DOCTOR 2020 | JU

METABOLISM

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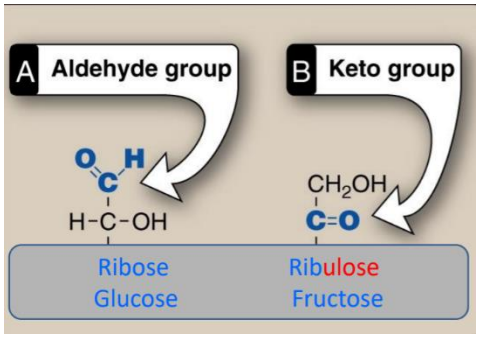
SUGARS : GENERAL OVERVIEW

Sugars are polyhydroxy aldehyde or ketone,

the simplest aldose is made up of 3 carbons and it's called **glyceraldehyde** , the simplest ketose is also made up of 3 Carbons and it's **dihydroxy acetone** these molecules can get more complicated when we add more carbons , ex : tetroses , pentoses , etc.



Note : sometimes "**ulose"** indicates a ketose.

The majority of sugars in our body are hexoses and pentoses, we have trioses and heptoses also but they are less abundant.

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

Ribose: it's present in the structure of the RNA

Neuraminic acid = sialic acid

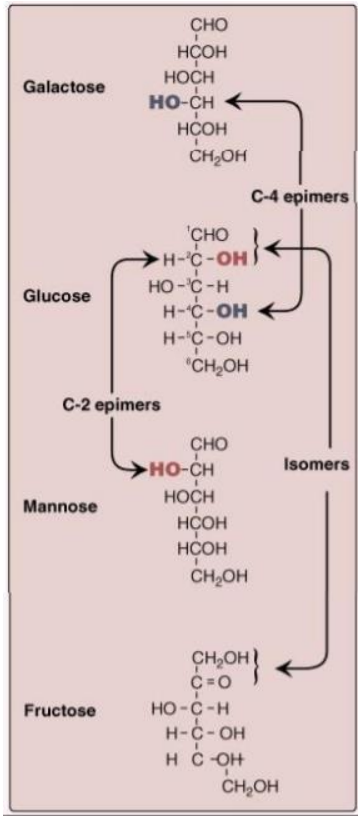
Chiral centers : a carbon that have 4 different groups attached to it.

How to calculate the no. of chiral centers?

1- Aldoses : no. of carbons - 2
2- Ketoses : no of carbons - 3

(the last and first carbon are achiral , and in ketose the carbonyl is achiral)

Stereoisomers : chemicals that differ in the orientation of molecules around a bond



We have stereoisomers due to the different orientation of groups around the chiral center, and they are divided into two groups :

1- enantiomers (non-super imposable mirror images produces D and L isomers of the same compound)

2- diastereomers (some chiral centers have the same orientation " D&L " but others are mirror images)

Epimers is a special case in diastereomers , where only one chiral center is differently oriented between both isomers, ex : Glucose and Mannose which differ in the orientation of "OH" group around carbon no.2 , glucose's hydroxyl is on the left whereas mannose's hydroxyl is on the right)

***Note** that glucose and fructose are constitutional isomers.

RING STRUCTURE OF SUGARS :

Ring structure is far more common than the linear structure which occurs only at a negligible amount of time, because the sugar is more stable in the ring structure.

The OH group on the anomeric carbon (the 1st carbon for aldose and 2nd carbon for ketose) if it's directed upwards it's a **beta** molecule and if it's directed downwards it's an **alpha** molecule.(anomers)

anomeric carbon : the carbon derived from the carbonyl carbon of the open-chain form of the carbohydrate molecule

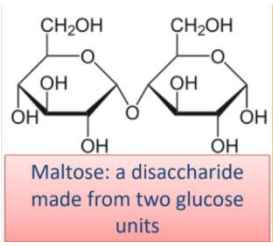
What is the difference **between enantiomers and anomers** (D & L vs α & β)?

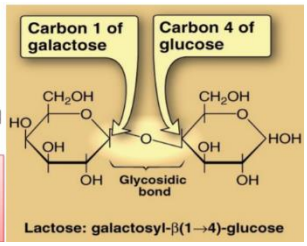
Anomers of a certain monomer are constantly changing it's conformation, between α & β and linear structure , but it stays more in the most stable form of that molecule , ex :Glucose is more stable in β configuration than α due to steric hindrance (67% of the time on β and 33% in α and a negligible amount of time at the linear structure which is also important specifically during reactions sometimes the linear structure is required).

But in enantiomers the configuration is fixed for each molecule

These monosaccharides can bond to each other and form disaccharides which can be different due to 4 factors :

1- It's monomers
2- The orders of these monomers
3- The type of linkage between them
4- The no. of carbons that make up the bond (1-4)(1-6) etc.





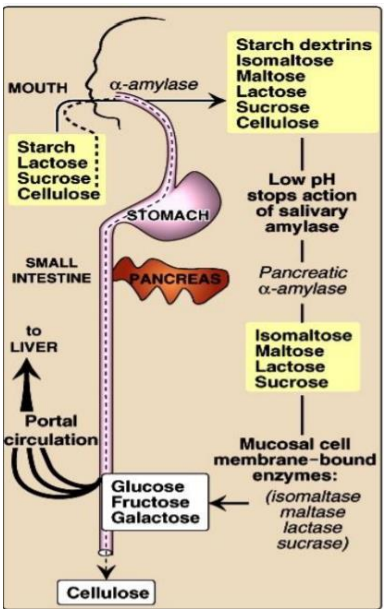
CARBS METABOLISM

Absorption doesn't happen to disaccharides so they should be hydrolyzed to monomers by glycosidases, and those glycosidases are specific for the 4 factors mentioned above, so for example cellulose isn't digested by the same enzyme that digest lactose , although they both have a β (1-4) linkage but the monomers differ between them, notice that glycosidases uses hydrolysis reactions (uses a H2O molecule)

Note : Starch is made up of 2 compounds: amylose (linearly α (1-4)) and on branches amylopectin (α (1-6))

The digestion of sugars starts in the mouth (Only a partial digestion happens in the mouth) by an enzyme called **Salivary α-Amylase** (in the saliva) this enzyme recognize **α (1-4)** linkage between **2 glucose residues** (which is present in starch mainly and maltose) , and this enzyme may result in unconventional carbs like :

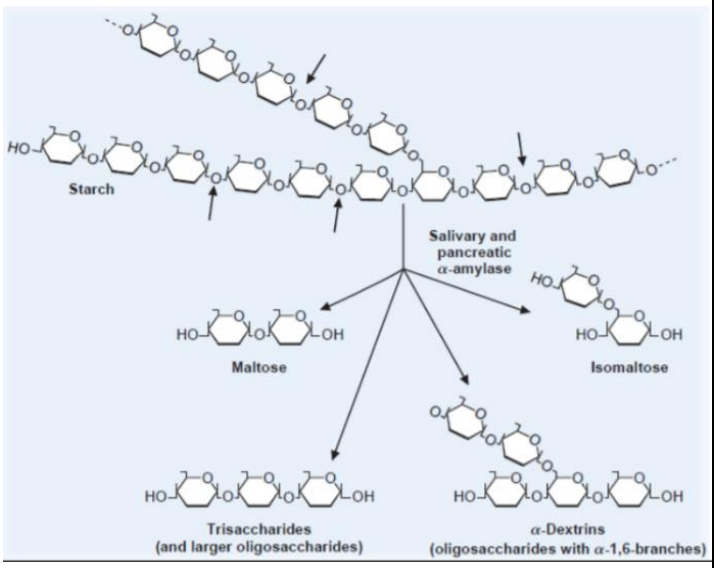
1- Isomaltose results when you cut at the branching point
2- It may generate large fragments like starch dextrins, as indicated in the picture below (we still haven't digested all α 1-4 linkages)



The sugar gets simpler but not to the point of complete digestion

Now this mixture of sugars (the one in the figure below) is going to travel to the stomach which doesn't contain digestive enzymes so they won't be hydrolyzed , so the compound will continue to the small intestine to the **duodenum** , which contains the secretions of the pancreases which is mainly α **amylase** (similar to salivary alpha amylase but the difference is that now the sugars **will stays in the intestine for a much longer period of time (more exposures to digestive enzymes)** so here we will end up having all the polysaccharides and the large fragments of starch **digested to monosaccharides or disaccharides**)

Downstream they will get exposed to mucosal cell enzymes (small intestinal enzymes which are actually **membrane proteins** that came out towards the lumen of the intestine) so for example lactose will be digested there by lactase which digest β-(1-4) linkage between **galactose and glucose** , sucrase digest α (1-2) linkage between **fructose and glucose** etc.



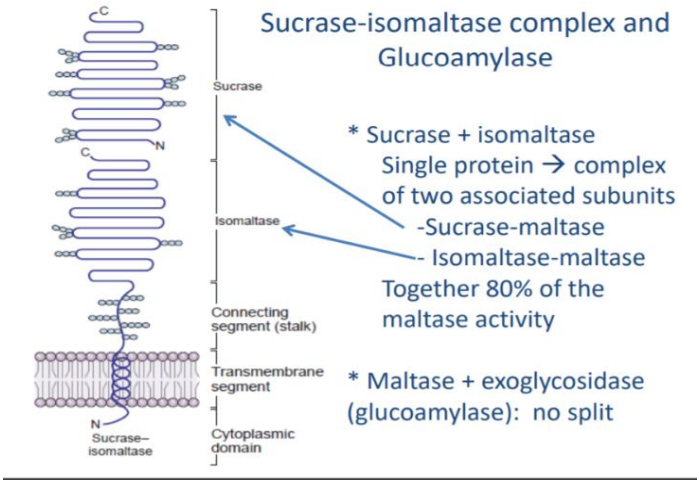
But we cannot absorb disaccharides because we only have transporters for monosaccharides and need transporters because monosaccharides are large and polar molecules

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

Then we end up with the basic units (Glucose, Fructose and Galactose) which get absorbed and enter the circulation and into the liver

So How these digestive enzyme work?

SUCRASE-ISOMALTASE COMPLEX AND GLUCOAMYLASE :



This complex is made up of a single polypeptide chain (expressed from the same gene)

The **bulky** part is directed towards the lumen where the function is taking place

The **Small** part is intracellularly

This complex might seem like 2 separated polypeptide chains but in fact the chain was cleaved post-translationally (remember the molecular biology lecs) and they are connected via **non-covalent interactions** to each other , this structure causes **flexibility** in the movement of sucrase

The same idea applies to maltase and exoglycosidase complex but they are **not split**

What are the causes of deficiency for this complex ?

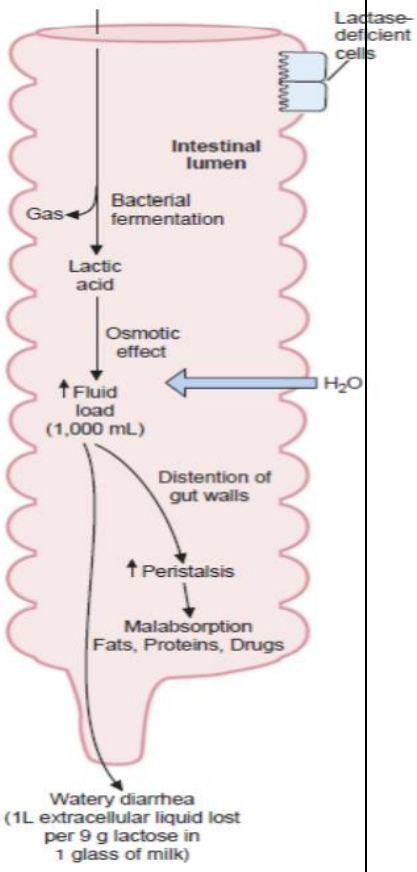
1- Genetic mutations
2- Intestinal disease like **Crohn's disease or Ulcerative colitis** (those are chronic diseases , due to inflammation in intestinal cells, **those cells are destructed and removed** so they lose cells. Although normally we regenerate intestinal cells within **3 days** but these patients lose cells with a much higher pace so it cannot be replaced quickly , so we will lose also those hydrolytic enzymes on these cells).
3- Malnutrition : there is no activity of the enzyme because of substrate depletion (so in fact the enzyme is not deficient)
4- Injury of mucosa i.e. by drugs
5- Severe diarrhea (because of chronic diseases like Crohn's disease, so they will lose the substrate before using it on the enzyme)

LACTASE DEFICIENCY : reduced activity or amount of the enzyme

Normally lactase increases it's activity and reached **the peak at the age of 1 month** , then it starts decreasing until the age of 5 years old and it stays constant then.

When adults consume lactose it will accumulate in the intestine due to the deficiency of lactase , which leads to high concentration of lactose in the lumen , so the osmotic pressure is increased , then H2O gets out of the cells to the lumen which causes diarrhea , and also lactose can be consumed by the normal flora that is present in the intestine producing some side product like Co2 and Ch4 (methane) gases which leads to **cramps**.

Note : 1 cup of milk (9 grams of lactose) leads to **1 liter of accumulated fluids**



People with this condition should :

1- Stop drinking milk (they can obtain Ca from cheese, eggs , yogurt etc. , and they can obtain vitamin D by standing in sun light which contain UV light, that is an activator of the initial steps for synthesizing vitamin D (by reacting with cholesterol that is present in the skin)

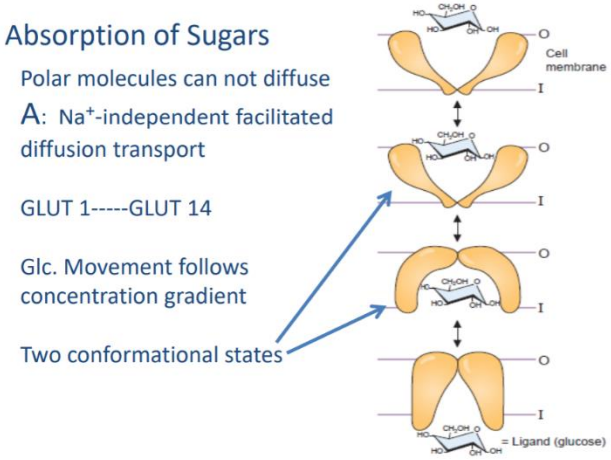
BTW ; vitamin D is not that abundant in milk , you should drink 10 liters of milk daily to obtain the needed amount of vitamin D for your body يعني هو و قلته واحد بالحليب

2- Drink milk without lactose
3- Drink milk with lactase

SUGAR TRANSPORTATION

There are different types of transporters that transfer monosaccharides into the intestinal cells but they share the presence of 2 conformations (as indicated in the figure)

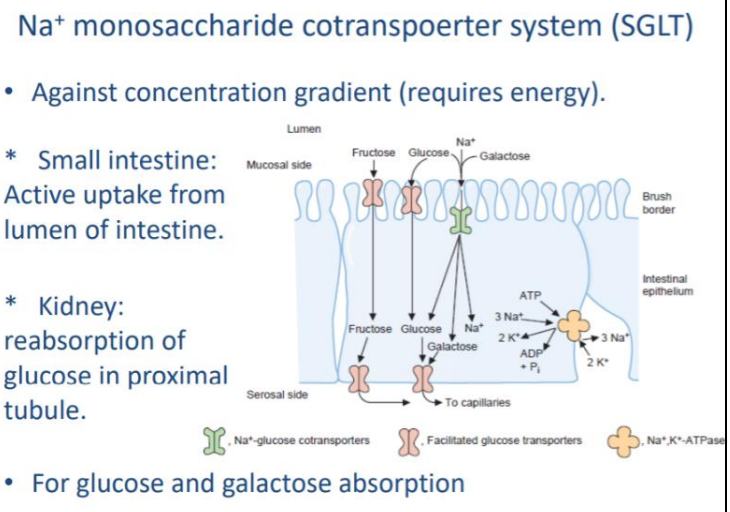
Once the monosaccharide bounds, the transporter changes its shape to open into the intestinal cell



The **Major** transporter type is a Na independent **facilitated diffusion** transporter (GLUT1-GLUT14)

facilitated diffusion: doesn't need ATP, because it travels down the concentration gradient between the lumen of the intestine and the cell.

The second type of transporters which transport sugars against the concentration gradient which is the **Minor** type of transporters (Na momnosaccharide cotransporter system) and it's not always active but it's activated at certain conditions and sites , for example**; if there is only a small amount of sugar left inside the lumen we can absorb it through this type because at that stage the concentration of sugars inside the cell will be high and the energy of the conc. Gradient will be gone** , this is a **Na-dependent** co-transporter which need energy , those transporters are also present in **the kidney** for reabsorption from the urine , in urine analysis we measure the amount of sugar in the urine , and if we found any sugar; that might indicate the presence of diabetes or a problem with the kidney.



POST-ABSORPTION PATHWAY

Intestinal cells are **polar cells**, we have to move part of these molecules through the basolateral surface and then through the circulation , the transporters that are present at the basolateral surface are those of **facilitated diffusion (down the concentration gradient)**

How about **Na** that enter the cell?

Na – K pump should be activated to return the electrical potential to its homeostasis

Monosaccharides now move to the **capillaries** and then to the **portal** circulation to go to the **liver** to be checked that it is free of any toxins and able to be used (the live is like check point), it these molecules are normal they will exit to the general circulation and redistributed to all body tissues , but if there is a problem the defected molecule will get trapped in the liver and degraded.

Portal circulation: the circulation of nutrient-rich blood between the gut and live

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SUGARS DELIVERY TO CELLS

When sugar concentration (specially glucose) is increased in the general circulation , **insulin** is going to be secreted , which will increase the uptake of sugars into the cells. insulin does that by binding to a certain receptor that activates the synthesis of sugars transporters specifically **GLUT4** (insulin sensitive transporter) , which will increase the number of these receptors dramatically.

If the amount of sugar inside the cell is low or normal it will get metabolized to obtain **energy**, and if there is an excess it will be stored in the form of **glycogen.**

Note: all body cells can synthesize glycogen but it's stored in large amounts in **hepatocytes and myocytes** (liver and muscles)

Differences between transporters:

GLUT1-GLUT14 (there are 14 types of transporters)

GLUT1: present in **BARRIERS**, as in blood-brain barrier , because the CNS is the control center of the body we should protect it and this barrier is mainly formed from **tight junctions** between **endothelial** cells, so these **sugar transporters are super important in the Brain capillaries; because glucose won't go there by diffusion because of this barrier.**

The brain depends mainly on glucose as a source of energy so this transporter is super important for it

Note : because of that when blood sugar concentration decreases some people might lose conscious and that is easily treated by taking some glucose through a sweet drink or some food.

This condition is called a vasovagal attack and it can occur due to fear also

This transporter is also present in all mentioned barriers in the slide.

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

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