Subject :	Glycogen Metabolism
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Number :	14

Glycogen Metabolism

Glucose is the greatly preferred energy source for the brain and without it the brain would stop functioning leading to impending death. It is also the required energy source for sells with few or no mitochondria.

*Note: the brain needs 120 grams of glucose per day (you don't have to memorize this number))

Blood glucose can be obtained from three primary sources:

1. ***The diet:*** Dietary intake of glucose and glucose precursors such as polysaccharides (starch), disaccharides and monosaccharides is sporadic, it's not always a reliable source of blood glucose. There's no continuous or regular eating, what you eat each day differs. So, you can't depend on the diet alone and the glucose it provides because it changes from time to time. We are not nibblers! Also, the diet might not contain any carbohydrates. For example, someone may eat only protein.

2. ***Gluconeogenesis*:** it can provide sustained synthesis of glucose, but it is somewhat slow in responding to a falling blood glucose level. Therefore, the body has developed mechanisms for storing a supply of glucose in a rapidly mobilizable for, glycogen.

3. ***Glycogen*:** the storage form of glucose. It is characterized by rapid response and mobilization. The problem here is we have limited amounts of glycogen that are only sufficient 16-18 hours.

   *Here were are talking about liver glycogen as a source of glucose in fasting conditions not muscle glycogen. Muscle glycogen is not affected by short periods of fasting (a few days) and is only moderately decreased in prolonged fasting (weeks), but muscle glycogen is synthesized to replenish muscle stores after they have been depleted following strenuous exercise

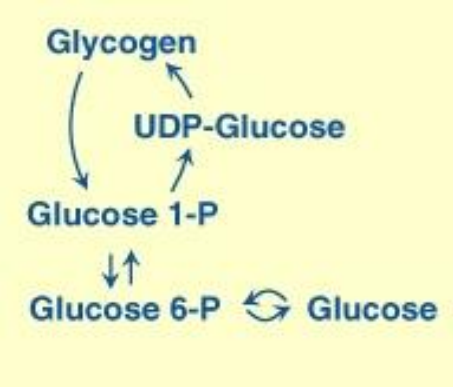
*Glycogen is the storage form of glucose. But why do our bodies synthesize glycogen? Why don't we store glucose? What would happen if we did so?

-If this happened there would be very high concentration of glucose. Imagine we have these two situations: **1.** if we stored 0.5 million glucose units as one glycogen molecule, or **2.** 0.5 million glucose molecules. The osmotic pressure would be very high if glucose was stored as such as in the second situation. If we make 1 glycogen molecule from many glucose units, as in the first situation, the osmotic pressure would be low. Also, glycogen is not sweet. So, if glucose is not stored as glycogen, the taste of the liver or the muscles, when you eat meat, would be sweet.

→Glycogen is easily degraded to glucose 1-phosphate which can be converted to glucose 6-phosphate and that in turn might be converted to glucose. The synthesis, on the other hand, is a bit different. Glucose is converted to glucose 6-phosphate. Next, it is converted to glucose 1-phosphate then to UDP-glucose and finally, it forms glycogen. So, synthesis and degradation are not catalyzed by the same enzymes.

Degradation of Glycogen:
glycogen >> glucose 1-p >> glucose 6-p >> glucose(it is not always produced (according to the tissue type))

Synthesis of Glycogen:
glucose >> glucose 6-p >> glucose 1-p >> UDP-glucose >> glycogen



The difference between glycogen of the liver and glycogen of the muscle.

*Why does the liver produce glycogen?
-The liver produces glycogen to provide glucose which is transported to the blood to reach different tissues.

*Why do muscles make glycogen?
-Muscles produce glycogen as energy molecules for its own use not for other tissues.

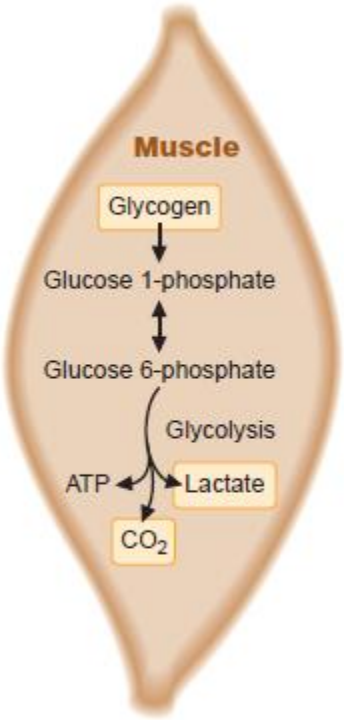
Why is that??

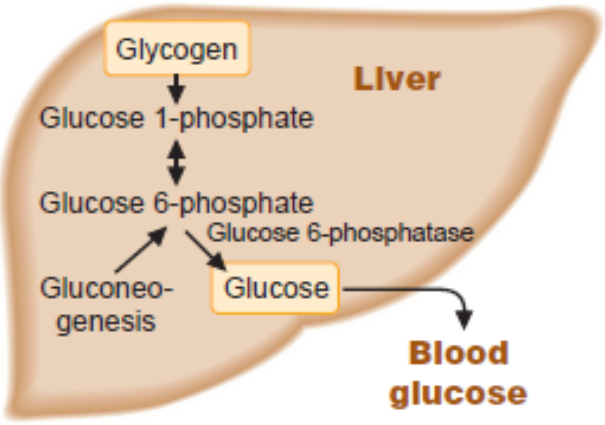
-In the liver, after we get glucose 6-p from glycogen it will be converted to glucose by the enzyme *glucose 6-phosphatase*. But this enzyme is <u>not</u> available in the muscle, so we can't make glucose from the glycogen in the muscle but in the liver we can. In the muscle, we get glucose 6-p which is used in glycolysis to produce lactate and ATP (anaerobically) or CO_2, H2O and ATP (aerobically).
Note: During fasting, muscles don't get glucose from the liver.

**Muscle glycogen is for energy production whereas liver glycogen is for making blood glucose.

**The presence of the enzyme *glucose 6-phosphatase* <u>in the liver</u> and not in the muscle makes the liver able to produce <u>glucose</u> from glycogen.

Recall: *glucose 6-phosphatase* is also present in gluconeogenesis.





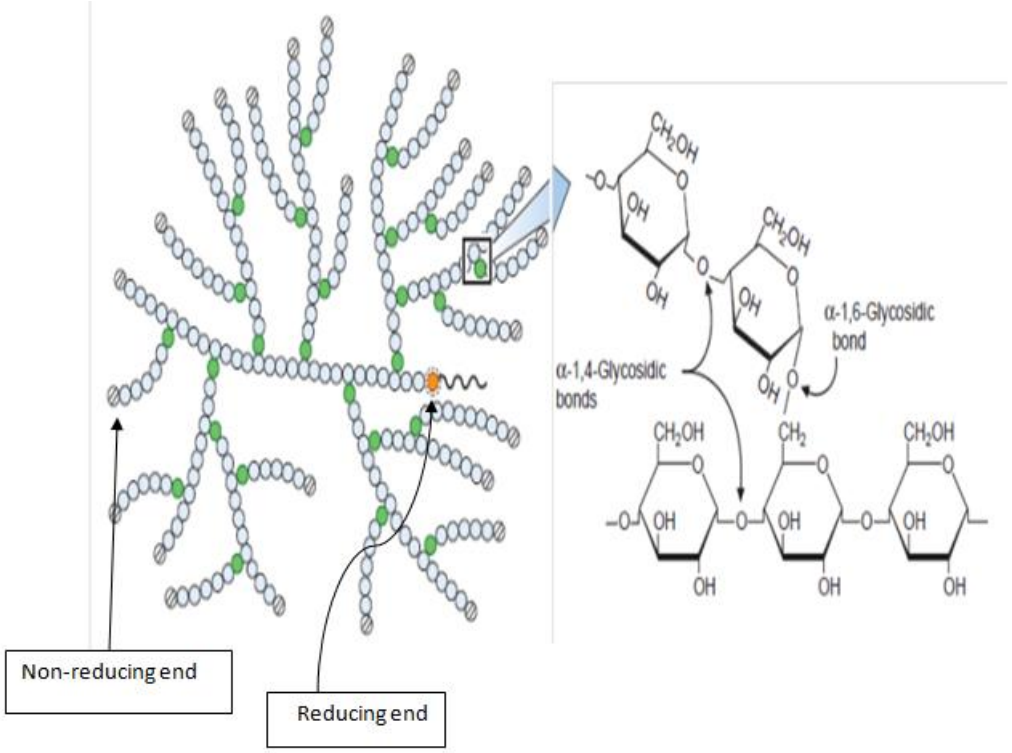
00:00-10:15

Structure of Glycogen

It is an extensively branched homopolysaccharide. One molecule of it consists of hundreds of thousands of glucose units (0.5 million glucose molecules are joined to make a large glycogen molecule).

There is the original chain and the branches that occur very frequently. The type of bond connecting glucose units with each other is a glycosidic bond, α-1,4 along the chains and α-1,6 at each branching point. The two

ends of the main chain are different from each other. In the very last glucose, C-4 (carbon #4) has a free hydroxyl group (non-reducing end because the anomeric carbon (C-1) is linked by a glycosidic bond to make full acetal), while in the other end, C-4's hydroxyl group is joined to the next glucose molecule and the hydroxyl on C-1 is free (reducing end).



As you see in the figure above, there is one reducing end but many non-reducing ends. (There is a non-reducing end for each branch as every branch ends with a non-reducing end. There is also a non-reducing end in the main chain.)

*Why is it made with this structure? What is the importance of having many non-reducing ends?

-Synthesis and degradation of glycogen occur at the non-reducing ends. The enzymes involved in both processes work on the non-reducing ends. So the enzymes have many ends for synthesis and degradation. If the enzymes worked at the reducing end the reaction would be very slow because there is only one reducing end. The reaction is actually very

rapid because there are tens of thousands of non-reducing ends. (This is why it is useful for glycogen to be highly branched. Moreover, the high level of branching makes glycogen more soluble in water)

Degradation of Glycogen

In the degradation of glycogen one glucose unit is removed at a time from the non-reducing end by the enzyme *glycogen phosphorylase*. The product is glucose 1-phosphate and the remaining glycogen gets 1 glucose shorter.

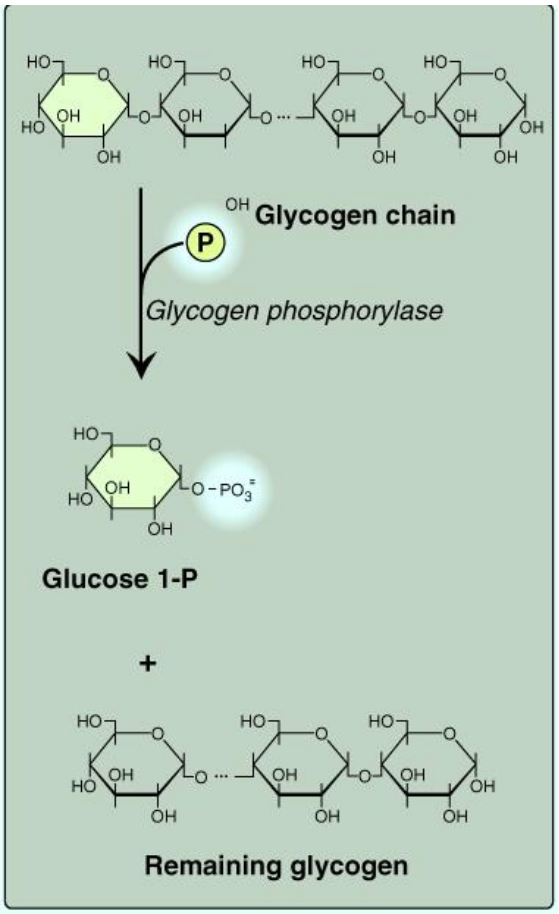
*From where did the name *glycogen phosphorylase* come?

-Suppose we hydrolyzed the bond and broke it by adding water, the reaction is hydrolysis and the enzyme would be a hydrolase. But here we broke the bond by adding a phosphate. Therefore, it's a phosphorolysis reaction (breaking with phosphate rather than breaking with water), and the enzyme is called a *phosphorylase*.

-The enzyme: *glycogen phosphorylase*
-The type of the reaction: phosphorolysis
-release of glucose 1-p from the non-reducing end.

*Why did we add phosphate not water?

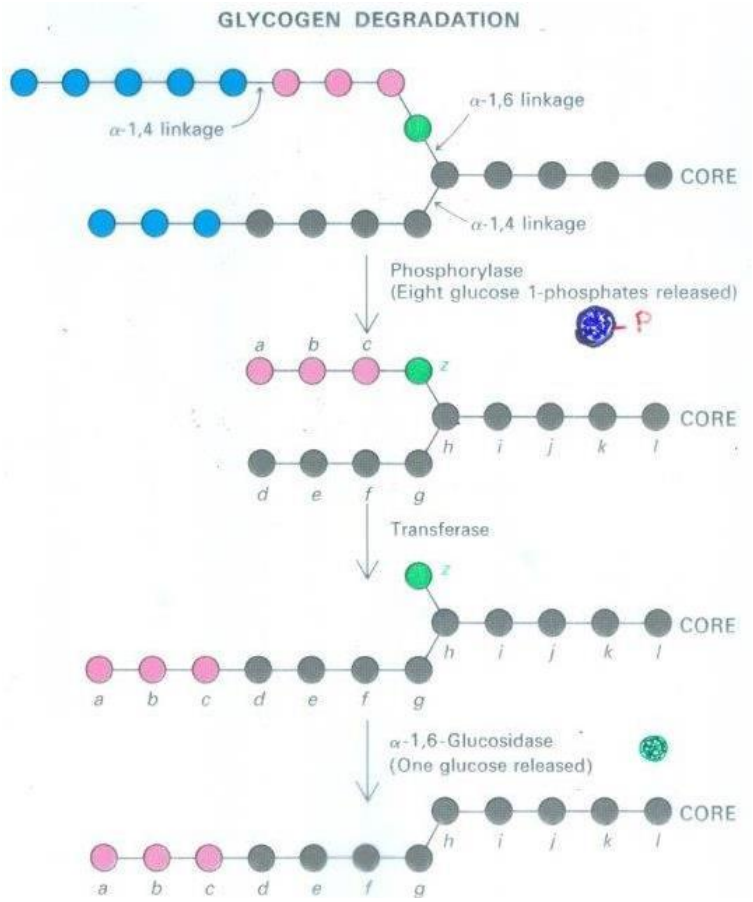
-Because it's much better. If we added water and produced glucose, we would need ATP to make glucose 6-p again but with phosphorolysis, we produce phosphorylated glucose directly and ultimately save energy. In muscles, where glycogen is the source of energy (by glycolysis), for every glucose unit produced from glycogen 3 ATP molecules will be produced (not 2) because we saved 1 ATP molecule. Instead of using ATP to convert glucose to glucose 6-p for glycolysis, we produced an already



phosphorylated glucose.

*Remember: phosphate is added to C-1 of the terminal glucose producing glucose 1-p. We have many ends and degradation happens at each end, that's way degradation of glycogen is very rapid.

10:15-20:15



The figure above shows the action of glycogen *phosphorylase* which removes one glucose molecule at a time. When glycogen *phosphorylase* is 4 units away from the branch point it stops. After glycogen phosphorylase stops working, another enzyme (*transferase*) takes 3 units from the branch and puts them on another branch, 3 units are transferred from this branch to the non-reducing end of another chain (Thus, an α(1-4) bond is broken and an α(1-4) bond is made and the enzyme functions

as 4:4 transferase) . Then, the unit that remained on the branch is removed by hydrolysis producing glucose (not phosphorylated). Now the *phosphorylase* can continue its work.

*If we assumed that after every 8 residues there is a branch, how many glucose 1-phopsphate and glucose molecules would we get after complete degradation?

-For every 8 glucose 1-phopsphate molecules we will get 1 glucose molecule. This reflects the number of branching; the more branched glycogen is the more glucose we get.

*What are the enzymes required for degradation?

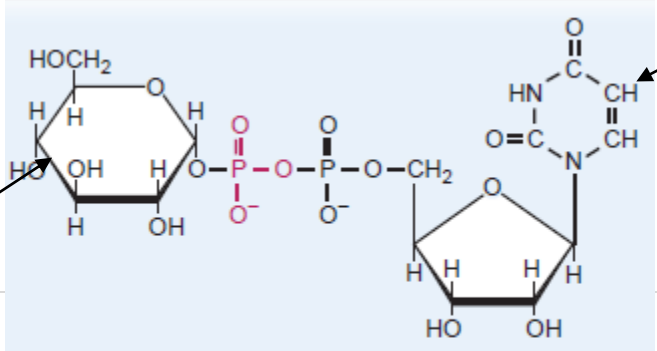
Phosphorylase (which liberates glucose 1-p) and the *debranching enzyme*. The debranching enzyme does 2 things:

1. transfer of 3 units (as explained before)(this domain of the enzyme is called oligo-α(1-4) –α(1-4)-glucotransferase)
2. hydrolysis of the unit at the branching point (the α-1,6 bond so this domain is called amylo- α(1-6)glucosidase)) which liberates free glucose.

Synthesis of Glycogen

Glycogen is synthesized by adding glucose one by one at the non-reducing end. UDP-Glucose is the active donor of glucose units. You can't put glycogen and glucose together with the enzymes and expect glycogen to be synthesized. Why?! Because adding glucose to glycogen requires energy; it is an energy-requiring process (building always needs energy). You need the active donor UDP-Glucose.
(Note: almost all sugars are activated once they bind to UDP, while lipids are activated once they bind to CDP)

uracil



Uridine diphosphate glucose
(UDP-glucose)

glucose

ribose

*you don't have to know how to write the structure, you just have to recognize it and know the features of UDP-Glucose: ribose, diphosphate, glucose, uracil (It looks like UTP but it has glucose rather than the third phosphate).

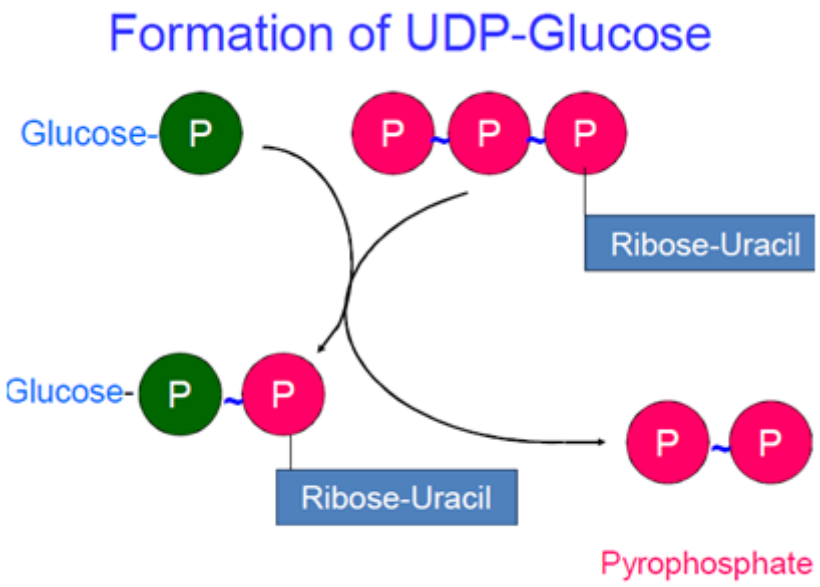
*What is the purpose of UDP-Glucose?

-To carry glucose and transfer it to glycogen during synthesis.

Formation of UDP-Glucose

Glucose 1-phosphate + UTP $\rightarrow$ UDP-Glucose + PP_i (this reaction is catalyzed by the enzyme UDP-glucose pyrophosphorylase)

(We get Glucose 1-p from Glucose 6-p by the action of phosphoglucomutase)



We are going to break the bond between phosphate #1 and phosphate #2 in UTP and then join phosphate #1 with the phosphate of Glucose 1-phosphate. The result is UDP-Glucose and pyrophosphate.

*We broke a high energy bond and we made a high energy bond. Will this reaction have + or – or 0 ΔG?

- ΔG would be equal to 0 because we are breaking a high energy bond and making a high energy bond. Since ΔG=0, the reaction is completely reversible and depends on the concentrations.

*How can we make the reaction irreversible?

-There is an enzyme named *pyrophosphatase* which hydrolyses pyrophosphate rapidly as soon as it is produced. PP_i will be hydrolyzed to 2 P_i continuously by this enzyme. So, if we continuously take one of the products of a reversible reaction, the reaction would become completely irreversible and would proceed in the forward direction (this is how it actually goes). (A note from the book that the doctor hasn't mentioned : the hydrolysis of pyrophosphate is exergonic , ensuring that the UDP-glucose pyrophosphorylase reaction proceeds in the direction of UDP-glucose production)

20:15-30:30

*How is glucose added one at a time?

-Firstly, glucose 6-phosphate is isomerized to glucose 1-phosphate. Then glucose 1-phosphate and UTP produce UDP-Glucose as we said.

An enzyme called glycogen synthase makes the α(1-4)linkages in glycogen. This enzyme can't initiate chain synthesis using free glucose as an acceptor of a molecule of glucose from UDP-glucose. Instead, it can only elongate already existing chains of glucose and; therefore, requires a primer :

1- A fragment of glycogen can serve as a primer: this is found in cells whose glycogen stores are not totally depleted (short period of fasting) … note that, in this situation the glycogen synthase is the enzyme which starts the reaction.

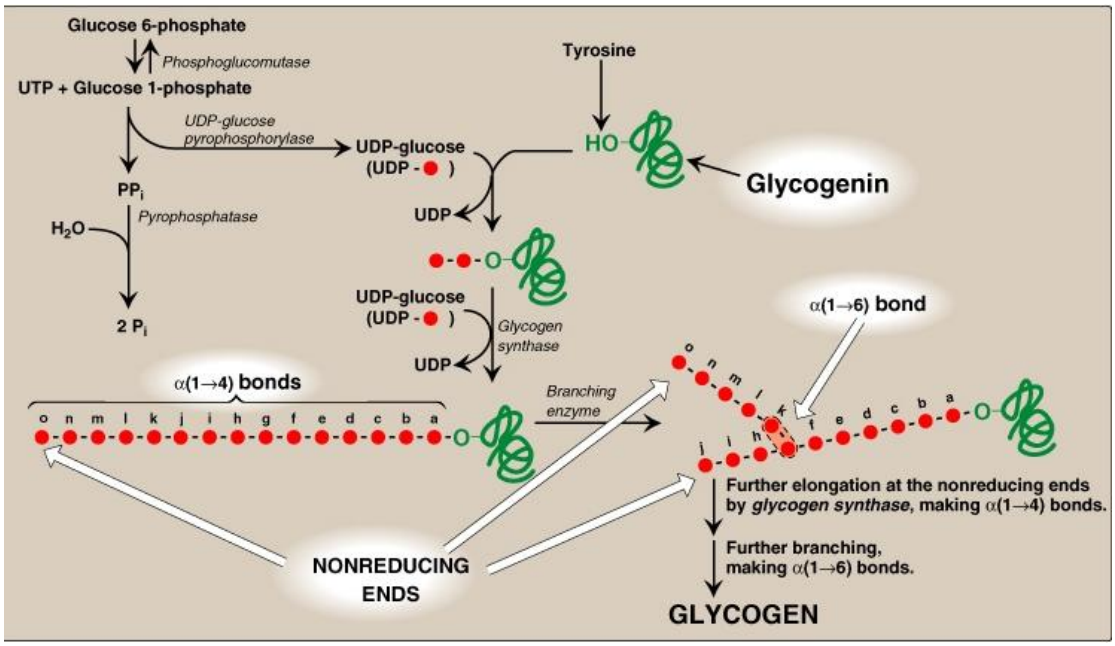
2- In the absence of a glycogen fragment, a protein called glycogenin can serve as an acceptor of glucose residues from UDP-glucose (long fasting): The side chain hydroxyl group of a specific tyrosine in the protein serves as the site at which the initial glucosyl unit is attached. Glycogenin protein acts as enzyme; it catalyzes autoglucosylation (adding glucose to itself) until about 8 glucose residues are added to it. At this point, its enzymatic activity is stopped and glycogen synthase starts working by adding glucose residues to the formed oligosaccharide which acts as a primer. (Note that, in this situation glycogen synthase is not the enzymes which starts the process).
(Glycogenin stays associated with and forms the core of a glycogen granule)

Then an enzyme called *brancher* or *4:6transferase* takes 5-8 sugars from this chain (it breaks (1-4) linkage) and joins them to the chain by an α-1,6 bond as a branch. Now we have 2 non-reducing ends we can continue from.

(In glycogen, there are about 8 residues between each two successive branches, while in starch they are about 20 residues apart. So, glycogen is more branched than starch)

*What are the enzymes needed for the synthesis of glycogen?

-We need an enzyme that adds glucose (*glycogen synthase*) and an enzyme that does the branching (branching enzyme) which is *4:6-transferase* (transfers the sugars from C-4 to 6).



In a well fed state: glycogenesis should be activated and glycogenolysis should be inhibited

In fasting conditions: glycogenesis should be inhibited and glycogenolysis should be activated. (So both processes are regulated in an opposite manner)

The regulatory enzymes for these two processes are glycogen synthase and glycogen phosphorylase.

Glycogen Storage Diseases

*How do glycogen storage diseases occur?

-Because there are many enzymes and enzymes are proteins, it is possible for mutations to occur in one of these enzymes decreasing its activity. A disease would be developed from the absence of this mutated enzyme (we mean: the absence of the normal form). So any time there is a problem in the gene of a specific enzyme the product would be an abnormal or inactive enzyme.

We call this group of diseases glycogen storage diseases because there is a problem with the storage of glycogen. There are various types and they are designated by names and numbers.

They are genetic diseases caused by defects in enzymes required for glycogen degradation or, to a smaller extent, glycogen synthesis. They result in:

1- If one of the enzymes required for glycogen degradation is involved, it would lead to an accumulation of excessive amounts of normal glycogen because it is not normally degraded.
2- If the enzyme involved is for the synthesis of glycogen, it would lead to the formation of glycogen that has an abnormal structure.
3- It might result in both abnormal structures and excessive accumulation.

It can occur in one (because the defect may be in a specific isozyme that is expressed in a specific tissue) or more tissues. Some occur in the liver or in the muscles and some occur in all tissues (It must be already known for you that most tissues store small amounts of glycogen for their own use, so GSDs can affect all tissues). The severity of these diseases ranges from FATAL in Infancy to a mild disorder that may not be recognized. These are rare diseases, you won't probably see them unless you become a pediatric, then you might see a baby with a glycogen storage disease.

Some of the glycogen storage diseases:

- 0 glycogen synthase I defects
- I Glucose-6-phosphatase (von Gierk's) disease: (this is the most frequent among GSDs , but this doesn't mean it is a frequent disease)
  -a defect in *Glucose-6-phosphatase* enzyme

  -Tissues affected: Liver, kidney and intestines (the enzyme exists in small amounts in the intestines). Why not in the muscles? Because in the muscles there is no *Glucose-6-phosphatase*

  - Severe fasting hypoglycemia, Why? Because glycogen produces glucose during fasting (normally), but here glucose is not produced during fasting in the liver and this would develop hypoglycemia. (The patient can't even get glucose from gluconeogenesis because it also ends with this enzyme) so the patient requires frequent feeding.

- Hepatomegaly (تضخم الكبد) fatty liver: because the liver can just use some glucose for energy production and the excess glucose would be converted to fat (glucose … pyruvate… Acetyl CoA … fat)
- Normal glycogen structures, they accumulate in the liver because they are not utilized... So, it might make up 20% of the liver (normal liver consists of 10%glucose)
- Progressive renal disease because of problems in the kidney.
- Growth retardation and probably early death
-Hyper-lactic-academia (lactic acidosis) because high amounts of glucose will be converted to pyruvate which can generate lactate.
-Hyperuricemia: we will study this later (glucose 6-phosphate -> pentose -> purines and pyrimidines (nucleotides) -> uric acid)

- V Muscle glycogen phosphorylase (McArdle syndrome):
-Only muscle is affected. (But the liver won't; because it is a different enzyme)

  - Weakness and cramping of muscle after exercise: Because the problem is in the muscle *glycogen phosphorylase*. We need this enzyme for providing the muscle with glucose during exercise so that there wouldn't be mobilization of glucose and there would be shortage in energy , and if someone has this disease his muscles would be weak after exercise.

  - No increase in blood [lactate] level during exercise: the muscles will not produce lactate because they are not using the anaerobic pathway; they are only oxidizing fat to get energy (but normal people mobilize glycogen to use glucose in aerobic and anaerobic glycolysis)

- VII Phosphofructokinase deficiency : it is similar in consequences to type (V) because glycolysis is a continuation to glycogen breakdown , so if we stop at glycogen breakdown or at glycolysis it would be same; we won't get energy)
-But this gene exists in muscles and RBCs …. SO in addition to the symptoms revealed in type (V), type (VII) patients suffer from hemolytic anemia because RBCs will be defective in producing ATP during glycolysis.

30:30-42:00

- II Lysosomes α (1→4) glucosidase → POMPE Disease: (fetal disease)

  -The problem is in the degradation of glycogen in the lysosomes: The function of lysosomes is to degrade macromolecules. Actually, ≈ 3% of glycogen is degraded in the lysosomes but in a different pathway than the one we talked about. The enzyme that catalyzes this is called *α (1→4) glucosidase* (a hydrolase).

  - Affects liver, heart and muscle (everywhere): because this enzyme (*α (1→4) glucosidase*) is in the lysosomes.

  - Excessive glycogen in abnormal vacuoles in the lysosomes
  - Massive cardiomegaly (تضخم عضلة القلب)
  - Normal blood sugar, normal glycogen structure: there's no problem in the blood sugar because the degradation of storage glycogen is normal.
  - Early death from heart failure

Energy needed for glycogen synthesis

Synthesis of glycogen requires energy and the degradation does not produce energy.

*For each glucose unit added to glycogen, how much energy do we need?

-These are the reactions that happen for each glucose molecule added:

Glucose + ATP→ Glucose 6-phosphate + ADP
Glucose 6-phosphate → Glucose 1-phosphate
Glucose 1-phosphate +UTP→ UDP-Glucose+ PPi
PPi + H2O →2Pi
UDP-Glucose + Glycogen(n) → UDP + Glycogen(n+1)

Now to know the net reaction, we will cancel any product that is used in the next reaction:

Glucose + ATP→ Glucose 6-phosphate + ADP

Glucose 6-phosphate → Glucose 1-phosphate

Glucose 1-phosphate +UTP→ UDP-Glucose+ PPi

PPi + H2O →2Pi

UDP-Glucose + Glycogen(n) → UDP + Glycogen(n+1)

Glucose + ATP + UTP+Glycogen(n)→ ADP + UDP +Glycogen(n+1)

*How many ATP equivalents are used?

-2, with every glucose added to glycogen, we consume 2 ATP molecules.

In degradation we save 1 ATP because we produce glucose 6-phosphate. And each glucose 6-phosphate molecule that enters glycolysis will produce 3 ATP (instead of 2) because glucose is already phosphorylated (in the muscle).

So, if synthesis and degradation of glycogen continue, 1 ATP will be produced each time (we used 2 ATPs and saved 1 ATP). And that's why there should be regulation.

42:00-47:00

"There is no elevator to success, you have to take the stairs"

Sorry for any mistakes