SHEET NO. 9

METABOLISM

DOCTOR 2019 | MEDICINE | JU

DONE BY : Doctor 2018

SCIENTIFIC CORRECTION : Reem Albadow, Noor Shahwan & Dra'a Megdady

GRAMMATICAL CORRECTION :

DOCTOR : Faisal Al-Khatib

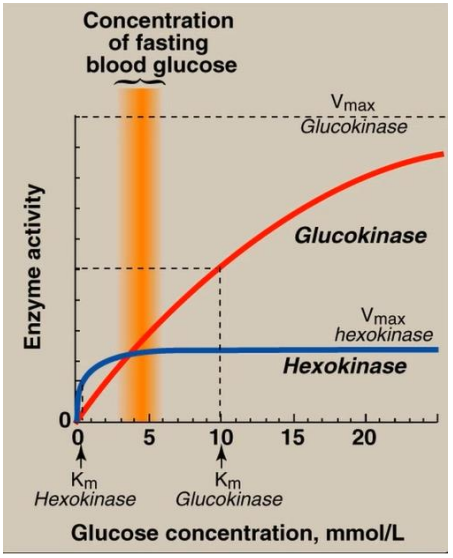
REGULATION OF GLYCOLYSIS AND GLUCOGENESIS :

The processes of gluconeogenesis and glycolysis are regulated in a reciprocal fashion, that means that when one process is highly active, the other one is inhibited, this is because **if** both processes took place at the same time, there would be a net amount of ATP molecules (and GTP) that would be used up and none would be produced. the net effect will be hydrolysis of 4 ATP (loss of ATP)>>(6-2=4).

This regulation is applied on the **ENZYMES** of the irreversible steps :
Step 1 , the phosphorylation of GLUCOSE to GLUCOSE 6-PHOSPHATE by hexokinase and glucokinase .
Step 3 , the phosphorylation of FRUCTOSE 6-PHOSPHATE to FRUCTOSE 1,6-BISPHOSPHATE by phosphofructokinase-1 (PFK-1).
Step 8 , the conversion of PHOSPHOENOLPYRUVATE to PYRUVATE by pyruvate kinase .

For Step 1 regulation
the phosphorylation of GLUCOSE to GLUCOSE 6-PHOSPHATE by hexokinase and glucokinase .

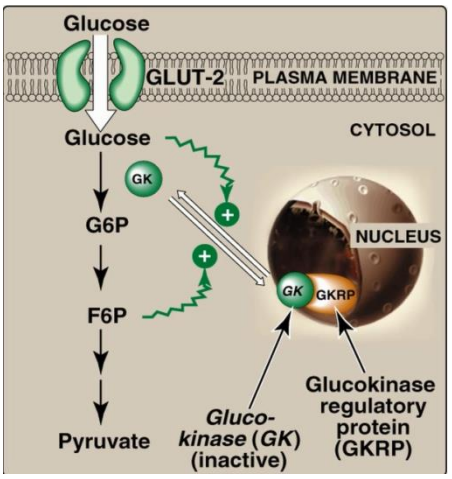
the substrate concentration that produces V max in the liver (Km) is 10 mmol/L , that means we need high conc-entration of Glucose to be phosphorylated by Glucokinase and that make sense because liver is responsible of Glucose storage and if the blood has low Glucose concentration our bodies prefer to use it rather than storage as glycogen or as a source of energy or to be converted into fatty acids , while the substrate concentration that produced V max in other body tissues (Km) is approximately 0.01 mmol/L , that means even low concentration of Glucose will be phosphorylated by Hexokinase in other body tissues that use it as a source for energy production like brain which will die if there is no Glucose supplied .



The effect of glucose concentration on the rate of phosphorylation catalyzed by Glucokinase (in the liver) and Hexokinase (in the other tissues) .

- **This is the first type of regulation (having two enzymes that have different properties and act in different ways).**

The inhibition of glucokinase activity :



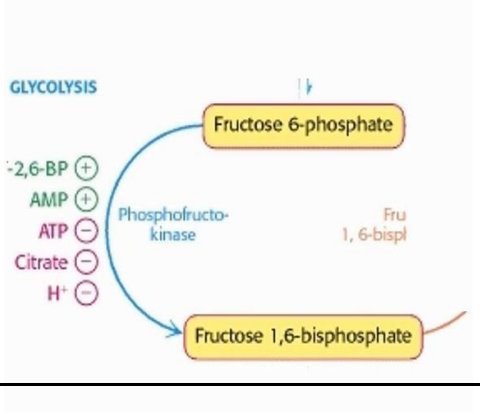
Glucokinase activity is not directly inhibited by glucose 6 - phosphate as are the other hexokinases Instead, it is indirectly inhibited by fructose 6 – phosphate (fructose 6 – phosphate is in equilibrium with glucose 6 – phosphate (reversible reaction)).
Regulation is achieved by reversible binding to the Glucokinase regulatory protein (GKRP).
In the presence of fructose 6 - phosphate, glucokinase binds tightly to GKRP and is translocated to the nucleus, thereby rendering the enzyme inactive , when glucose levels in the blood increase, glucokinase is released from GKRP,
and the enzyme reenters the cytosol where it back to the active form.

NOTE that :
This regulation will prevent the accumulation of phosphorylated sugars within the cytosol (the accumulation of phosphorylating sugars consumes the phosphate group supply of the cell (they trap the phosphate with them). Therefore, overproduction of phosphorylated sugars may cause depletion of our phosphate group stores. This will lead to a new problem, which is the inability to produce ATP, because ATP synthesis requires phosphate groups.) .

For step 3 regulation
the phosphorylation of FRUCTOSE 6-PHOSPHATE to FRUCTOSE 1,6-BISPHOSPHATE by phosphofructokinase-1 (PFK-1).
This is commit step (G6P cannot go except for this step) .

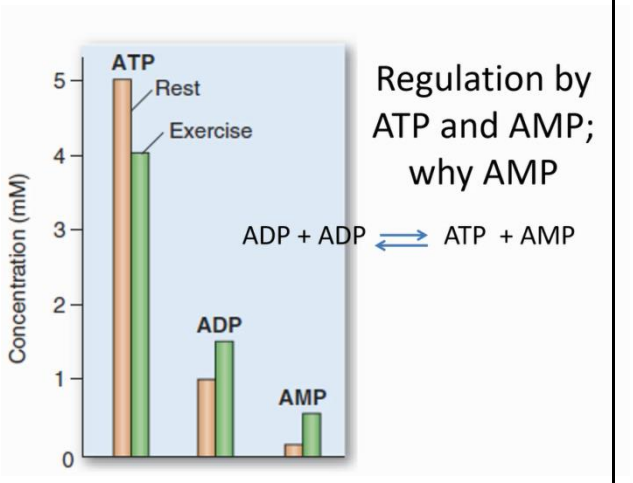
PFK-1 is inhibited by :
1. ATP; since the goal of glycolysis is to produce ATP, if the level of ATP is high the glycolysis should be switched off.
2. Citrate; high citrate levels mean high amount of building blocks.
3. H+ which indicates low pH since the end product of glycolysis is either pyruvate or lactate (both of them are weak acids that decrease the pH) so if the PH is decreased , glycolysis should stop.

PFK-1 is activated by:
1. AMP; it indicates a low energy state in the cell.
2. 2,6-bisphosphate; it is a regulator (activator) of glycolysis not an intermediate.



- **ATP and AMP Regulation .**

Why not ADP, although it also indicates a high energy state in the cell? If ATP is used up at a very high rate, ADP levels will increase but ADP cannot be used to replace ATP even though it has a lot of energy. The enzymes that depend on ATP can't use ADP to carry out the reaction.



✓ Let's start with ATP: ATP levels during exercise decrease from 5→4 mM because exercise needs energy which can be obtained from ATP hydrolysis.
✓ ATP (as a regulator of glycolysis) indicates a high energy state, inhibiting glycolysis.
✓ ADP levels increase slightly during exercise because ATP hydrolysis leads to formation of ADP and inorganic phosphate. ADP can't be used for regulation purposes.
✓ AMP activates glycolysis because it indicates a low energy state in the cell. It's used as a regulator of glycolysis due to its sensitivity to the energy state in cells.

AMP can be produced during ATP synthesis by the enzyme adenylate kinase, by combining 2 ADP molecules:

ADP + ADP → ATP + AMP

This reaction indicates that energy level is very low

It can also be produced by hydrolysis of one high energy phosphate bond of ADP.

- **2,6-bisphosphate regulation.**

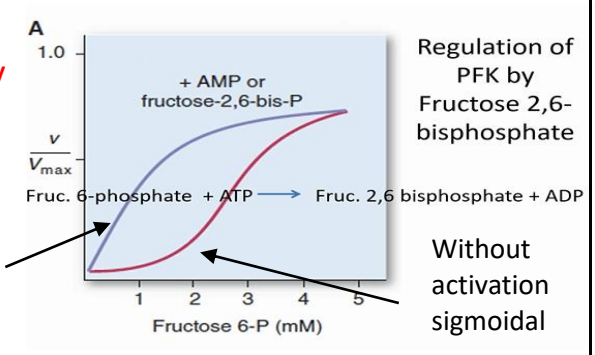
is an activator of glycolysis, produced by adding a phosphate group to fructose-6-phosphate by the enzyme phosphofructokinase-2.

How can we distinguish between PFK-1 and PFK-2?

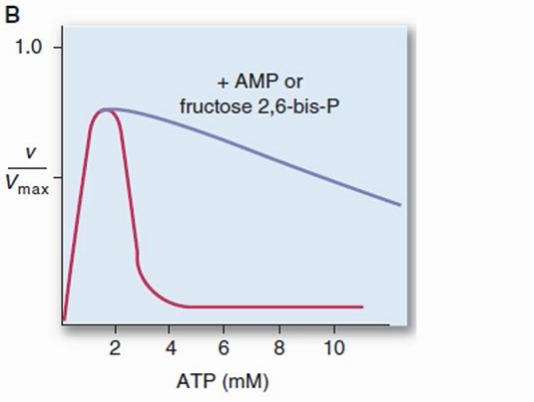
• Phosphofructokinase 1 → Adds a phosphate group to carbon number 1 of Fru-6- P.
• Phosphofructokinase 2 → Adds a phosphate group to carbon number 2 of Fru-6- P.

Looking at the red curve in the figure below, we can see the relationship between the velocity and the PFK substrate concentration which is Fru-6-P. If we increase the substrate concentration, the velocity increases until it reaches Vmax. But as we can see in the blue curve (with the addition of AMP and/or fructose-2,6- bisphosphate), the red sigmoidal curve becomes hyperbolic due to increased activity of enzymes indicated by increased velocity at the same substrate concentration. Fructose-2,6-bisphosphate and AMP bind to the enzyme on the regulatory site **activating** the binding of the substrate, resulting in increased enzymatic activity.

AMP and fructose-2,6-bisphosphate act as regulatory molecules by decreasing the Km (higher affinity) and shifting the curve to the left (increasing activity).



ATP is a substrate of the enzyme PFK, so we expect that if we increase the substrate (ATP) concentration, the rate of the reaction will increase. But as we can see in the figure below, after the reaction gets to Vmax, it sharply decreases which indicates that ATP is an activator of PFK at low concentrations but has an inhibitory effect at some high substrate (ATP) concentrations.
however, the presence of AMP and/or Fru-2,6-bp removes the inhibitory effect of ATP and the reaction of the enzyme (PFK) proceeds.



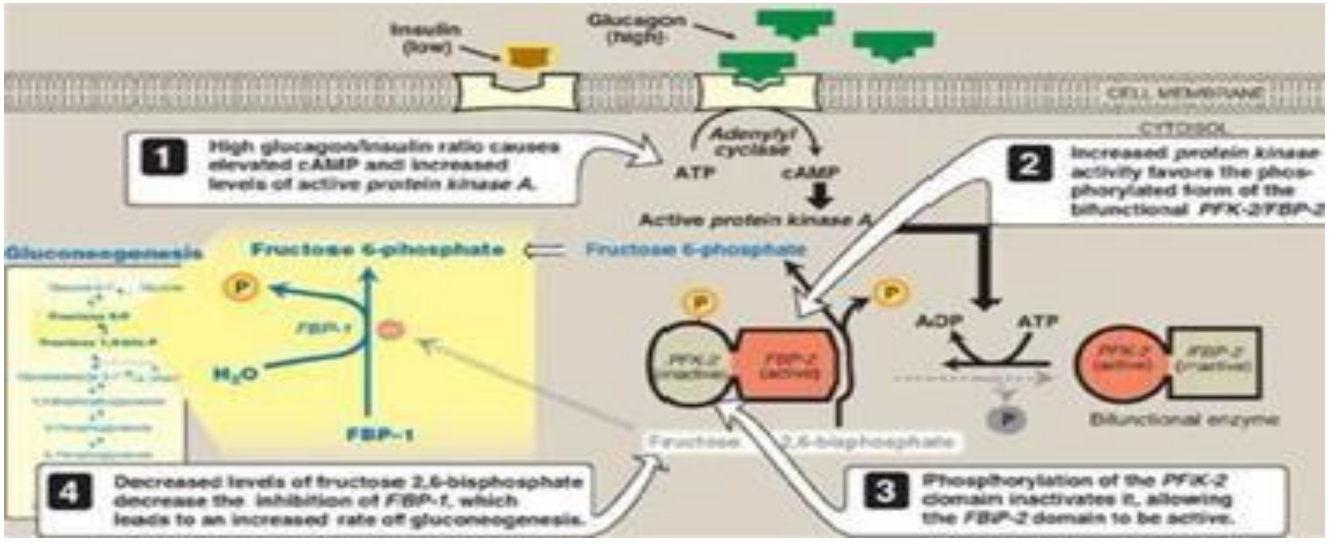
PFK-2 is a bifunctional protein that has both the kinase activity (PFK-2) that produces Fru-2,6-bp and the phosphatase activity (fructose-2,6-bisphosphatase FBP-2) that dephosphorylates Fru-2,6-bp to Fru-6-p.
Phosphorylated form of PFK-2 is inactive, while the dephosphorylated form is active.
Phosphorylated form of FBP-2 is active, while the dephosphorylated form is inactive.

> **During the well-fed state:** decreased levels of glucagon and elevated levels of insulin cause an increase in hepatic Fru-2,6-bp indicating high activity of PFK-2 (<u>dephosphorylated</u> active form) and thus Fru-2,6-bp activates PFK-1 leading to the activation of glycolysis.
> *Glucagon indicates low blood sugar, Insulin causes an increase in glucose uptake.
>
> So we can say that Fru-2,6-bp is an intracellular signal of glucose abundance leading to activation of glycolysis.

During fasting: elevated levels of glucagon and low levels of insulin lead to a decrease in hepatic Fru-2,6-bp indicating low activity of PFK-2 (phosphorylated inactive form). Low Fru-2,6-bp leads to less activation of PFK-1 causing inhibition of glycolysis but activation of gluconeogenesis (production of glucose from non- carbohydrate sources).

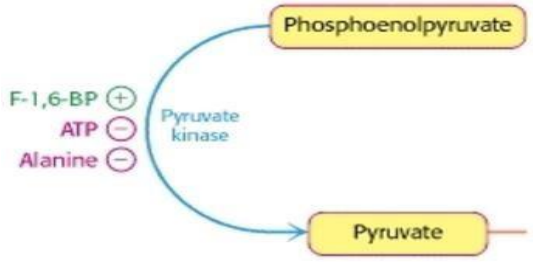
- Steps of PFK-2/FBP-2 regulation;

1. High insulin/glucagon ratio causes decreased cAMP and reduced levels of active protein kinase A.
2. Decreased protein kinase A activity favors dephosphorylation of bifunctional protein PFK-2/FBP-2.
3. Dephosphorylated PFK-2 domain is active, whereas FBP-2 is inactive. The dephosphorylated active PFK-2 favors formation of fructose-2,6-bisphosphate.
4. Elevated concentration of Fru-2,6-bp activates PFK-1 which leads to an increased rate of glycolysis; needed to reduce the large amount of glucose.
   (increased uptake due to high insulin concentrations) As you can see in the figure ..



✓ Now let's start talking about the third and last irreversible reaction which is the conversion of phosphoenolpyruvate into pyruvate by pyruvate kinase. This reaction is inhibited by ATP and Alanine (which indicates abundance of building blocks) and is activated by fructose-1,6-bisphosphate.
1,6-bisphosphate is an early intermediate (activator of the enzyme downstream).

Feed forward activation

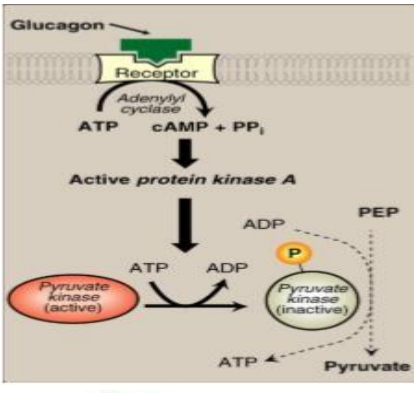


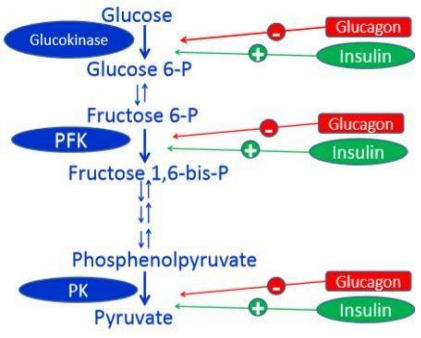
Pyruvate kinase (PK) is also regulated by phosphorylation;

high level of glucagon ❼ stimulates adenylyl cyclase ❼ activates protein kinase ❼ phosphate group to pyruvate kinase (phosphorylation) ❼ inactivates the enzyme PK.

Adding a phosphate group to many enzymes such as pyruvate kinase will spare the glucose (decrease its degradation, utilization, glycolysis AND increase its availability).

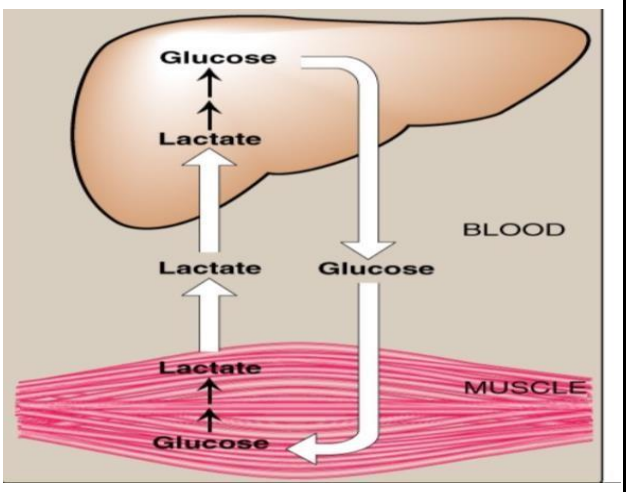
- Insulin and glucagon regulate the amount of expression of enzymes (i.e. affect the amount of transcription into mRNA and its translation), thereby regulating metabolism of carbohydrates.
- Glucagon decreases the amount of enzymes (inhibition of enzymes ❼ inhibition of glycolysis).
  Glucagon indicates low blood sugar, meaning we need to keep the glucose.
- Insulin increases the amount of enzymes (activation of enzymes ❼ activation of glycolysis).





As we have a huge amount of glucose uptake by insulin which needs to go through glycolysis.

The following figure shows that the two reactions can occur at the same time but **NOT in the same tissue,** the muscle during severe exercise converts glucose to lactate then lactate gets released into the blood stream, because it's like a waste or by-product that's not needed by the muscle, lactate goes to the liver where it's converted back to glucose, glucose is then released to the blood stream to return back to the muscle.



The cori cycle

To sum up,
Yes, we said before that if these two processes occur together, we lose 4 ATP, but here the two reactions occur in two different tissues and this is necessary to keep the muscle function in order to keep it contracting.
To better understanding, assume that you are running from a wild animal and there is insufficient supply of oxygen to the muscle which means that anaerobic glycolysis will occur, it will produce 2 ATP and lactate, the liver will take the lactate to convert it back to glucose to be used again by the muscle. That's **the Cori Cycle.**

Regulation of Gluconeogenesis:

Gluconeogenesis can also be regulated by AMP/ATP ratio.

❖ High ratio means that we need to form ATP, so it inhibits Fructose 1,6- bisphosphatase, thus inhibiting Gluconeogenesis.

❖ Low ratio means that there is high ATP so no need to glycolysis thus activating Gluconeogenesis.

❖ Citrate inhibits glycolysis and stimulates gluconeogenesis because citrate is indicative of high level of building blocks.

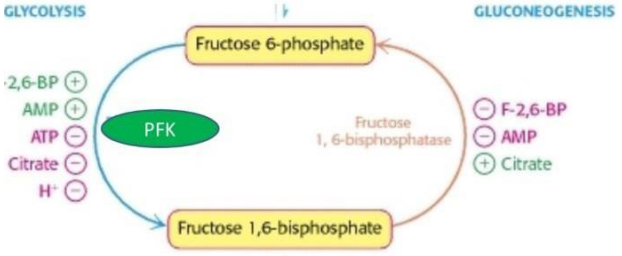
❖ First let's have a quick recap (recap 3):

∝ Fructose 2,6-bisphosphate is the most potent activator of PKF (Phosphofructokinase 1).

∝ Fructose 2,6-bisphosphate is formed from fructose 6-phospate by the addition of a phosphate group at carbon # 2 , by the enzyme PFK2.

∝ F2,6BP is affected by **insulin to glucagon ratio** >> remember when we talked about glucagon which is a peptide hormone used to raise blood sugar levels by promoting certain processes, high level of glucagon gives an indication of low blood glucose, thus the production of F26BP by PKF2 decreases and there'll be activation of phosphotase.

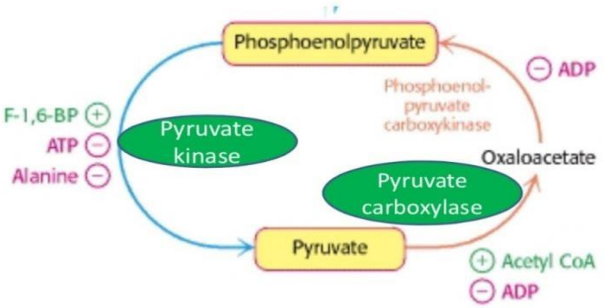
∝ Always remember that gluconeogenesis has the opposite effect of glycolysis .



Allosteric activation by acetyl CoA:

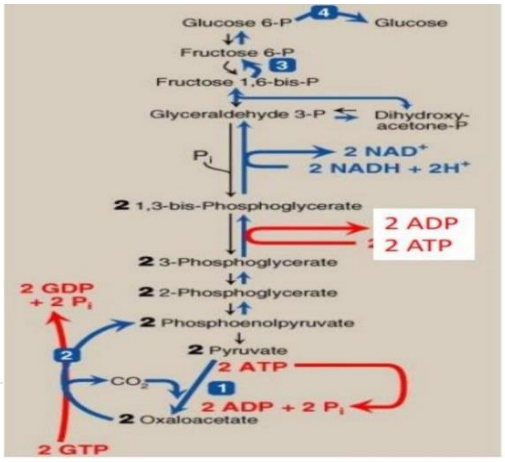
❖ **Pyruvate carboxylase (gluconeogenesis) is activated by acetyl CoA, Pyruvate dehydrogenase (glycolysis) is inhibited by acetyl CoA.**

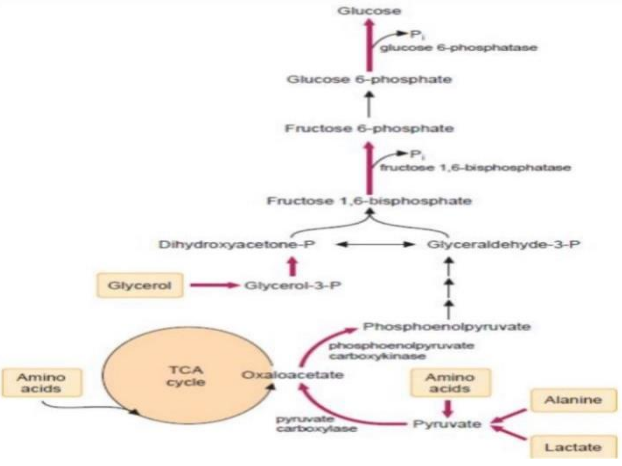
❖ **During fasting, fatty acids are converted to acetyl CoA in muscles so there is no need to dehydrate pyruvate, instead we need glucose for the brain and RBCs.**



❖ **High level of ADP indicates that this is not the time for glucose formation, it's time for its degradation.**

Great Summaries for gluconeogenesis (shown in the video during the lecture but are not in the slides):





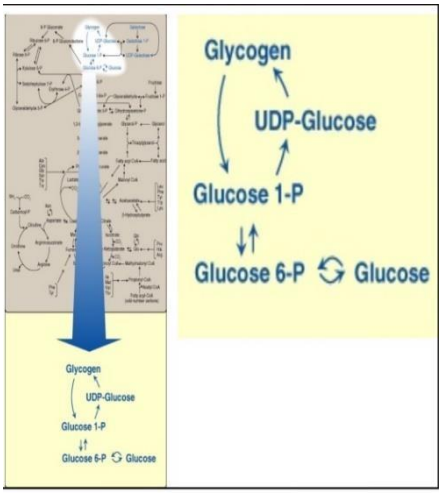
Glycogen Metabolism

What are the sources of blood glucose? First: **DIET**

- ✓ It contains starch, mono and disaccharides and glucose.
- ✓ The problem: its sporadic >> digestion and absorption occur in 3-4 hours, and there might not be any glucose in the diet so it depends on the type of diet.

Second source: **Gluconeogenesis**

- ✓ It can provide sustain levels of glucose.
- ✓ Slow in responding to the falling of blood glucose level: meaning that although it acts to produce glucose into the blood stream, but its slow in responding to that >> (if the blood glucose level goes down, gluconeogenesis is not that fast in responding to produce glucose).



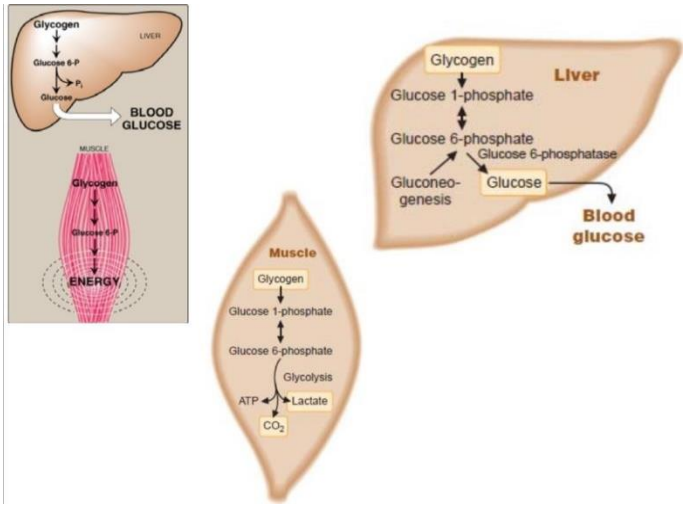
Third source: **Glycogen**

- ✓ Storage form of glucose
- ✓ Rapid response and mobilization.
- ✓ Limited amount
- ✓ Important energy source for exercising muscle.

➲ Glycogen is first converted to glucose 1-phosphate then to G6P and eventually to glucose.

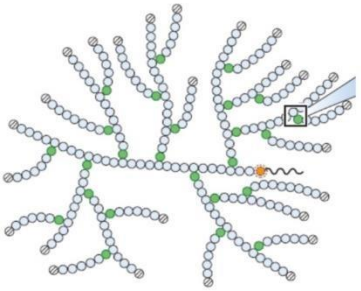
∝ Glycogen is stored in both the liver and the muscles.

Even though the mechanisms appear to be very similar, in the liver glycogen is converted to glucose which eventually goes to the blood stream to supply the organ in need. On the other hand, the muscle converts glycogen to glucose to supply itself (for its own needs), it doesn't produce glucose so that other organs can used it.



∝ **G6P is converted to glucose in the liver but in the muscle it's used for energy production.**

Glycogen structure:



* Extensively branched homopolysaccharide

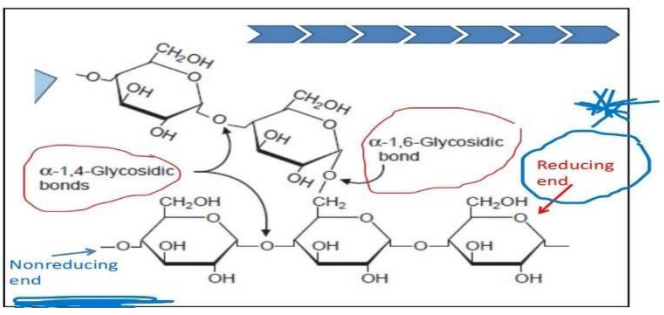
* One molecule consists of hundreds of thousands of glucose units

- This figure represents Glycogen, it consists of large number of glucose units and is an **extensively branched homopolysaccharide.**
- These sugar residues are connected to each other by a glycosidic bond (alpha 1-4) linkage, after 8-14 glucose residues there is a branching point in which two sugar residues are connected by an (alpha 1-6) linkage.
- The first glucose residue in the linear chain forms a reducing end (the only reducing end in glycogen), while glucose residues at the end of branches forms non-reducing ends which means that the anomeric carbon isn't free (in fully acetal form).

Quick Recap 4 >> -A reducing sugar is a sugar that has a free Anomeric carbon so it has the ability to reduce other molecules and get oxidized.

- Branches have great importance; they greatly decrease viscosity of the glycogen solution.

➲ **The non-reducing ends are the locations of all glucose addition and removal>> meaning that the enzymes that work on degradation and synthesis of glycogen act on the non-reducing ends and since there are huge numbers of branching which means more non-reducing ends ❼ There are many ends available for the enzyme, thus more efficient degradation and synthesis.**

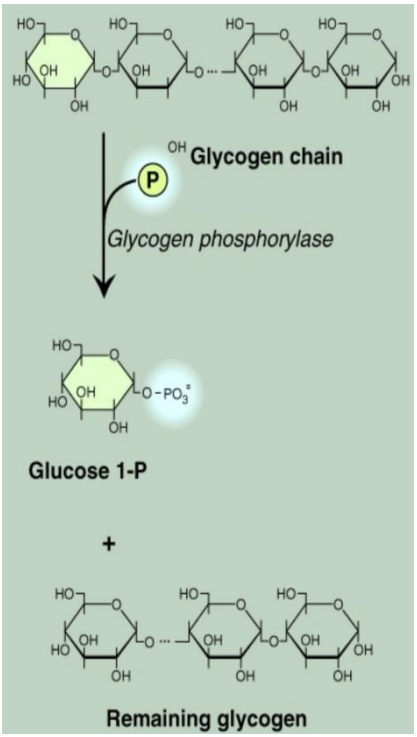


QUESTION YOU MAY ASK>>>>

Why store glycogen as one compound? why not store it as multiple of glucose residues?

Think of the concept of osmotic pressure, imagine we had 55 thousand free glucose molecules instead of having them in the form of glycogen, think of what would happen to the osmotic pressure! Osmotic pressure would greatly increase and the liver will absorb more water.

Degradation of glycogen :



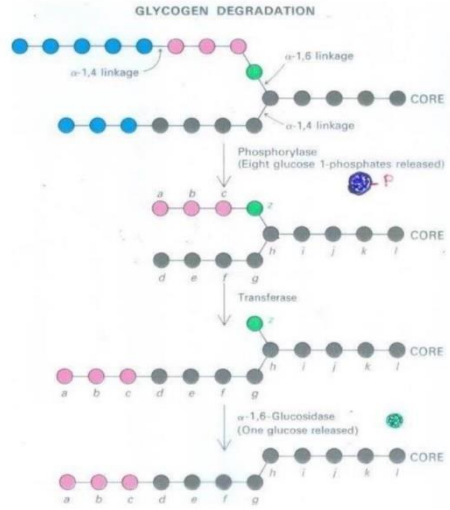
The degradation rxn occurs by the removal of one glucose unit at a time from the non-reducing ends. In the following figure, you can see the non-reducing ends being attacked by phosphorylase producing glucose 1-p and the remaining glycogen. This kind of degradation rxn is similar to hydrolysis, but its not hydrolysis, because as we said in the recap at the beginning of this sheet>> hydrolysis= breaking bonds by adding water , but here we're breaking the bonds by adding phosphate .
This phosphorolysis is carried by the enzyme glycogen phosphorylase.

- Glycogen phosphorylase sequentially cleaves the α-1,4- glycosidic bonds between glucose residues at the non-reducing ends of the glycogen chains producing glucose 1-P (one at a time), when it's 4 residues away form a branch point (α-1,6 bond) the enzyme stops (it can't work anymore).

- Branches are removed by the two enzymic activities of a single bifunctional protein (has 2 activities), the debranching enzyme (de: remove) >> so it removes the branch. This enzyme is known as **Glucosidase.** The two activities of glucosidase are:

a) Transferase activity: it removes the outer three of the four glucose residues attached at a branch. It next transfers them to the nonreducing end of another chain, lengthening it accordingly.

b) α-1,6-glucosidase activity: it releases the last residue as free glucose not glucose 1-P (non-phosphorylated glucose), now the glucose chain is available again for degradation by glycogen phosphorylase until it becomes 4 residues away from another branching point.



Glucose 1-phosphate, produced by glycogen phosphorylase, is converted in the cytosol to glucose 6- phosphate by phosphoglucomutase.

Now G6P is produced and it's an intermediate for glycolysis and gluconeogenesis, in the liver it is hydrolyzed to produce glucose, whereas in the muscle it will enter glycolysis because glucose 6-phosphatase is not found in the muscle, this enzyme is found only in the kidney and the liver, that's why glycogen degradation in the muscle is not a source of glucose for other tissues.

تلخيص سريع على الي بصير هون:

glycogen سكر متفرع ، يعني branched كل ٨-١٤ سكرة ، مشان نكسره بنحتاج انزيم اسمه glycogen phosphorylase هاد االنزيم بشتغل ع ال non reducing end و بطلع سكرة وحدة كل مرة ع شكل G one phosphate, بعدين بس يقرب يوصل التفرع و تحديدا بينه و بين التفرع ٤ residues هون ببطل قادر يشتغل و ببطل يقدر يكسر ، بهاي الحالة بنحتاج انزيم تاني اسمه enzyme debranching يعني مزيل التفرع , هاد االنزيم بسوي شغلتين ، اول اشي بوخد ٣ من ال ٤ سكرات الي قبل التفرع ، و بنقلهم ع chain تانية ، و السكرة رقم ٤ الي ضلت هاي بضيف مي و بطلعها ع شكل glucose free , يعني مش زي الي قبل عليها فوسفات ، ال بتكون هاي unphosphorylated, و بعدين بكمل عادي

Question asked by the doctor:

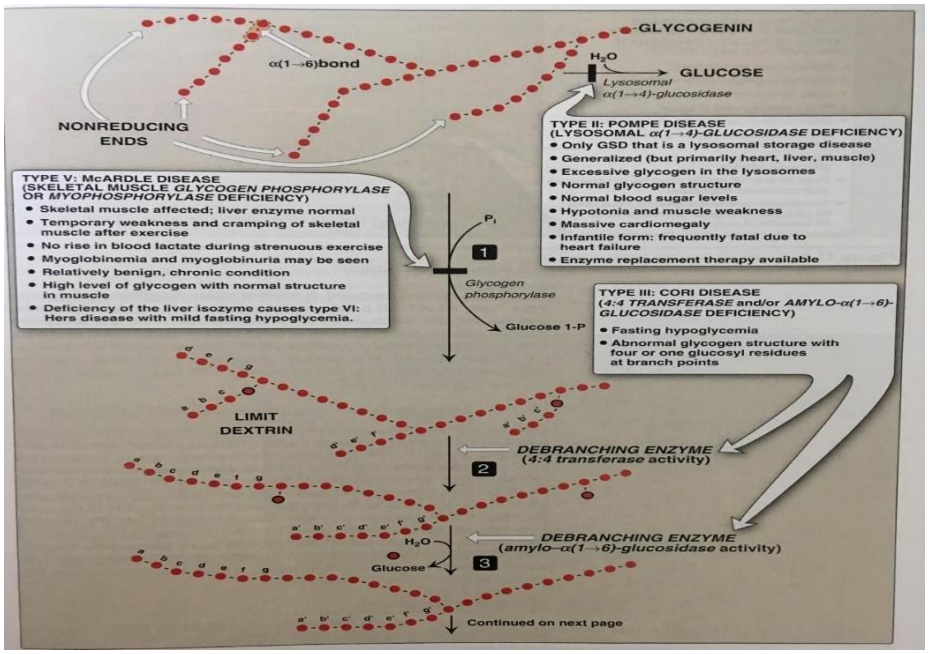
How many ATP can be produced from glucose in glycogen of the muscle? 3 ATP.

التفسير:

The glycogen in the muscle is degraded by the enzyme >> " glycogen phosphorylase" producing G1P , this molecule will be converted to G6P by simple isomerization rxn , changing the location of phosphate group from the carbon # 1 to carbon # 6 , and there is no ATP being consumed in this rxn , then as we know the G6P is converted to F6P , then to f1,6bisp consuming one ATP , and then continuing the pathway + generating 4 ATP , so the net will be 3 ATP

الفرق بين ال ATP بال glycolysis الي اخدناه من اول خطوة لالخر الي كان ينتج ٢ATP , هو انو زي ما هو واضح بالصورة كان في ATP تستهلك اثناء تحويل Glucose ل G6P فكان يقلل من النتيجة النهائية و بالتالي الناتج ككل هو ٢ ATP , بال muscle

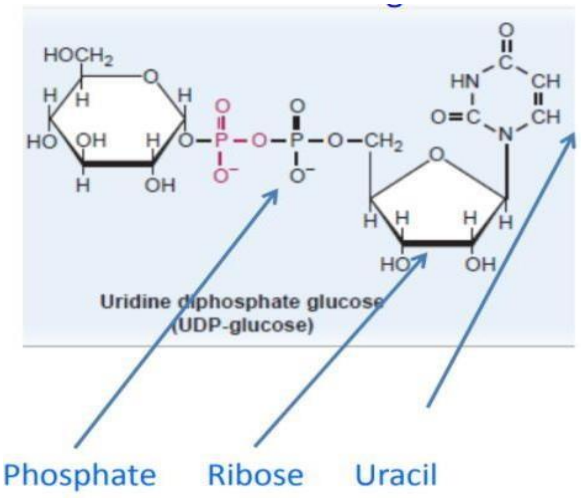
There is no ATP to be added to glucose to produce G6P , since its already released as G1P then its converted to G6P without ATP being consumed >> because as we said its just a simple isomerization rxn



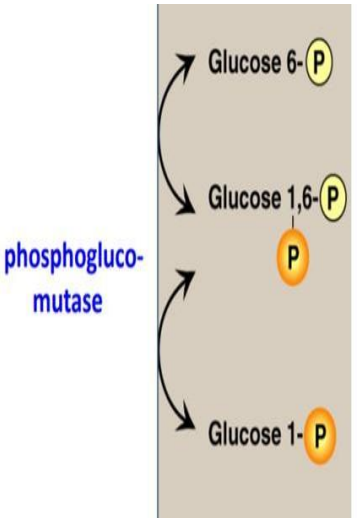
Formation of UDP-Glucose:

- Firstly, free glucose **can not** be added to glycogen directly because no enzyme is capable of adding glucose to glycogen.
- The glucose molecule must be added to a carrier (UDP), which assists in the addition of glucose to glycogen one by one (this is similar to coenzyme A which carries an acyl group to the Krebs cycle).
- UDP also adds sugar residues to proteins to form the glycoproteins.

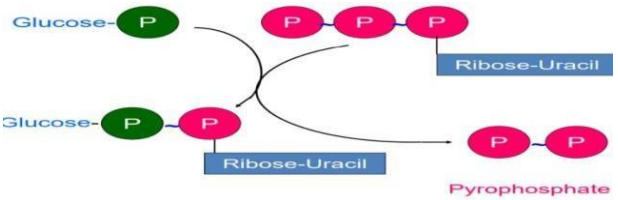
This figure shows the structure of UDP-Glucose



- Glucose is phosphorylated by **glucokinase** to form glucose-6-P, then glucose-6-P is converted to glucose-1-P by **phosphoglucomutase**. UTP can now react with glucose-1-P to form UDP-Glucose.
- Note that: phosphoglucomutase adds a phosphate group to glucose-6-P to form glucose-1,6-bisphosphate. The same enzyme then removes the phosphate group on carbon number 6 to produce glucose-1-P.
- Phosphoglucomutase is capable of catalyzing the reaction in both directions.



Mechanism of formation of UDP-Glucose:



From the figure on the right we notice that:

UDP-glucose pyrophosphorylase adds Glucose-1-P with its own phosphate to the first phosphate of UTP, the two terminal phosphates of the UTP molecules are subsequently released as pyrophosphate.

This reaction is reversible? why? →→→

when the high energy bonds between the first phosphate and the second phosphate break, and a high energy bond between the Phosphate group in glucose-1-Phosphate and the first phosphate in the UTP molecule simultaneously form, no net energy is released, making this reaction reversible (high energy bond break and high energy bond are formed so no net energy is released) . In this case, the reaction clearly has a low ΔG. (close to 0)

But this reaction occurs irreversibly inside the cell, why??

Because there is a rapid removal of pyrophosphate by enzyme pyrophosphatase, so the concentration of pyrophosphate decreases, and the equilibrium of this reaction shifts to the forward direction, forming more UDP-Glucose.

Glycogen synthesis:

- Firstly, you need to know that the enzyme, which is responsible for early synthesis of glycogen, is different than that used in adding glucose unit to glycogen.
- We now know that glycogen synthase makes an α(1→4) linkage in glycogen but this enzyme cannot initiate chain synthesis using free sugar molecule, it canonly elongate already existing chain of glucose, therefore, it requires a primer (an already existing fragment of glycogen can serve as a primer).
- A protein called **Glycogenin** can serve as an acceptor of glucose residues from UDP-glucose. The side-chain hydroxyl group of a specific tyrosine in glycogenin serves as the site in which the initial glucosyl unit is attached. Because the reaction is catalyzed by glycogenin itself via autoglucosylation, **glycogenin is** an enzyme. Glycogenin then catalyzes the transfer of the next few molecules of glucose from UDP-glucose, producing a short, α (1→4)-linked glucosyl chain.
- This short chain serves as a primer that is able to be elongated by glycogen synthase.

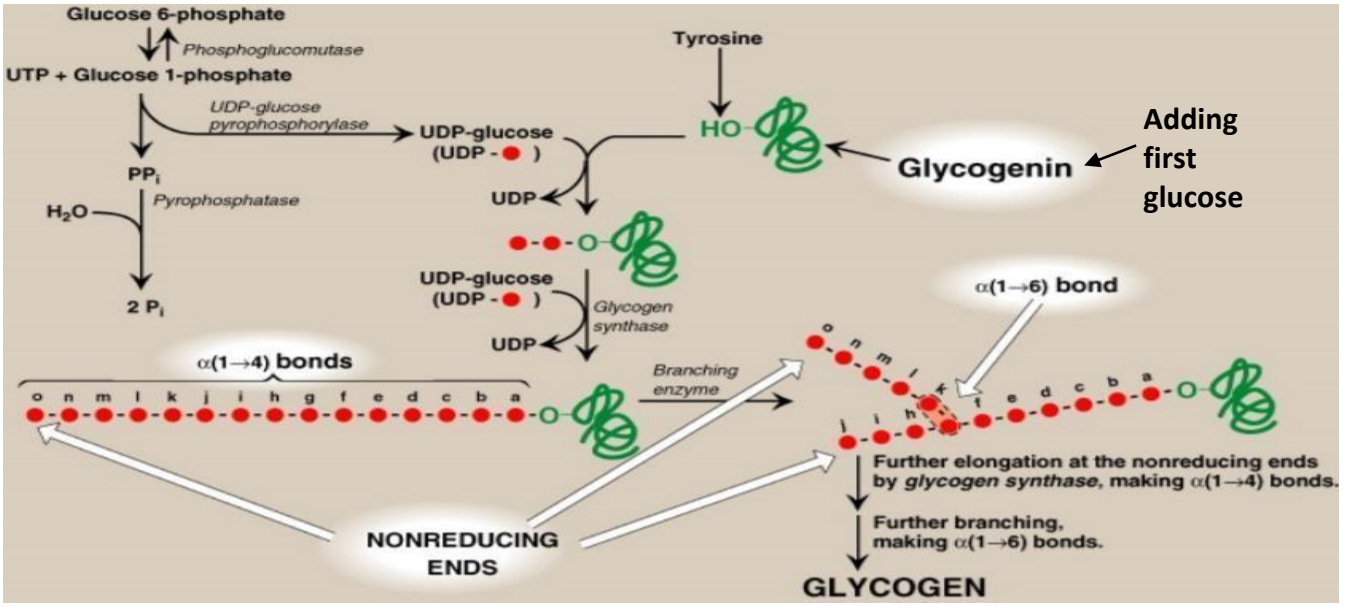
Glycogen elongation:

- Elongation of a glycogen chain involves the transfer of glucose from UDP-Glucose to the non-reducing end of the growing chain, forming a new glycosidic bond.
- The enzyme responsible for making the α(1→4) linkages in glycogen is known as **glycogen synthase.**

Synthesis of additional Branches:

- If no other enzymes acted on the chain, the resulting structure would be a linear (unbranched) chain of glucose residues attached by α (1→4) linkages, such as amylose, a starch found in plants. In contrast, glycogen is highly branched. Branching also increases the number of non-reducing ends to which new glucose residues can be added and more glucose residues can be removed from glycogen as well, so glycogen has high rate of synthesis and metabolism.
- After the elongation of linear chain, an enzyme called **branching enzyme** removes fragment from non-reducing end of glycogen chain (the terminal six to eight glucose residues) to make additional branches. This takes place by breaking an α(1→4) bond then attaching the fragment to a non-terminal glucose residue by an α(1→6) bond.
- Branching increases the number of non-reducing end in glycogen.
- Consecutive activity of both the glycogen synthase enzyme and the branching enzyme result in the elongation of the branches and the original glycogen chain (glycogen becomes larger and larger).

This figure recaps the glycogen synthesis. Take a look.

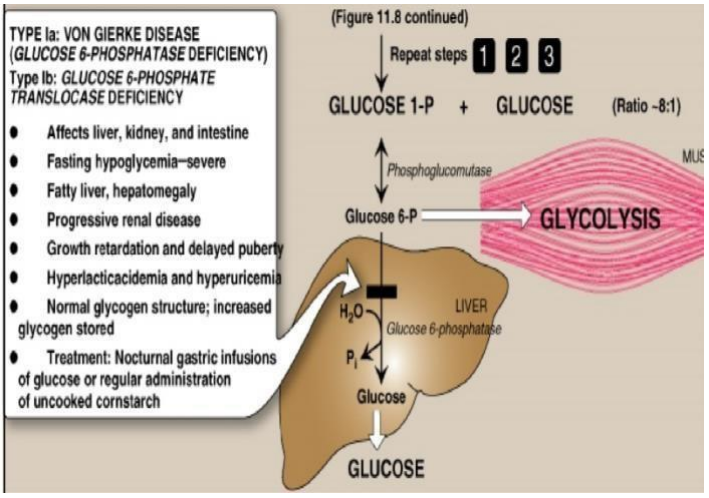


After 4 glucose molecules, we use glycogen synthase.

Glycogen storage diseases:

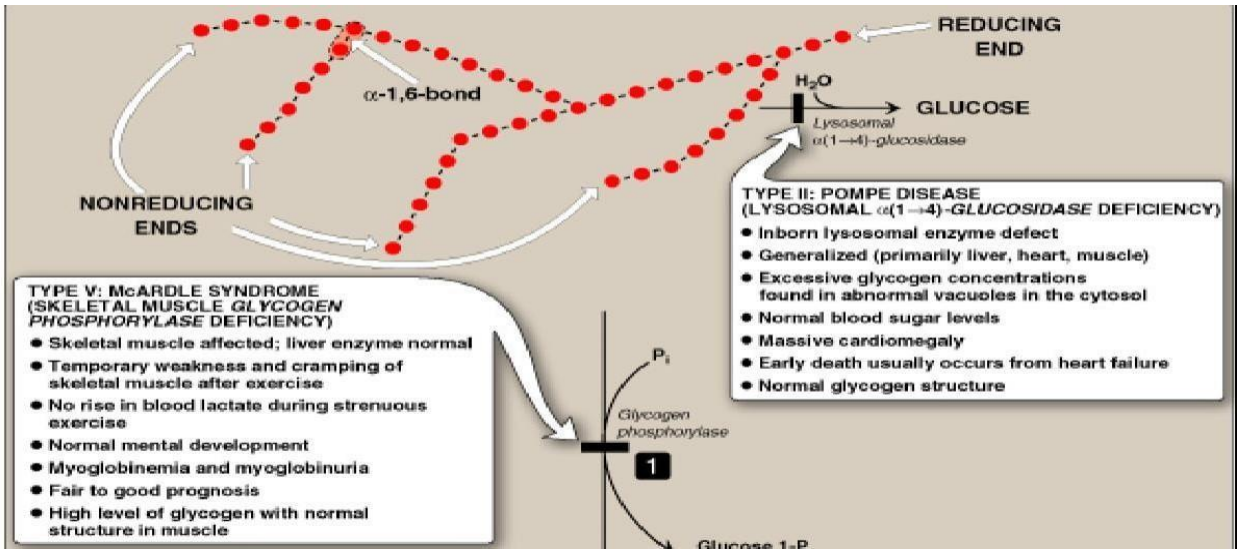
- Genetic diseases are usually caused by a mutation in a gene which results in the generation of inactive proteins. Some of these diseases are inherited.
- Defect in an enzyme required for synthesis or degradation.
- Accumulation of excessive amount of glycogen in one or more tissue.
- Severity: FATAL in Infancy……. Mild disorder (patient can cope with disease).

1. **I (type 1) Glucose-6-phosphatase deficiency disease (Von Gierk's disease):**
   - Glucose-6-phosphatase is an enzyme required to produce glucose that can be exported outside the liver, and it is common in glycogen synthesis as well as glycogen degradation.
   - Affects the liver, kidney, and intestines.
   - Severe fasting hypoglycemia. (liver can't covert Glucose-6-phosphate to glucose to transport it to blood during fasting).
   - Hepatomegaly fatty liver. (fat synthesis in liver will be activated)
   - Normal glycogen structure when it is examined by microscope.
   - Progressive renal disease.
   - Growth retardation.



   - Muscles aren't affected by the disease because there is no Glucose-6-phosphatase in the muscles.
   - Treatment to avoid hypoglycemia: nocturnal gastric infusions of glucose or regular administration of uncooked cornstarch in order to provide glucose from the small intestines for longer time.

2. **V (type 5) muscle glycogen phosphorylase (McArdle syndrome):**
   - Only muscle is affected; normal in the liver.
   - Weakness and cramping of muscle after exercise.
   - no increase in [lactate] during exercise.
   - Normally, when we do exercises, lactic acid level in the blood will increase as a result of anaerobic glycolysis (there's no glycolysis because the muscle glycogen isn't degraded).

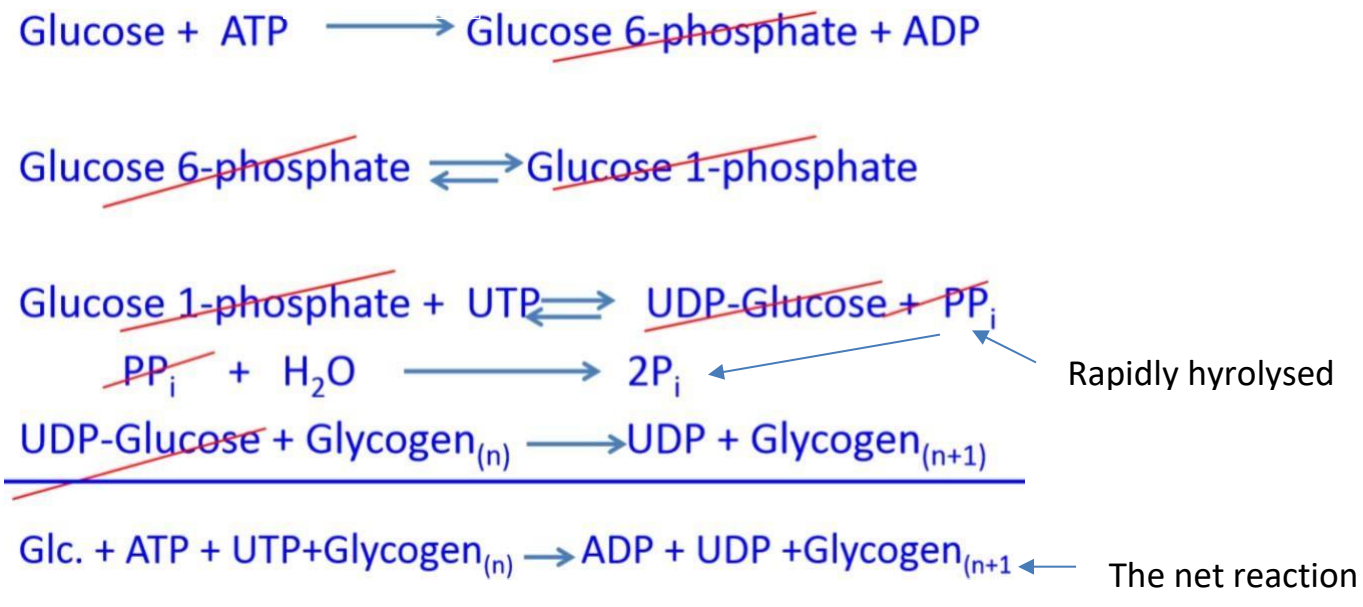


3. II (type 2) Lysosomes α (1→4) glucosidase (POMPE Disease):

- Lysosomes are organelles in the cell that degrade large molecules.
- Degradation of glycogen in the lysosomes.
- ≈ 3% of glycogen is degraded in the lysosomes.
- Affects liver, heart and muscle.
- Excessive glycogen in abnormal vacuoles in the lysosomes.
- Massive cardiomegaly (increased size of the cardiac muscle).
- Normal blood sugar, normal glycogen structure.
- Early death from heart failure.

Energy needed for glycogen synthesis:

Any intermediate used by one step and produced by another step will be canceled out.



So, how many ATP and UTP molecules are required for the addition of one glucose molecule to synthesize glycogen?

- 2; one from ATP, and the other from UTP (if we start with glucose).
- UDP can't be used, unless phosphate is transferred from ATP to UDP.

The net reaction in glycogen synthesis and degradation

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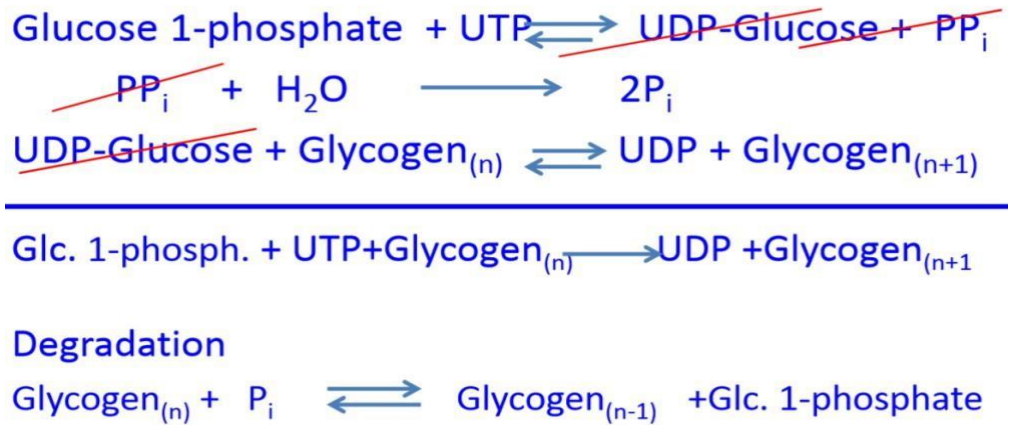

Here we start with glucose-1-phosphate, so we require only one high require energy bond.

Degradation

It is not logical to have synthesis and degradation occurring at the same time and in the same cell, because this achieves nothing, energy is wasted in the form of heat. So, these two processes should be regulated.

If you reach here, know that you are a hero.
Keep going and studying.
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