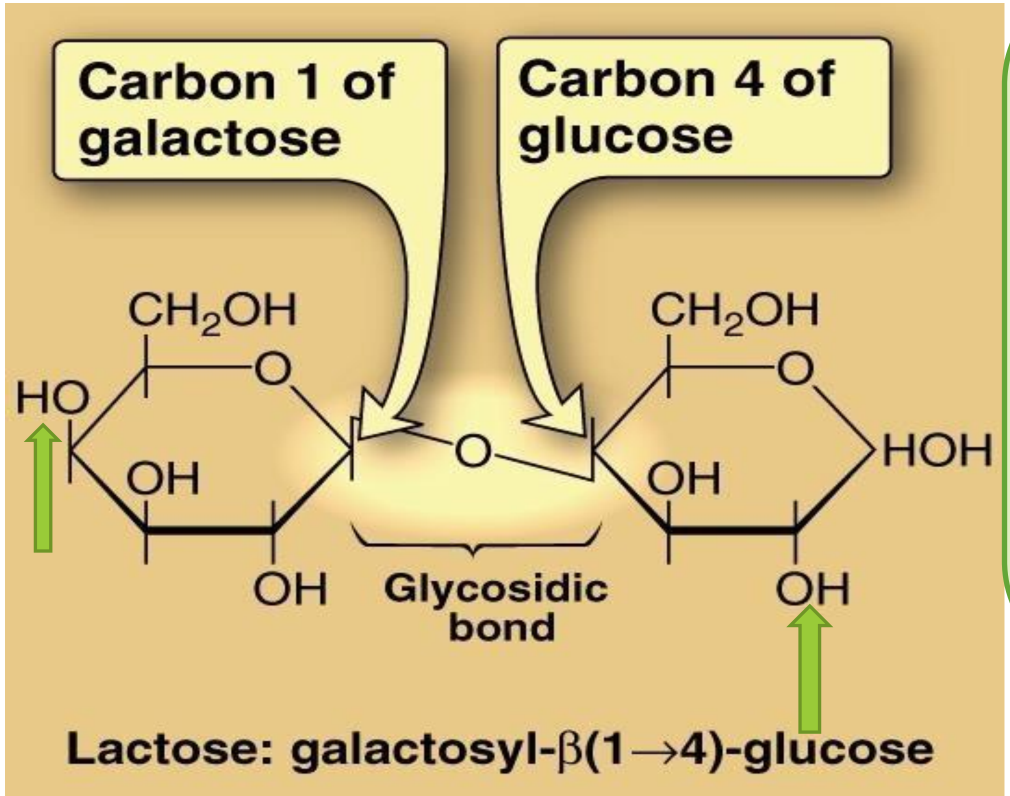


Disaccharides

Sugars made of two monosaccharide units joined by a glycosidic bond



Maltose: a disaccharide made from two glucose units

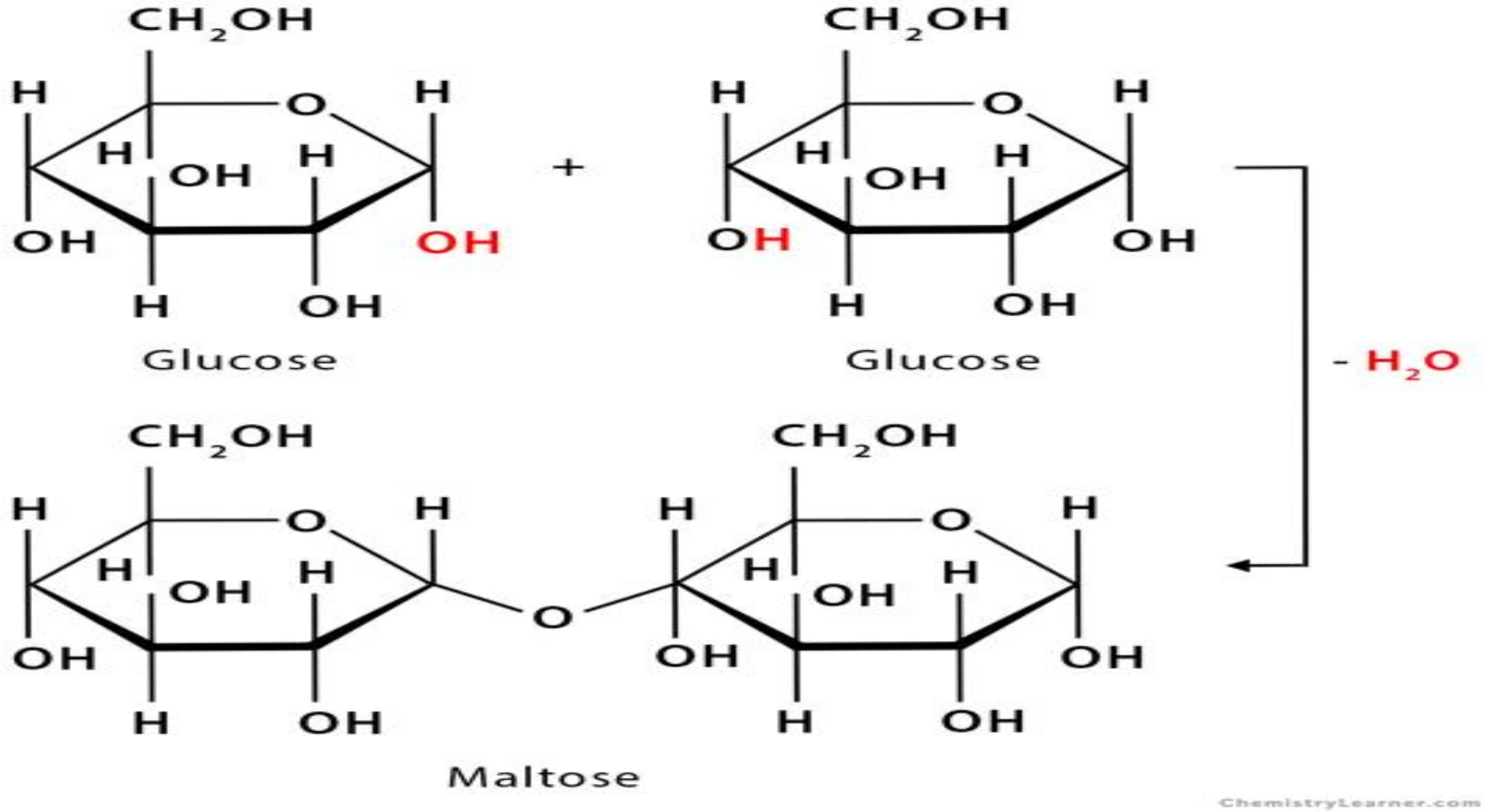


- Each two monosaccharides are joined by a glycosidic bond in a dehydration reaction , by this, we form disaccharides.

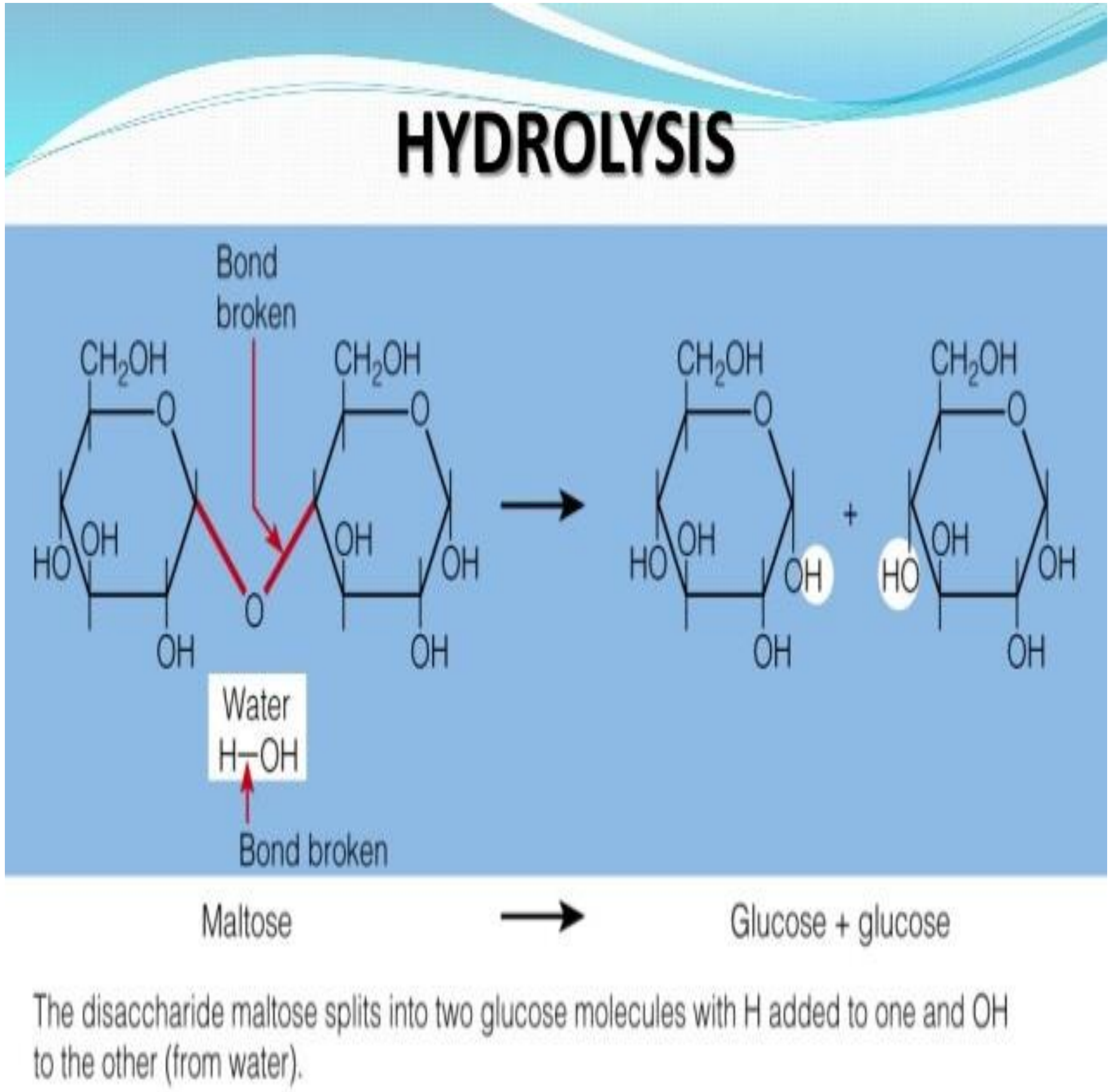
- NOTE: maltose is a Homodisaccharide , its built from the same type of monomers .

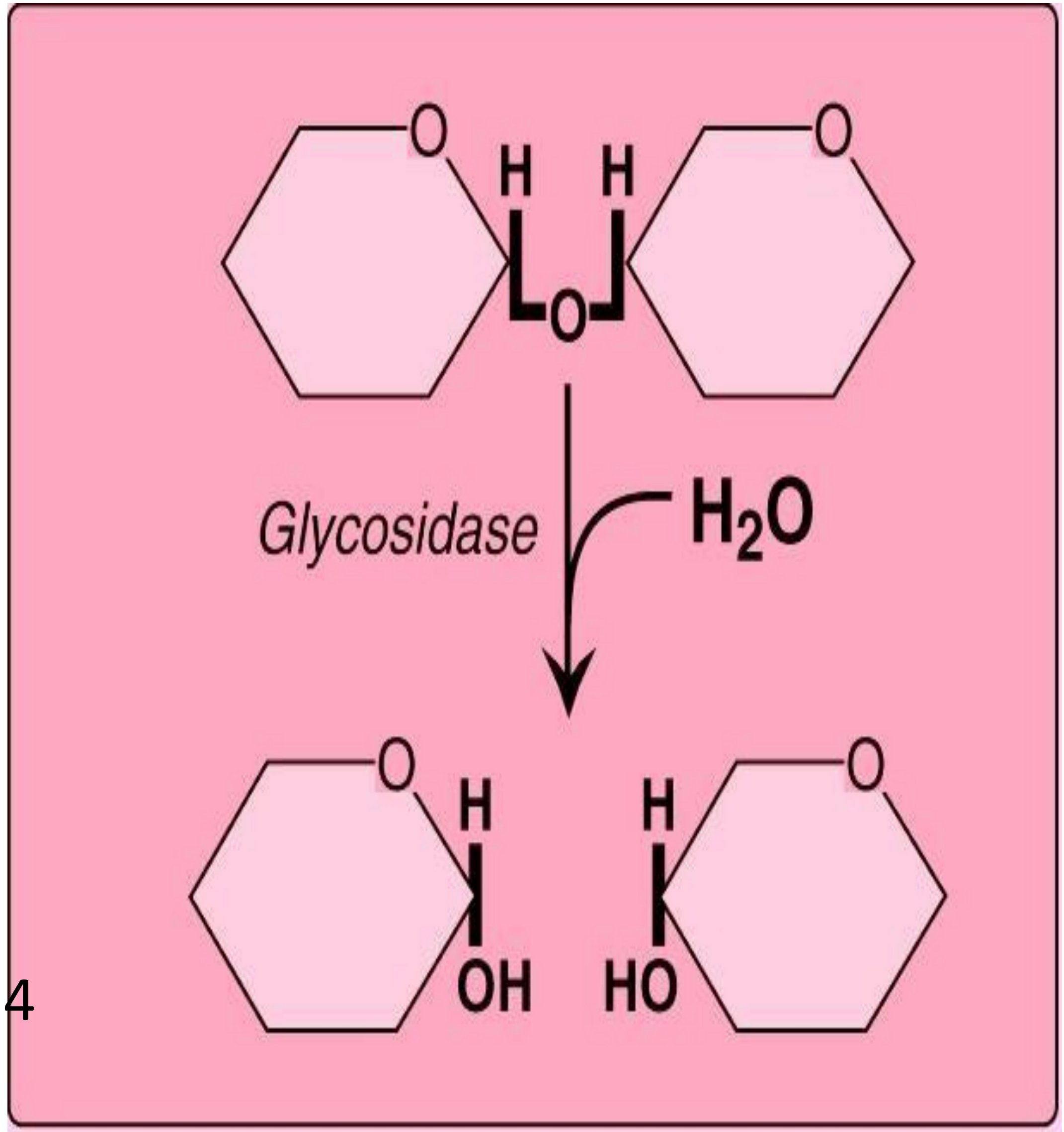
- NOTE: The OH groups of two monomers are in different opposite directions so the product (lactose) is in beta conformation .

Dehydration Synthesis with Glucose



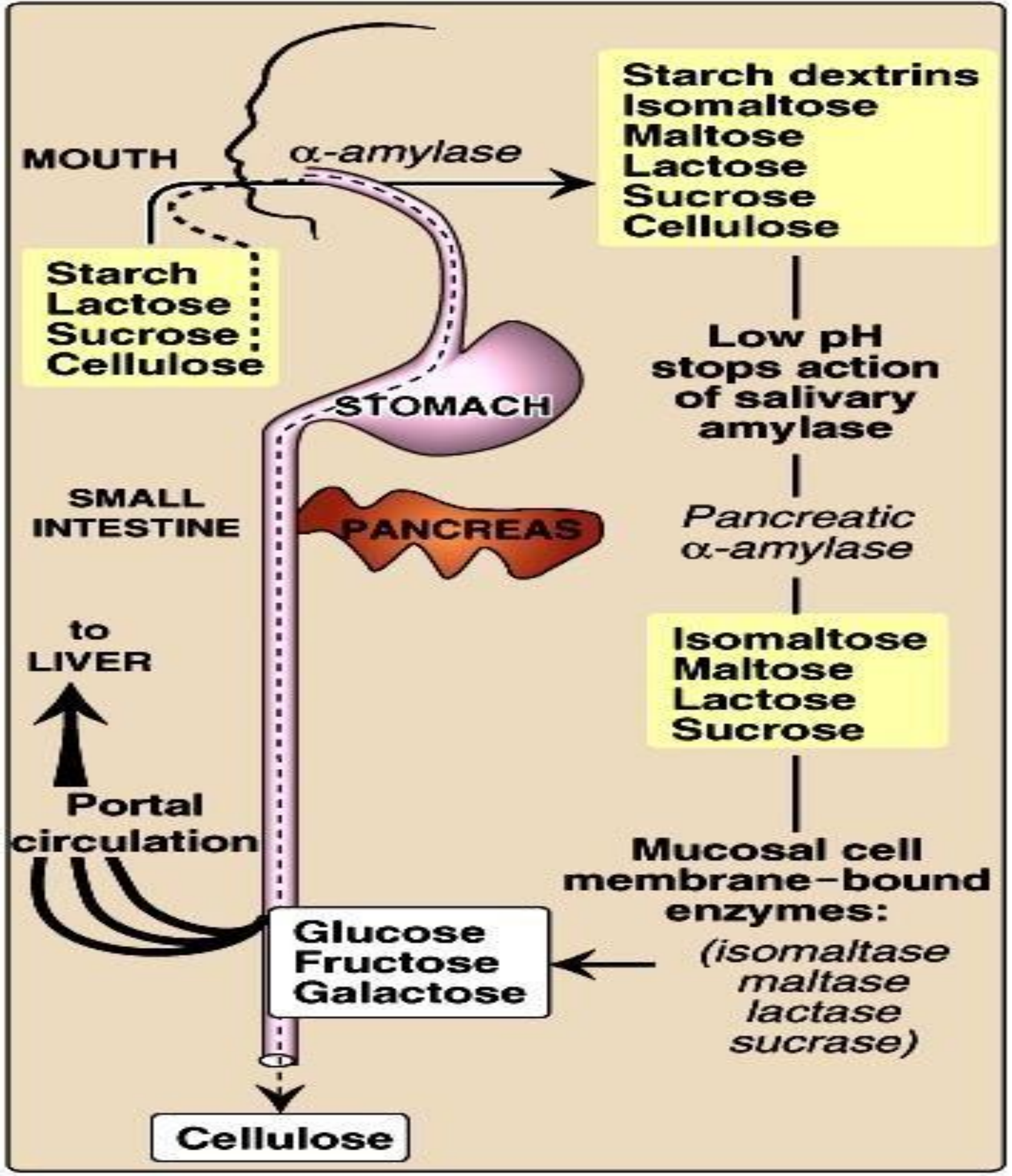
Glycosidic bond is cleaved by glycosidase enzyme





Formation and Cleavage Of Disaccharides

- **The complement in this slide:** As we said before , the formation of glycosidic linkage (sugar + sugar) is done by **a dehydration reaction** , so we have a loss of a water molecule (H_2O)→ one monomer loses a (OH) group, and the other monomer loses a (H) , then they get connected to each other by **a covalent bond (glycosidic bond).**
- Whenever we eat disaccharides , our body is unable to absorb it in this form , so it has to be digested by cleaving the glycosidic bond by **a hydrolysis reaction** (addition of a water molecule) , this reaction is carried by enzymes called **glycosidases.** A glycosidase is a general group of enzymes that cleave glycosidic bonds, by which each one is specialized in cleaving a specific bond .



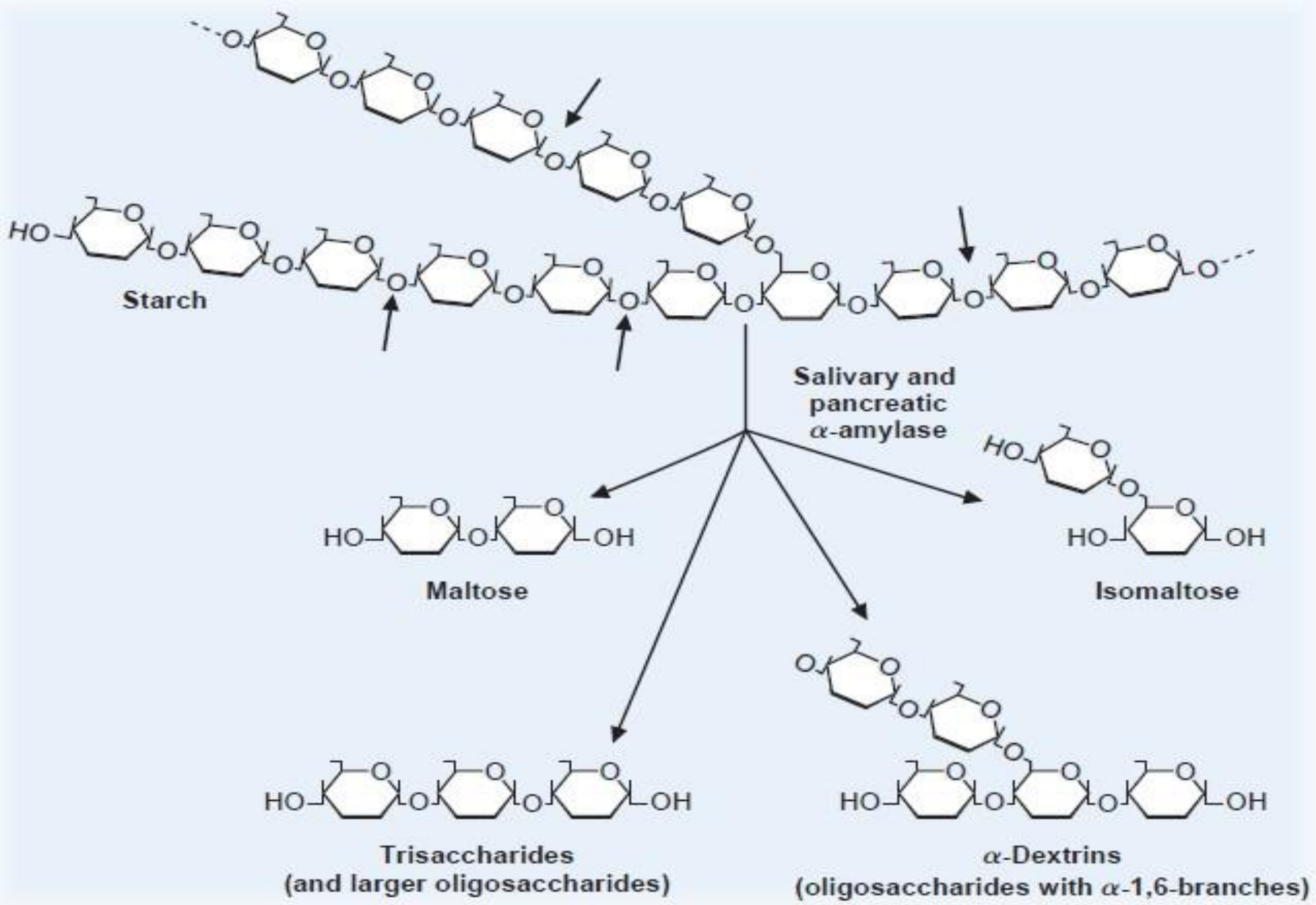
- **NOTE:** we are going to talk about the digestion in our body.

- **NOTE:** remember this picture very well.

Digestion of Carbohydrates

- **The complement in this slide:** firstly, digestion starts in the oral cavity by teeth and then by a specific saliva enzyme called α amylase.

- **NOTE:** information about α amylase :
- The only digestion enzyme between all saliva enzymes.
- Can only hydrolyze α 1-4 glycosidic linkage, which is present in starch and maltose, but this enzyme is only specific to starch not maltose (can digest starch, but can not digest maltose)



- **NOTE:** this picture represents how the enzymes work on starch, and what the products are.

- **NOTE:** dextrin has many branches.

Starch Digestion

- **The complement in this slide:** but the food stays seconds in the mouth, so sugars become only fragments.

- **The complement in this slide:** the next stage is the stomach, that contains several enzymes, but there is no one for sugars (pepsin is a protease; works on protein not sugar), so nothing happens to sugars inside the stomach, so sugars go to the next stage which is the small intestine.

- **The complement in this slide:** the first step in the small intestine is the pancreas, which has an enzyme called pancreatic α-amylase that makes sugars (disaccharides) . Now, the mucosal cell membrane-bound enzymes work after pancreatic enzymes (monosaccharides) .

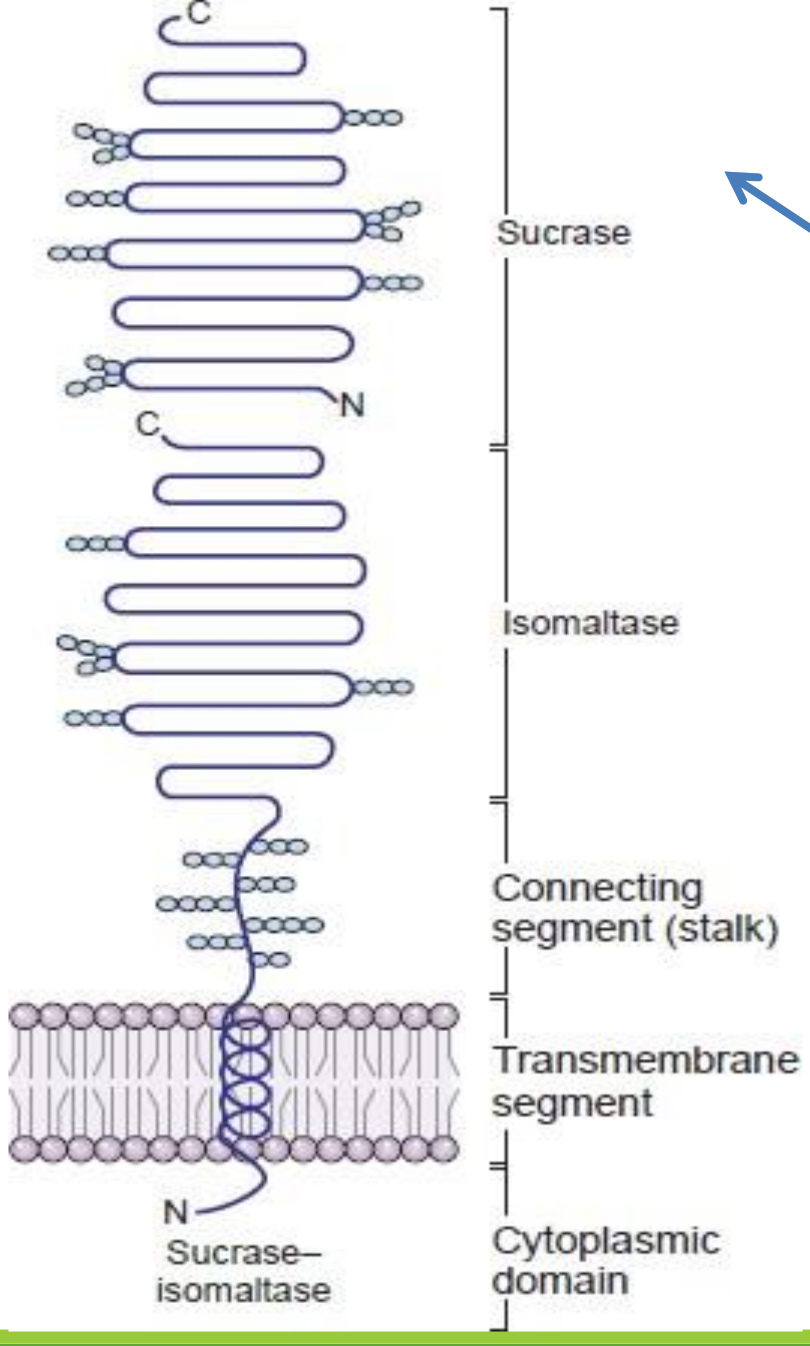
ENZYME	Bond Cleaved	Substrates
Isomaltase	1→ 6α	Isomaltose
Maltase	1→ 4α	Maltose
Sucrase	1→ 2α	Sucrose
Lactase	1→ 4β	Lactose
Trehalase	1→ 1α	Trehalose
Exoglycosidase (Glucoamylase)	α1→ 4 and α 1→ 6	Starch

Mucosal cell membrane-bound enzymes

- **The complement in this slide:** intestine enzymes are specific, meaning that they should recognize the kind of the bond and the two monomers of that bond.

- **The complement in this slide:** trehalose is a homo sugar of glucose, it is an inert sugar (due to the stable bond between the anomeric carbons), it is positively modified by the normal flora in the intestine.

- **The complement in this slide:** Exoglycosidase works on the terminal monomers of the molecule (EXO), and cleaves them one by one .
- Can work on the branches (α 1-6)



Sucrase-isomaltase complex and Glucoamylase

Sucrase + isomaltase *
Single protein → complex of two associated subunits

-Sucrase-maltase

- Isomaltase-maltase

Together 80% of the maltase activity

Maltase + exoglycosidase (glucoamylase):no split *

- **The complement in this slide:** sucrase-isomaltase complex:
- It is a single polypeptide expressed from the same gene.
- It is a glycoprotein.
- Has a 2 enzymatic activity.
- Works on both maltase and isomaltase.
- Gets inserted into the membrane of the intestinal cells.
- Small N-terminus in the intracellular side, and the majority is into the lumen where the reactions take place.

- **The complement in this slide:** if we see the previous picture, the complex has 2 N-terminus and 2 C-terminus, so why did we say that it is a single polypeptide? Because it gets cleaved post translationally.
- Despite this cleaving , there are non covalent interactions (weak) between the two enzymes, this process gives flexibility to the complex to do the 2 enzymatic activity.

- **The complement in this slide:** there is another complex called glucoamylase, which has all the previous characteristics except that there is no splitting (stays connected).

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*.

Sucrase-isomaltase complex

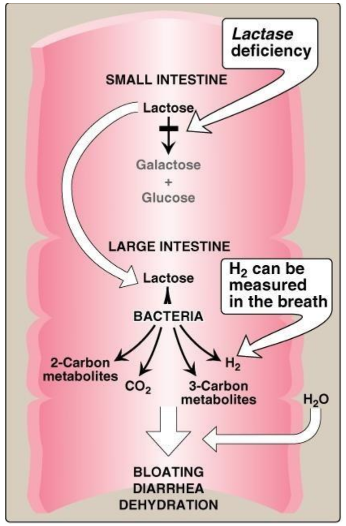
Clinical Hint: Abnormal Degradation of disaccharides
1. Sucrase-isomaltase deficiency:

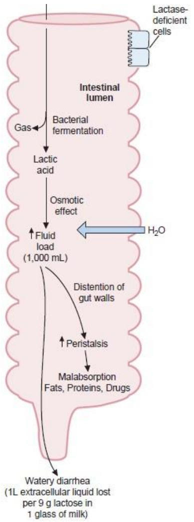
- Causes:
  - Genetics
  - Variety of intestinal diseases
  - Malnutrition
  - Injury of mucosa i.e by drugs
  - Severe diarrhea

- **The complement in this slide:** there are many causes of sucrase-isomaltase deficiency:
- Genetics : mutations decrease digestion which decreases absorption, causing a decrease in metabolism.
- Variety of intestinal diseases : like celiac and Crohn's diseases, loss of the intestinal cells leads to loss of their digestive enzymes and decrease the surface area, which decreases the efficiency of absorption.
- Malnutrition
- Injury of mucosa by drugs: especially strong drugs like chemotherapy
- Severe diarrhea

- **The complement in this slide:** there is a difference between digestion and metabolism.
- Digestion: due to eating, breaking the molecules down into smaller ones that are absorbable.
- Metabolism: happens inside the cell to all molecules either from food or the body synthesizes it (anabolic and catabolic)

Clinical Hint: Abnormal Degradation of disaccharides





2. Lactase deficiency: ½ world's population

- Lactase reached 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 lactose) loss of 1 liter of extracellular fluid

NOTE: due to a decrease in the number of enzymes or decreased efficiency.

NOTE: the activity of the enzyme for people in age 7 equals the activity for people in age 20

NOTE: the milk is not digested and therefore increases the osmotic pressure resulting in reabsorption of 1 liter of water, leading to diarrhea

NOTE: normal flora use lactose and produce side products as CO2 leading to blotting

- **The complement in this slide:** absorption : is the movement from intestinal lumen to intestinal cells to the portal circulation.
- The absorption of sugars happens by two mechanisms: first is the Na-independent facilitated diffusion , the second by Na monosaccharide cotransporter system.

Absorption of Sugars

Polar molecules can not diffuse

A: Na^+-independent facilitated diffusion transport

NOTE: with concentration gradient, no need for ATP

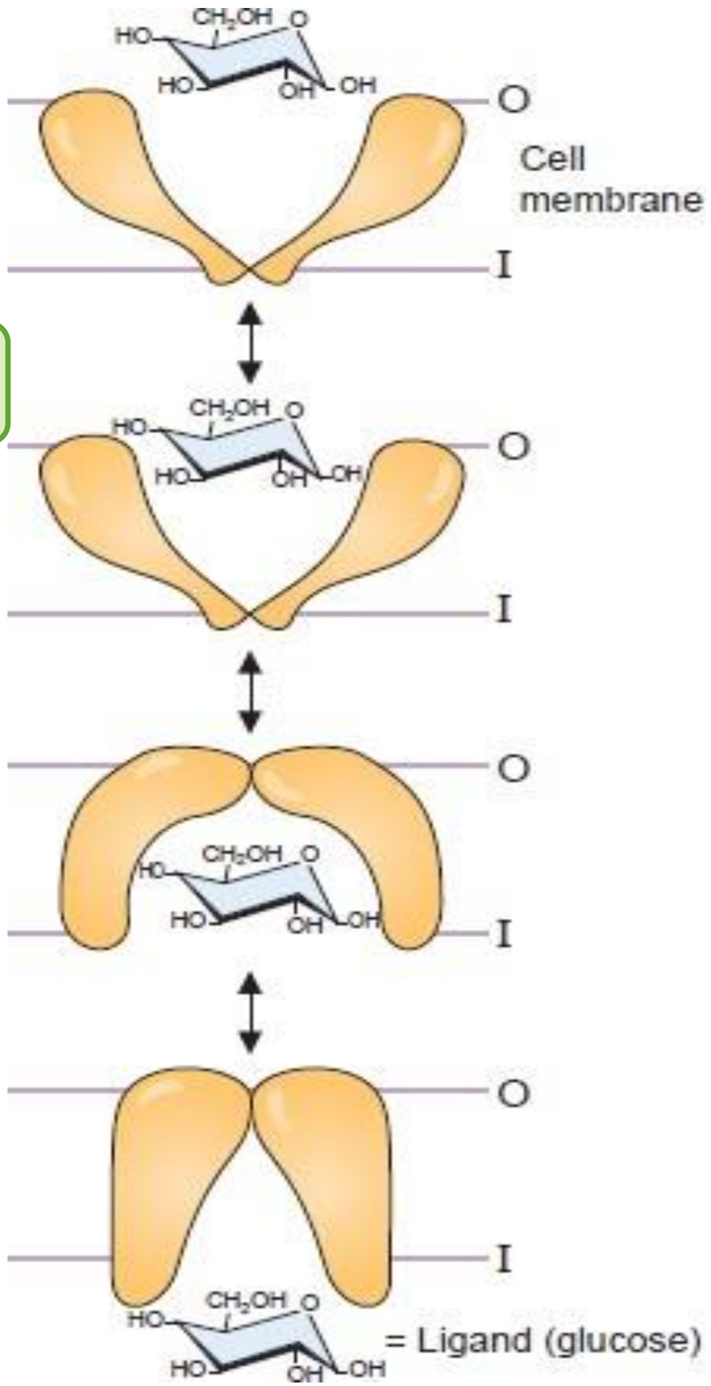
GLUT 1-----GLUT 14

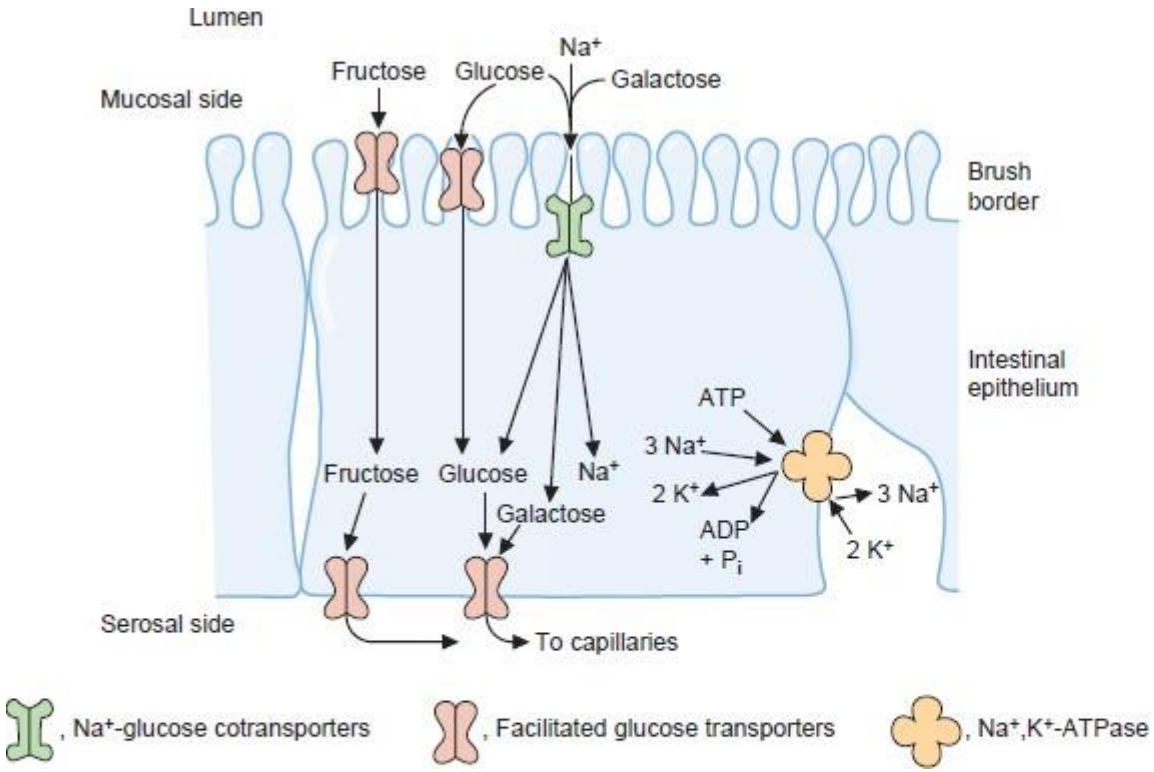
NOTE: from 1 to 14, not only for glucose, and it is bidirectional.

Glc. Movement follows concentration gradient

Two conformational states

NOTE: one opens to the outside, and one to the intracellular





Na+ monosaccharide cotranspoerter system (SGLT)

- Against concentration gradient (requires energy).
  - Small intestine: Active uptake from lumen of intestine.
  - Kidney: reabsorption of glucose in proximal tubule.
- For glucose and galactose absorption

- **The complement in this slide:** after a long time of transporting the glucose, the gradient will be changed, being low outside (due to some sugars) and high inside , but we want these outside sugars, so we need a mechanism to transport them against concentration gradient, so we need SGLT.

- **The complement in this slide:** another place where we need SGLT is the kidney, there must be No sugar in the urine, so we need SGLT to absorb sugars left.

- **The complement in this slide:** when glucose enters the SGLT, Na enters with it, leading to an increase in Na concentration, this increase is modified by Na-K pump and here we need ATP.

- **The complement in this slide:** note that the cell is polar, meaning that it has an apical surface and a basolateral surface.
- The molecules can not move between the 2 surfaces due to the presence of tight junctions.
- SGLT is only present on the apical surface.
- Facilitated transporters are present at both surfaces to transport glucose from the intestinal lumen to the cells, and from the cells to the capillaries.

NOTE: MEMORIZE WHAT'S IN RED

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

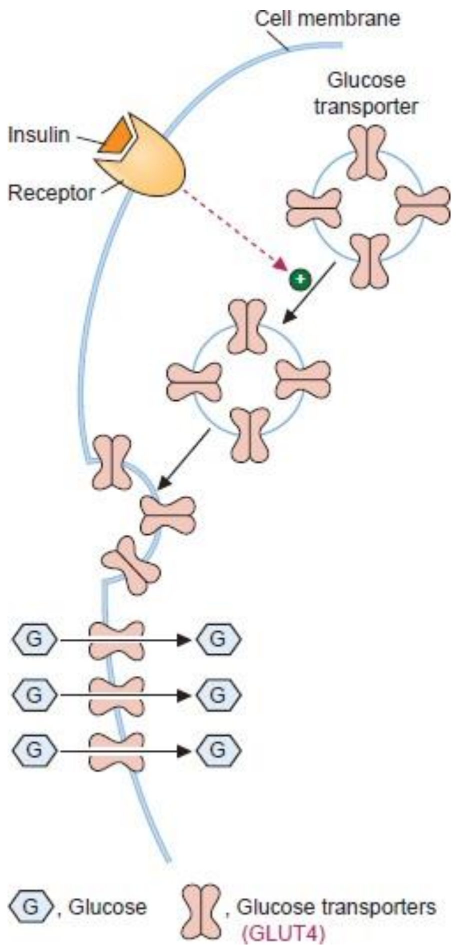
Transporter	*Tissue Distribution*	*Comments*
GLUT 1	Human erythrocyte Blood–brain barrier Blood–retinal barrier Blood–placental barrier Blood–testis barrier	Expressed in cell types with barrier functions; a high-affinity glucose transport system
GLUT 2 Glucose, galactose and fructose	Liver Kidney Pancreatic β-cell Serosal surface of intestinal mucosa cells	A high-capacity, low-affinity transporter May be used as the glucose sensor in the pancreas (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	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 Fructose	Intestinal epithelium Spermatozoa	This is actually a fructose transporter Na independent
GLUT 7	Glucogenic tissues	at endoplasmic reticulum membrane

NOTE:GLUT1 found in barriers

NOTE:GLUT2 is non specific

بدخّل كلّ اشي بكميّات كبيرة

NOTE: GLUT5 is specific to fructose. (some cells prefer fructose as an energy source like sperms)



Insulin stimulates transport of glucose into muscle and adipose tissues

- **The complement in this slide:** **insulin binds to its receptor on the cell(tyrosine kinase receptor), activates it, then activates certain transcription factors associated with the expression of GLUT4, packaging it into vesicles that fuse with the cell membrane, thus increasing its concentration.**

اللهم إنّا نشكو إليك...

أنفسًا أُزهقت ، ودماءً أُريقت ، ومساجدَ هُدّمت ، وبيوتًا دُمّرت ، وأطفالًا يُتِّمت ، ونساءً أُيّمت ، فاللهم عجّل بنصرهم.

اللهم عليك باليهود وأعداء الإسلام ، أفسدوا وأرهقوا وأسرفوا في الطغيان ، اللهم اجعلهم غنيمة للمسلمين ، أخرجهم من مقدّسات المسلمين، وأنقذ المسجد الأقصى من براثن الصهاينة المعتدين، اللهم إن لنا إخوانًا في غزة وفلسطين، أصابتهم البأساء والضّرّاء وأنت أعلم بحالهم ، اللهم فاجعل لهم الفرج والعافية ، وعجل بنصرهم يا قويّ يا عزيز ، وقوّ شوكتهم ، وحسبنا الله ونعم الوكيل.

لا تنسوا أهلكم في غزة وفلسطين
وسائر بلاد المسلمين من دعائكم

V2 : slide no. 16

the first step in the small intestine is the pancreas, which has an enzyme called pancreatic α-amylase that makes sugars→ (disaccharides) . Now, the mucosal cell membrane-bound enzymes work after pancreatic enzyme→ (monosaccharides) .

Instead of (the first step in the small intestine is the pancreas, which has an enzyme called pancreatic α-amylase that makes sugars either monosaccharides or disaccharides .