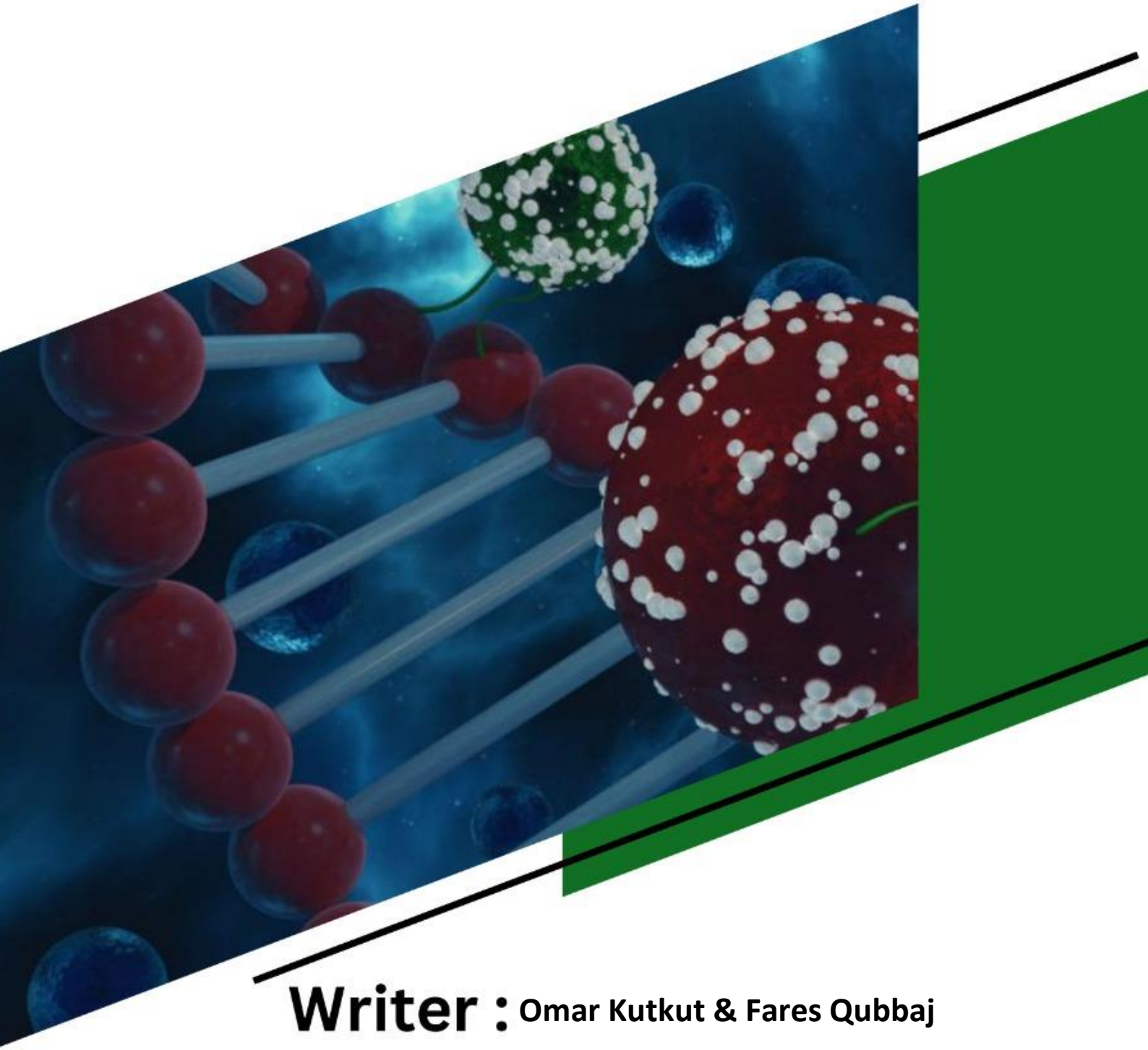
Doctor 021

METABOLISM

Sheet no. 10



Writer : Omar Kutkut & Fares Qubbaj

Corrector : Ahmad Qunbar &Othman Ammar

Doctor : Diala

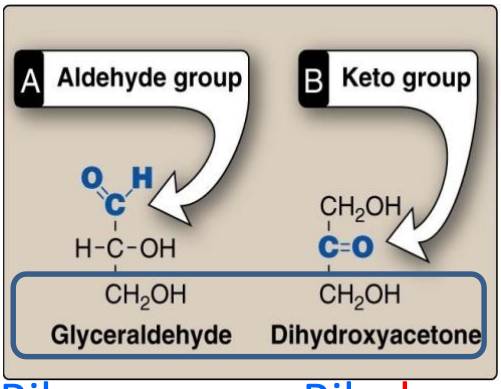
The first 5 pages are biochem1 revision if you think that you remember the basics then you are free to skip these 5 pages, GOOD LUCK!

CARBOHYDRATES METABOLISM TOPICS

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

MONOSACCHARIDES

Sugars are either aldoses(polyhydroxy aldehydes) or ketoses(polyhydroxy ketones).



Ribose Ribulose

Glucose Fructose

In sugars

Aldehyde group: carbon no.1 in aldoses

Keto group: carbon no.2 in ketoses

The simplest aldose: glyceraldehyde it's an aldotriose

The simplest ketose: dihydroxyacetone it's a ketotriose

5 carbon sugar aldose is called ribose while in ketose it's called ribulose(ulose means it's a ketose)

6 carbon sugar aldose is called glucose and fructose in ketose

EXAMPLES OF MONOSACCHARIDES FOUND IN HUMAN

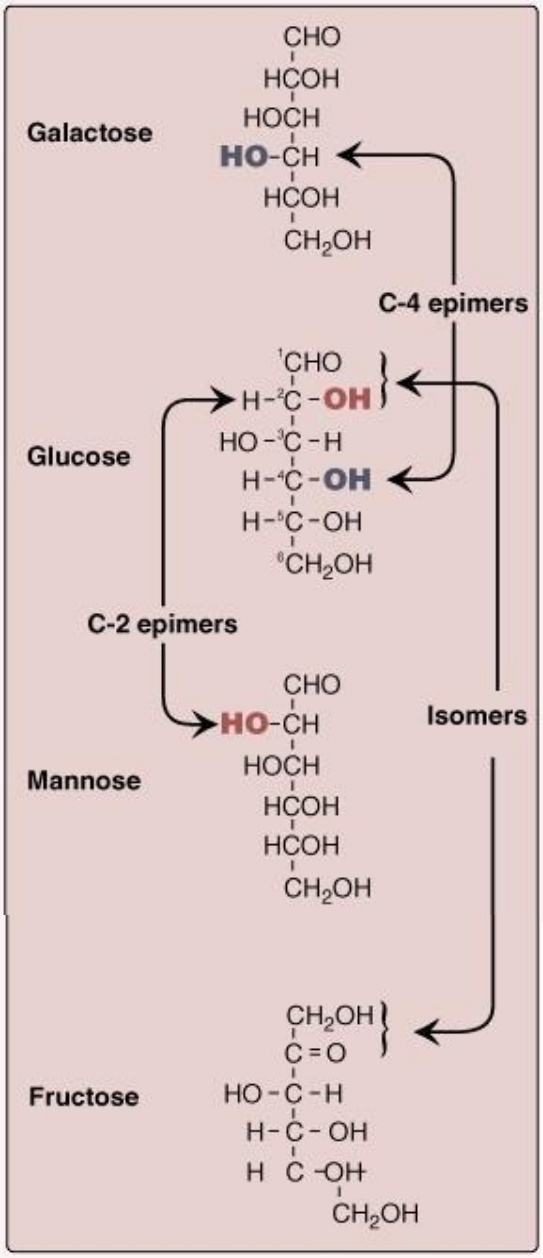
Generic names		Examples
3 carbons:	trioses	Glyceraldehyde
4 carbons:	tetroses	Erythrose
5 carbons:	pentoses	Ribose
6 carbons:	hexoses	Glucose
7 carbons:	heptoses	Sedoheptulose
9 carbons:	nonoses	Neuraminic acid

CHIRALITY AND ISOMERISM:

- **Sugars have Isomers**

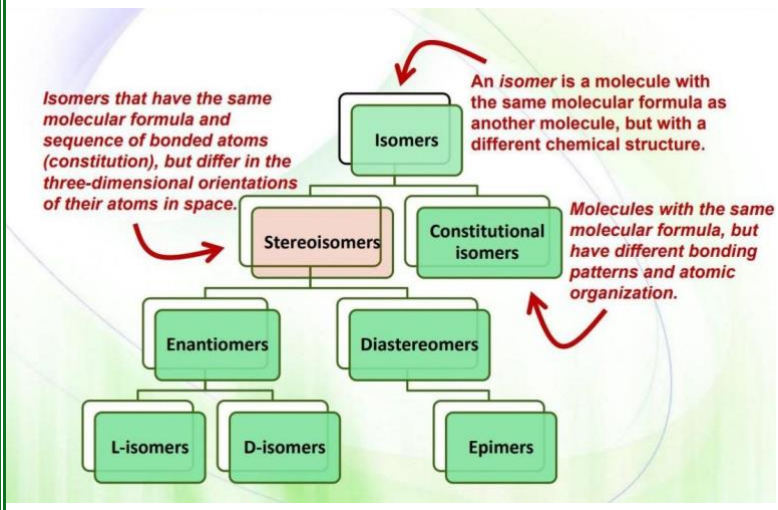
Epimers are isomers:

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



as you remember sugars can form isomers

a quick recap:



We have 2 types of isomers (constitutional and stereoisomers)

Stereoisomers can be of 2 types(thanks to biochemasters)

1) Enantiomers: Two stereoisomers that are mirror images of each other and are not superimposable (not identical) …They are expressed as (L-isomers and D- isomers).

2) Diastereomers: Two or more stereoisomers of a compound having different configurations at one or more (but not all) of the chiral carbons and are not mirror images of each other.

Epimers are considered as a type of diastereomers whereby two isomers differ in configuration at only one chiral carbon.

Remember that we deal with D-sugars only in our metabolic pathways, and this will bring us back to what we mean by D and L sugars

First of all recall this important concept:

Chiral carbon: carbon which is connected to four different groups.

now how can we determine whether this sugar is a D-glucose or L-glucose as in the picture below??

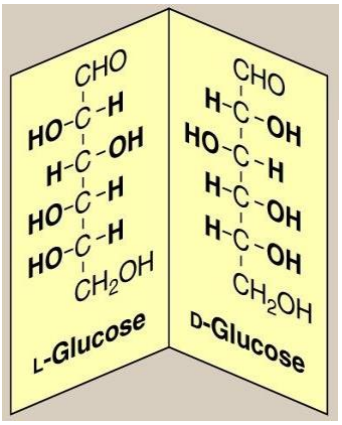
Simply by looking at the last chiral carbon(which is carbon no.5 in hexoses) if the hydroxyl group(OH) is heading right then it will be D-glucose and if its heading left then it is L-glucose

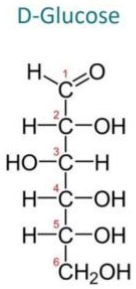
What is the relation between D-glucose and D-mannose? They are epimers

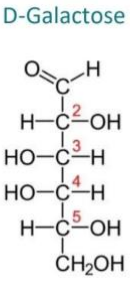
What about D-galactose and D-glucose? Epimers

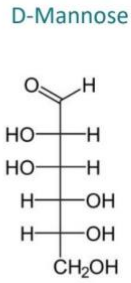
What about D-galactose and D-mannose? diastereomers

Glucose and fructose are constitutional isomers









RING STRUCTURE AND ANOMERIC CARBON

- **Alpha and Beta Sugars (Anomers)**

sugars can be found in a linear or cyclic form, most of the time as cyclic because it is more stable why more stable? Because of the reaction between hydroxyl group(OH) and keto or aldehyde groups.

By formation of ring structure we have a new chiral carbon which is the anomeric carbon and a new (OH) group that can be projecting downwards(α) or upwards(β).

Anomeric carbon: a carbon which is connected to (O) and (OH) at the same time in cyclic form.

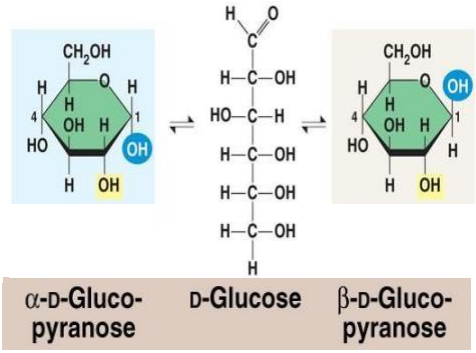
Anomeric carbon in aldoses is carbon no.1 while it's carbon no.2 in ketoses.

Sugars are found in the most stable form for the longest time and it is the (β cyclic) form for glucose because of less steric hindrance.

Anomers are cyclic monosaccharides that are epimers, differing from each other in the configuration of C-1 if they are aldoses or in the configuration at C-2 if they are ketoses (differing only in anomeric carbons)

Furan: five-membered ring (two carbons outside the ring in case of hexose).

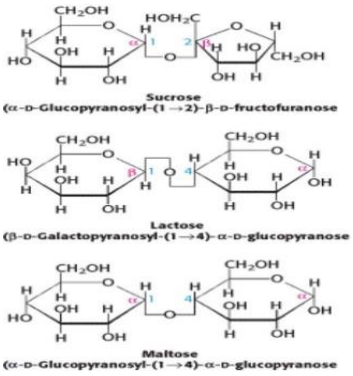
Pyran: six-membered ring (one carbon outside the ring in case of hexose)

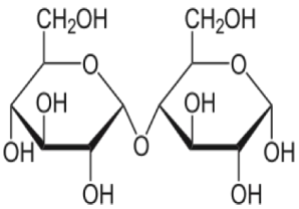


DISACCHARIDES

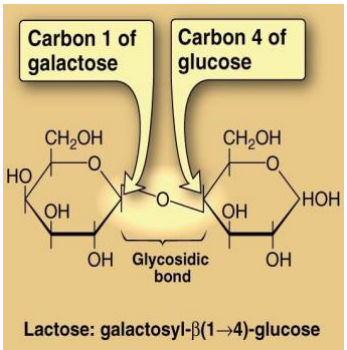
Sugars made of two monosaccharide units joined by a glycosidic bond

Can be made of 2 different monomers, even bonds can be different.



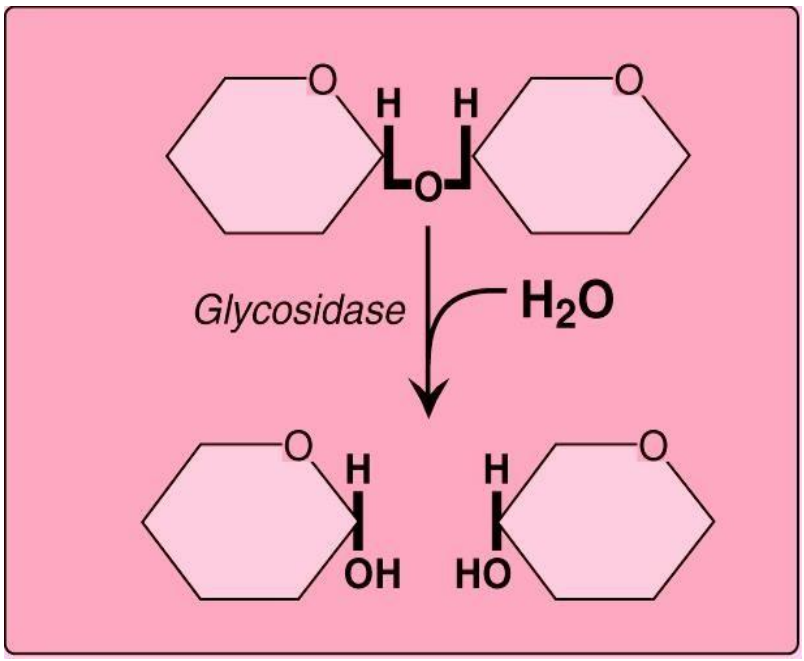


Maltose: a disaccharide made from two glucose units



PART 2:

GLYCOSIDIC BOND IS CLEAVED BY GLYCOSIDASE ENZYME



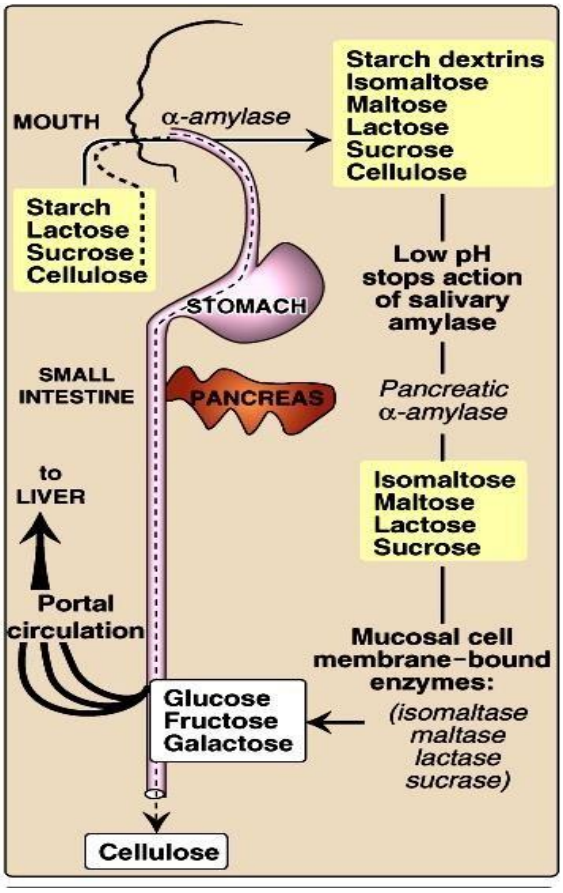
- The glycosidic bond is formed by a dehydration reaction in which one sugar molecule loses an oxygen atom and the other loses a hydroxyl group.
- To break this bond, the reverse reaction has to happen where a water molecule is added in the presence of the enzyme glycosidase

DIGESTION OF CARBOHYDRATES

After eating a carbohydrate rich meal (here we don't only mean the table sugar sucrose but any other type such as maltose, lactose, starch, cellulose ...)

A-The first encounter between the mixture of sugars and our body is in the oral cavity, where the enzyme alpha amylase does its work of digesting alpha (1→4) glycosidic linkages between glucose residues ONLY and that's why this enzyme can't break the bonds in lactose and sucrose.

(Cellulose can't be broken down because we lack the enzyme cellulase)



DON’T SKIP THE PICTURE!

The more you chew the food the more digestion takes place because:

1- The food will be encountered by the enzyme for a longer period of time

2-Surface area would increase allowing the other enzymes to perform better

But normally partial digestion happens since we chew for a few seconds(and of course some linkages can't be broken by alpha amylase)

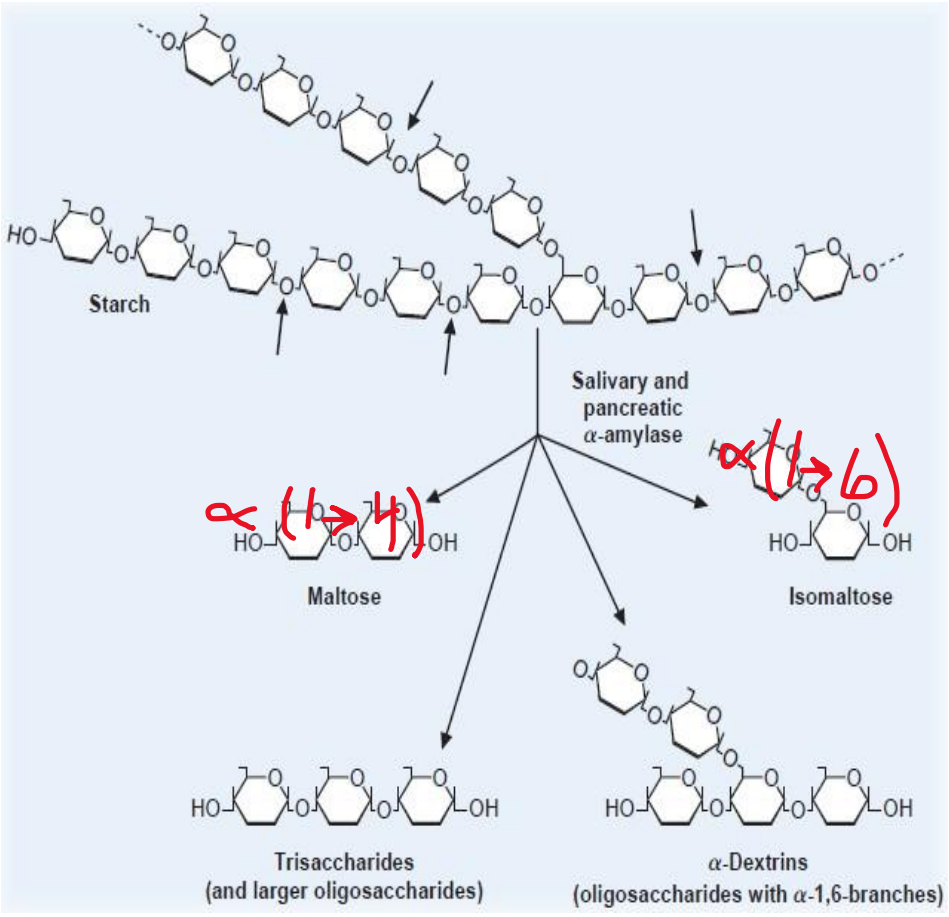
B-In the stomach, the major type of enzymes are proteases and not glycosidases(so we are not interested in the stomach today)

C-In the duodenum, the upper part of the small intestine, there is secretion of pancreatic enzymes that contain proteases, lipases, glycosidases(but ofc we are only interested in the pancreatic amylase)

Pancreatic alpha amylase works the same as the previous alpha amylase. This helps further breaking down of starch into disaccharides such as maltose and isomaltose, an isomer of maltose.

Remember we haven't encountered any enzyme yet that digests sucrose and lactose.

Isomaltose is formed at the branching points of starch when both bonds before and after the branch points, and the bond above the alpha (1→6) linkage are broken,resulting in a disaccharide of glucose connected by alpha (1 →6) linkage. The image on the right shows you that the body can digest starch into molecules as small as disaccharides(which are the maltose and isomaltose)before reaching the other intestinal enzymes.



So far only disaccharides are present in the intestinal lumen (maltose, isomaltose, sucrose, lactose, trehalose,and glucoamylose) Plus the indigestible polysaccharide cellulose

D- Intestinal Enzymes: These enzymes are protruding from the intestinal cells(membrane proteins).They further digest the disaccharides into monosaccharides so they can be absorbed .check the table below

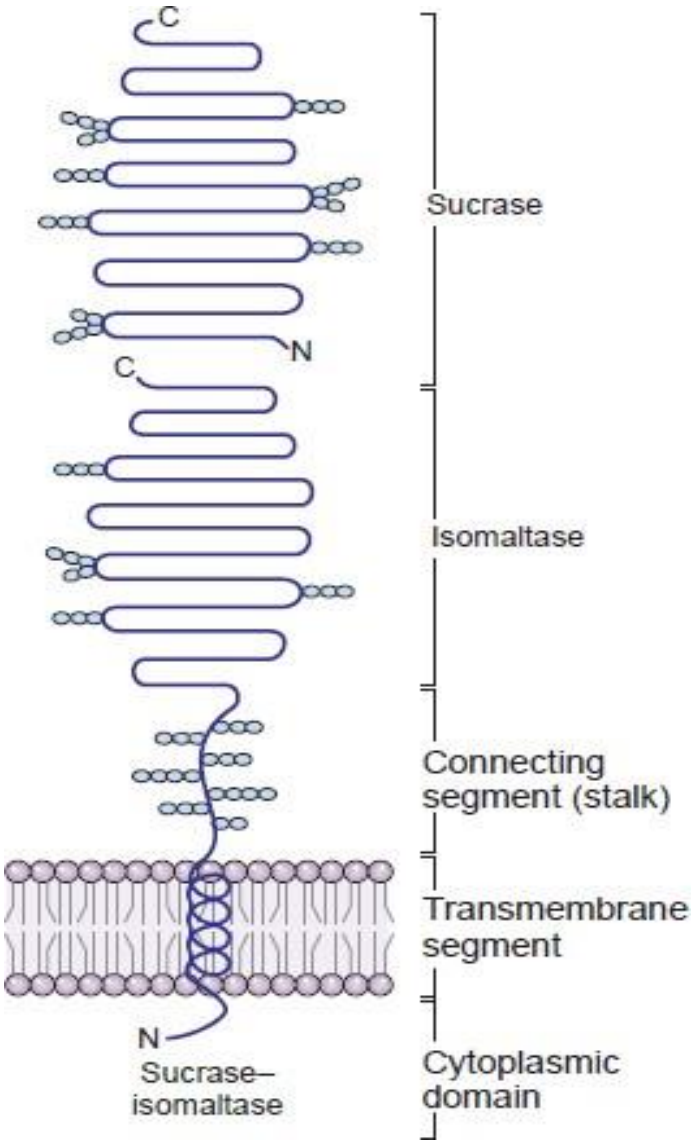
Absorption is when these monosaccharides move from the intestinal lumen through the intestinal cells to the portal circulation

Portal circulation reaches the liver for detoxification and metabolism.

ENZYME	Bond Cleaved	Substrates
Isomaltase	α1→ 6	Isomaltose
Maltase	α1→ 4	Maltose
Sucrase	α1→ 2	Sucrose
Lactase	β1→ 4	Lactose
Trehalase	α1→ 1	Trehalose
Exoglycosidase	α1→ 4	Glucoamylose

SUCRASE-ISOMALTASE COMPLEX AND GLUCOAMYLASE

as we said the majority of the intestinal enzymes lies extracellularly (because the substrates to be digested are in the lumen) .Only one helix is a transmembrane domain.



Sucrase + isomaltase Single protein à complex

of two associated subunits

-Sucrase-maltase

- Isomaltase-maltase Together 80% of the maltase activity

Maltase + exoglycosidase (glucoamylase): no split

At the time of synthesis(translation) , the protein complex is made of a single polypeptide chain with the C terminus at the top and the N terminus at the bottom.

Post-translation, the protein will be cleaved into two parts.The two parts remain connected through non covalent interactions though.

In this example , the sucrase isomaltase complex can have some maltase activity “as an extra job” and digest alpha (1 →4) linkages.

The glucoamylase (maltase exoglycosidase) has the same features as the other intestinal enzymes (transmembrane domain, small intracellular part , large extracellular part ,glycoproteins) BUT remains as a single polypeptide.

SUCRASE-ISOMALTASE COMPLEX

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*.

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 effects of this deficiency varies from one person to the other

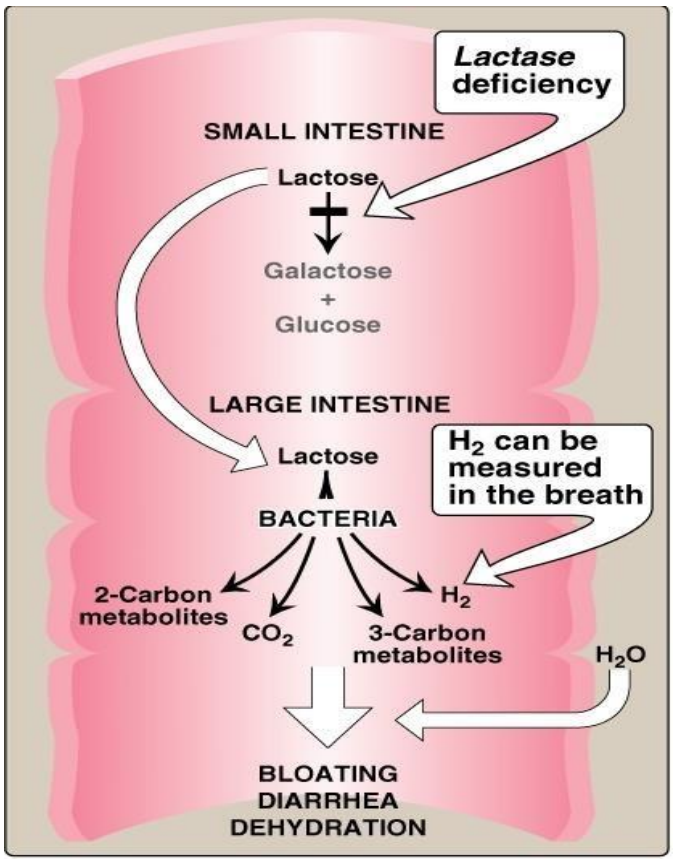
2. Lactase deficiency: ½ world's population

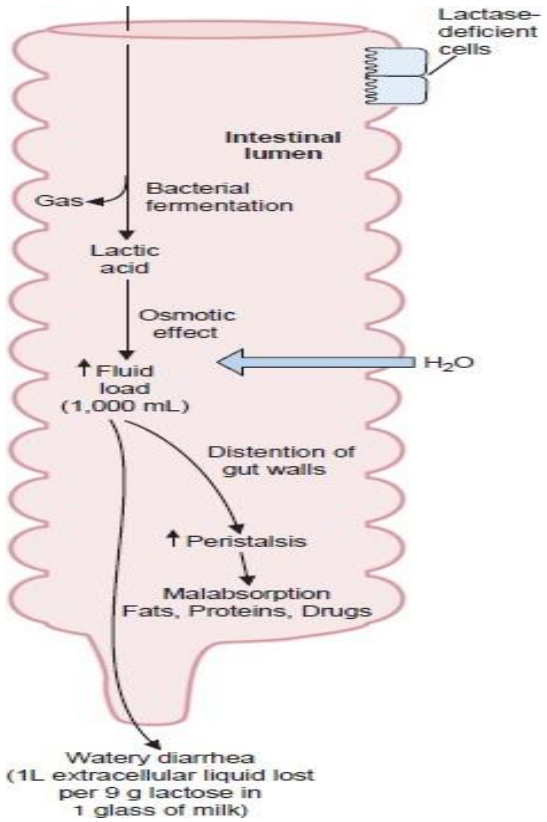
Lactase reached maximal activity @ 1 month of age

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





- In the beginning of our lives , we were highly dependent on lactase because lactose is the main sugar found in breast milk. This enzyme reaches its peak activity at one month of age. Then its activity decreases till the age of 6.

Side note: some references state that the lactase concentration decreases and not its activity.Anyways,whatever the real reason is, our bodies won't be able to digest lactose linkages (beta 1→4) as when we were infants.

- I cup of milk is able to withdraw I liter of EC fluid to the intestine lumen by changing the osmotic pressure .Presence of EC fluid in the lumen will cause stretching of the intestinal smooth muscles , and this would activate peristalsis →diarrhea
- Also, intestinal flora uses the accumulated lactose in their metabolic pathways.(by fermentation) producing methane and CO2.This causes bloating.

ABSORPTION OF SUGARS

Polar molecules can not diffuse A: Na^+-independent facilitated diffusion transport

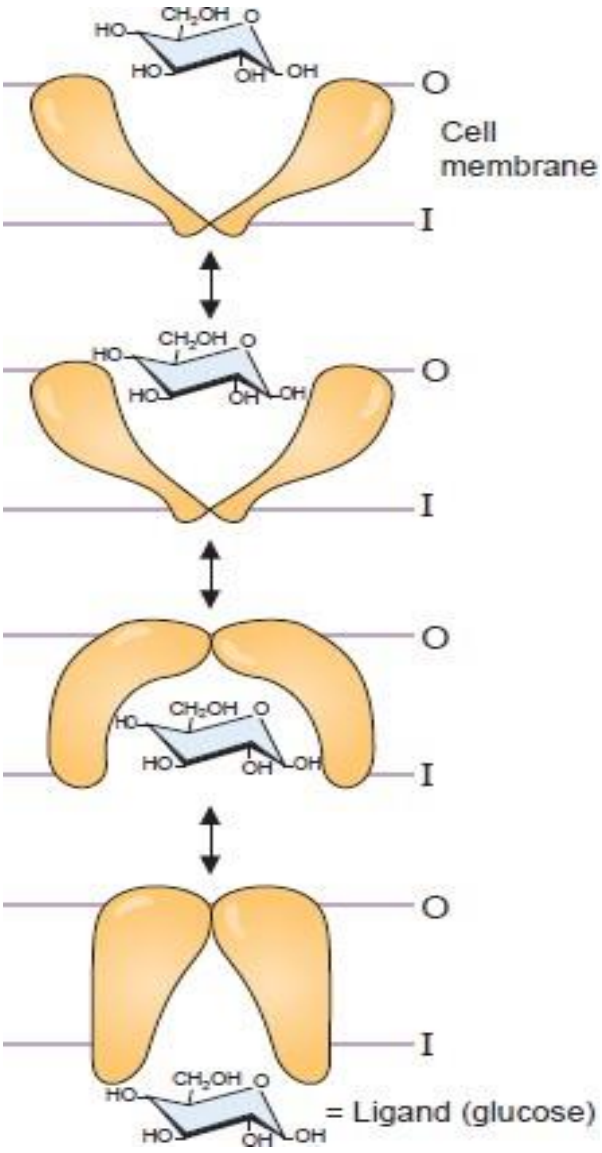
GLUT 1-----GLUT 14

Glc. Movement follows concentration gradient

Two conformational states

When the monosaccharide in the lumen binds to the transporter,this causes conformational changes in the protein.The transporter would change its shape delivering the sugar into the intestinal cell.

And this transporter keeps on alternating between these two conformations.



NA^+ MONOSACCHARIDE COTRANSPOERTER SYSTEM (SGLT)

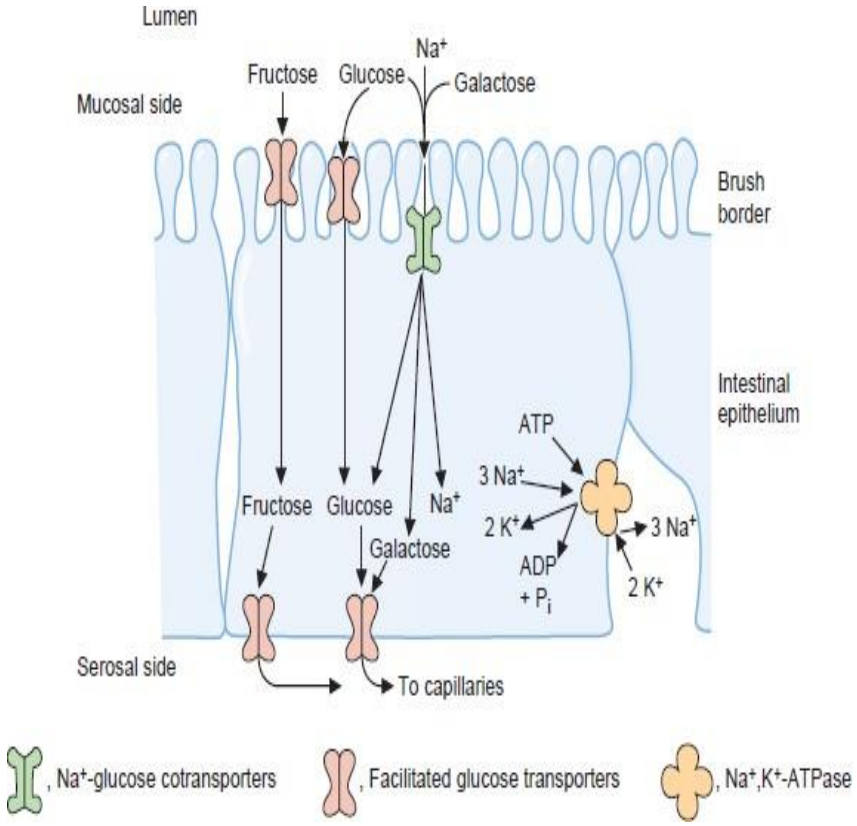
- **Against concentration gradient (requires energy).**

Small intestine:

Active uptake from lumen of intestine.

Kidney:

reabsorption of glucose in proximal tubule.



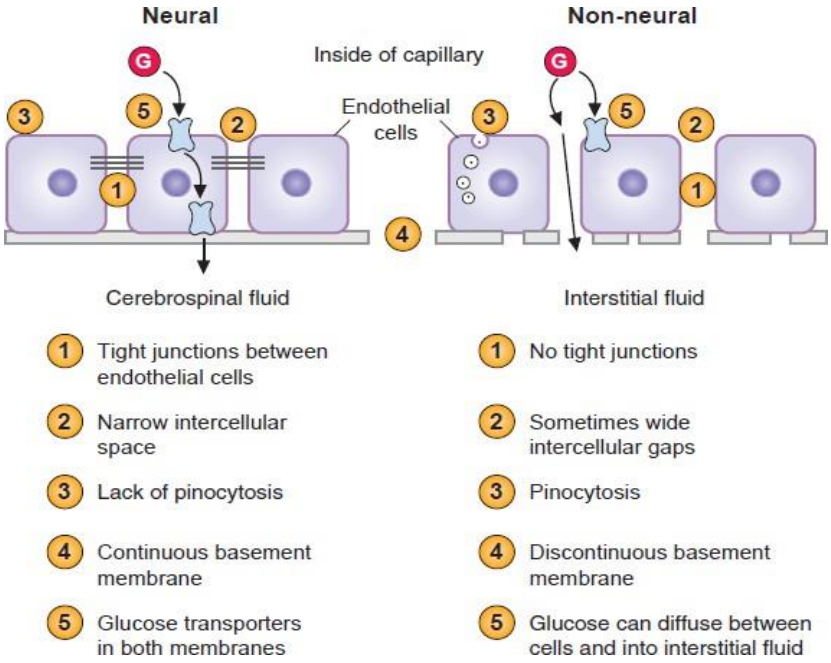
- **For glucose and galactose absorption**
- As the name implies this type of transporter depends on sodium
- It is a co transporter, so it couples the entry of sodium along with either glucose or galactose.
- Only found on the brush border (green transporter as illustrated in the figure)The GLUT transporter(shown in pink)is found on both the brush border and basolateral membrane.
- It requires energy; the sodium potassium pump as we know needs energy to keep the difference in concentration gradient. The diffusion of sodium along its concentration gradient is coupled to the entry of sugar ,allowing the sugar to enter against its gradient.

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

Glucogenic tissues: tissues that can synthesize glucose

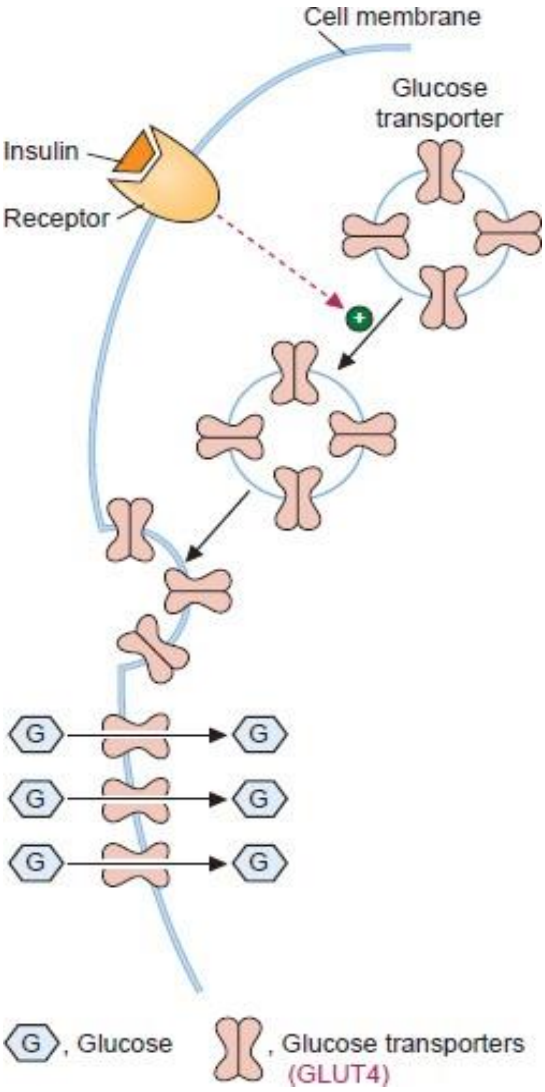
Glucose transport in neural vs. non-neural cells



Brain is exclusively dependent on glucose as a source of energy, but in severe starvation it can use keto bodies instead.

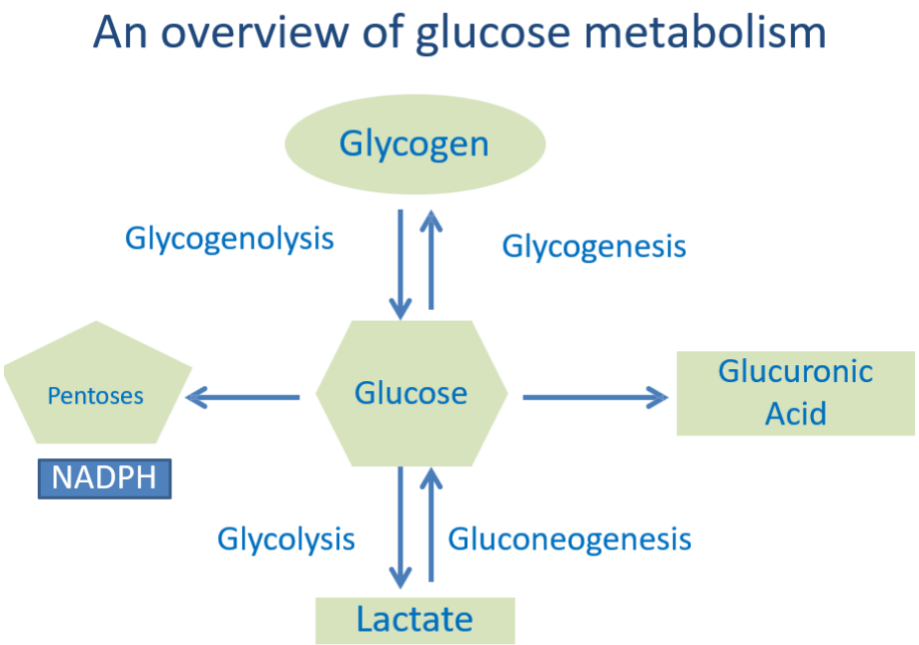
In neural cells ,the blood brain barrier doesn't let molecules get transported inter or paracellularly so that's why we need two transporters:One to transport molecules from the cell surface to the inside,and the other one continues the transportation from inside the cell to the CSF(cerebrospinal fluid)

While in non-neural cells we can transport molecules intra or para or intercellularly and only one transporter is needed.



Insulin stimulates transport of glucose into muscle and adipose tissues

After eating a carbohydrate rich meal ,Insulin is going to get secreted and it binds to its receptor (receptor tyrosine kinase(RTK))this will activate a series of proteins until it activates the transcription factor. GLUT4 gene is one of the target genes that gets transcripted and translated, so the transporter is produced and packaged through vesicles to get transported to the cell membrane so that we have a high concentration of GLUT4 on the cell membrane.As a result, the cell can uptake more sugar.



"1% CHANCE, 99% FAITH"

-GOOD LUCK-