فريق طوفان الأقصى

METABOLISM

Modifide N.14

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Glycogen Metabolism

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Textbook

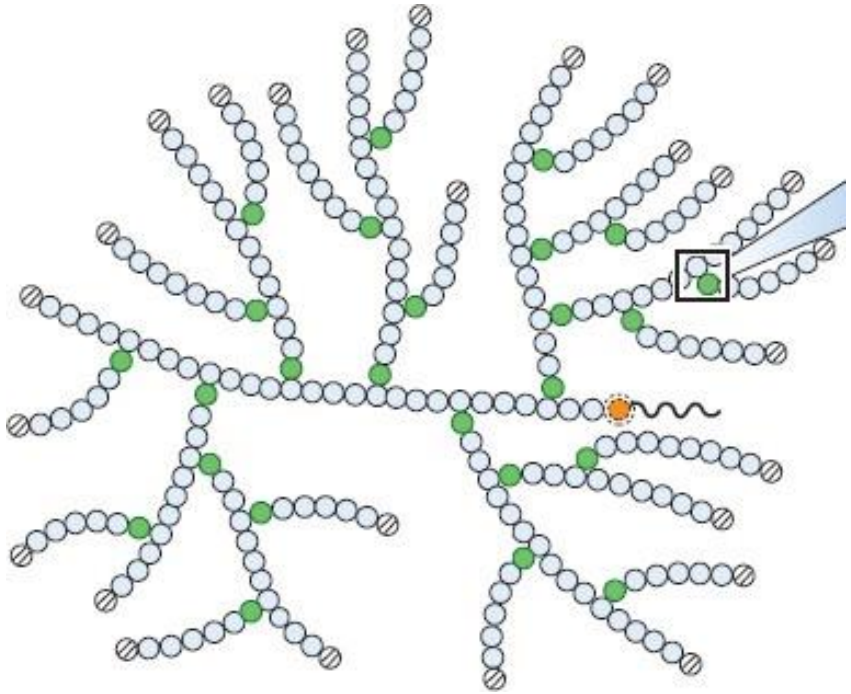
Lippincott’s Illustrated reviews: Biochemistry

Sources of Blood Glucose

- Diet
  - Starch, mono and disaccharides, glucose
  - Sporadic, depend on diet
- Gluconeogenesis
  - Sustained synthesis
  - Slow in responding to falling blood glucose level
- Glycogen
  - Storage form of glucose
  - Rapid response
  - Limited amount
  - Important energy source for exercising muscle

- **The complement in this slide:** About (Diet) as we all know when glucose reaches blood stream it will leads to secret insulin by liver which leads to increase GLUT 4 on cell surface , which leads to increase uptake of glucose by cells, part of the glucose will be phosphorylated (to be trapped it into the cell), part of the sugar will undergo glycolysis and other pathways, excess of glucose will be stored as glycogen once there is no supply of sugar from diet we will break it down into glucose in a quick response.

- **NOTE:** the amount of Glycogen is **very limited** , the 400 gram founds in the muscle is for its own use , so we still have 75 gram that will be released into the blood stream but remember that brain itself needs 120g/day….so that's why this amount doesn't last long



Glycogen Structure

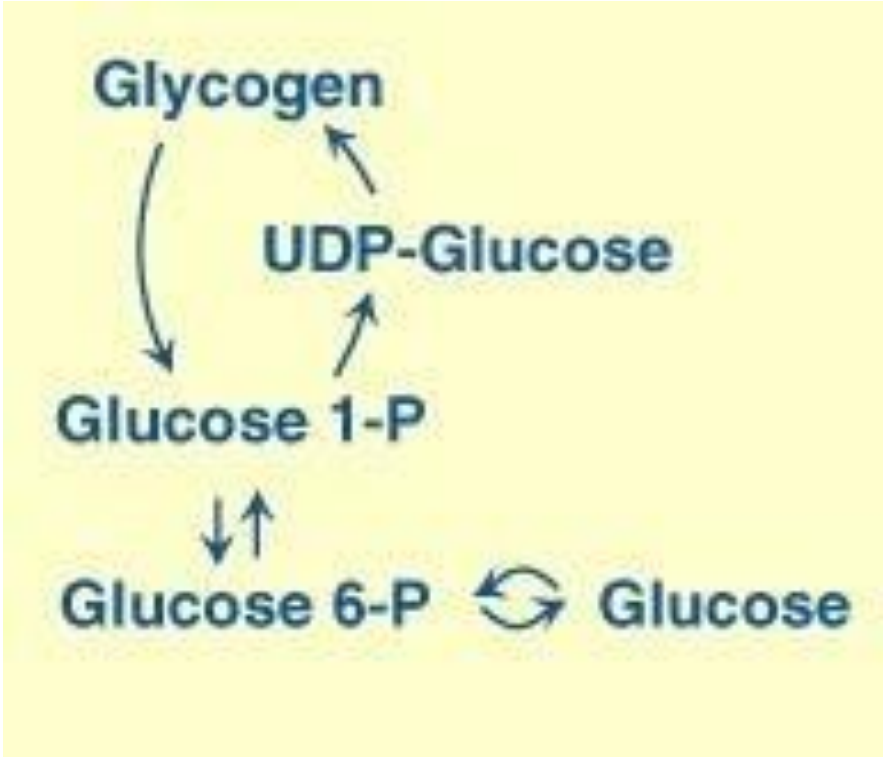
*Extensively branched homopolysaccharide

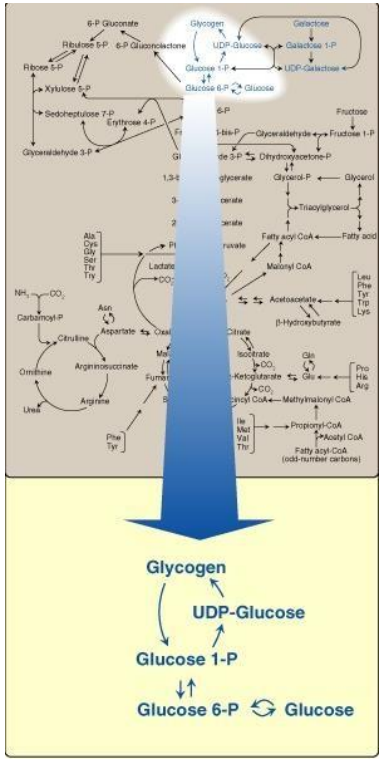
*One molecule consists of hundreds of thousands of glucose units

NOTE: **there are two types of bonds between glucose in glycogen, A (1,4) at main chain and A (1,6) at branches**

NOTE: It is highly branched , almost every 10 residues there is a branch

- **The complement in this slide :** The structure of glycogen ends with (non-reducing ends) , we would have enzymes at every these non-reducing ends that cut the bond and release the glucose residue from glycogen (that’s why it is a quick source of glucose) and that’s why it is highly branched.

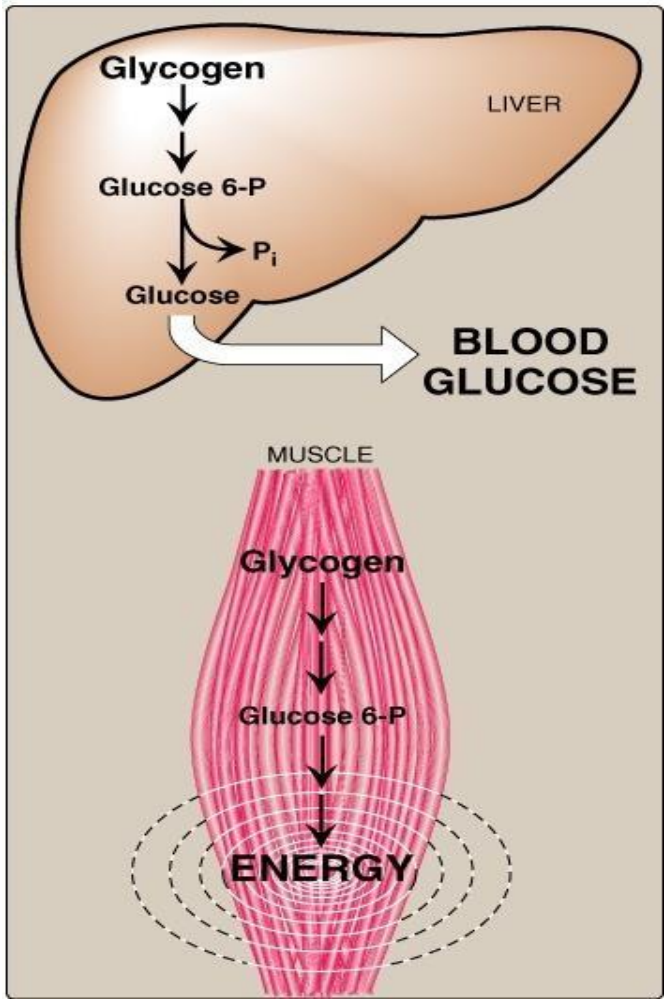


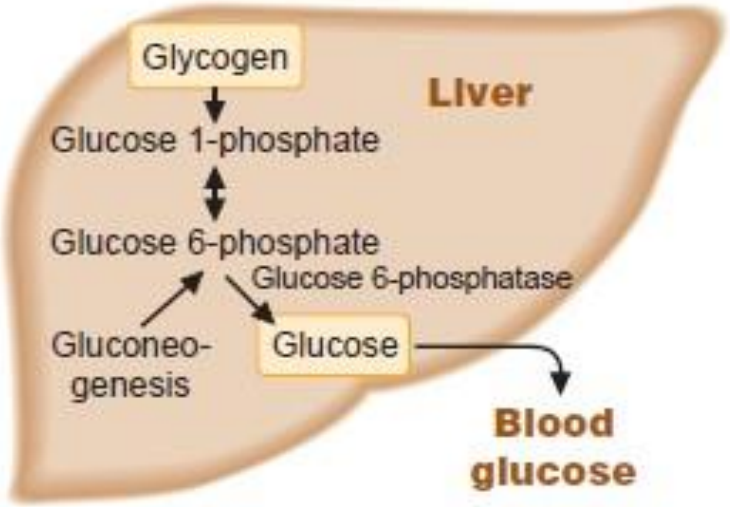


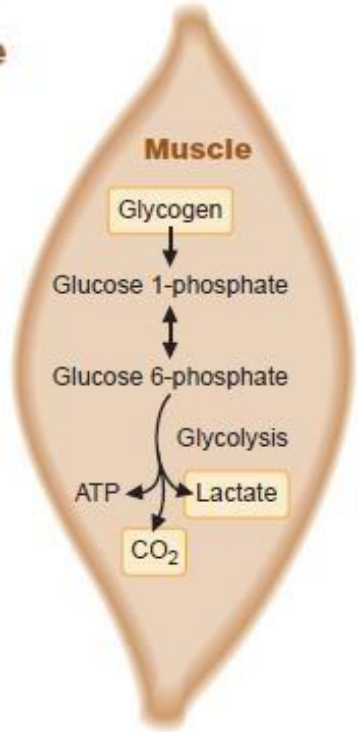
NOTE: In Glycogen synthesis, we need to load the glucose residue on a nucleotide (UDP) to be added (stored) to glycogen

Glycogen synthesis & degradation

Fates of Glucose that results from glycogen degradation







The complement in this slide: the mechanism of glycogen degradation to reach the blood stream (in the liver) , The glycogen breaks down into glucose1-p after that glucose1-p will be converted into glucose-6-p then converted to glucose , glucose will be released to blood stream to maintain its concentration in the blood and to supply the tissue that extensively depends on glucose as a source of energy

- **NOTE:** Liver (hepatocytes) will not use the released glucose (from liver's glycogen) as a source of energy , but liver is a very active organ it needs energy…. its gain energy from fatty acid oxidation

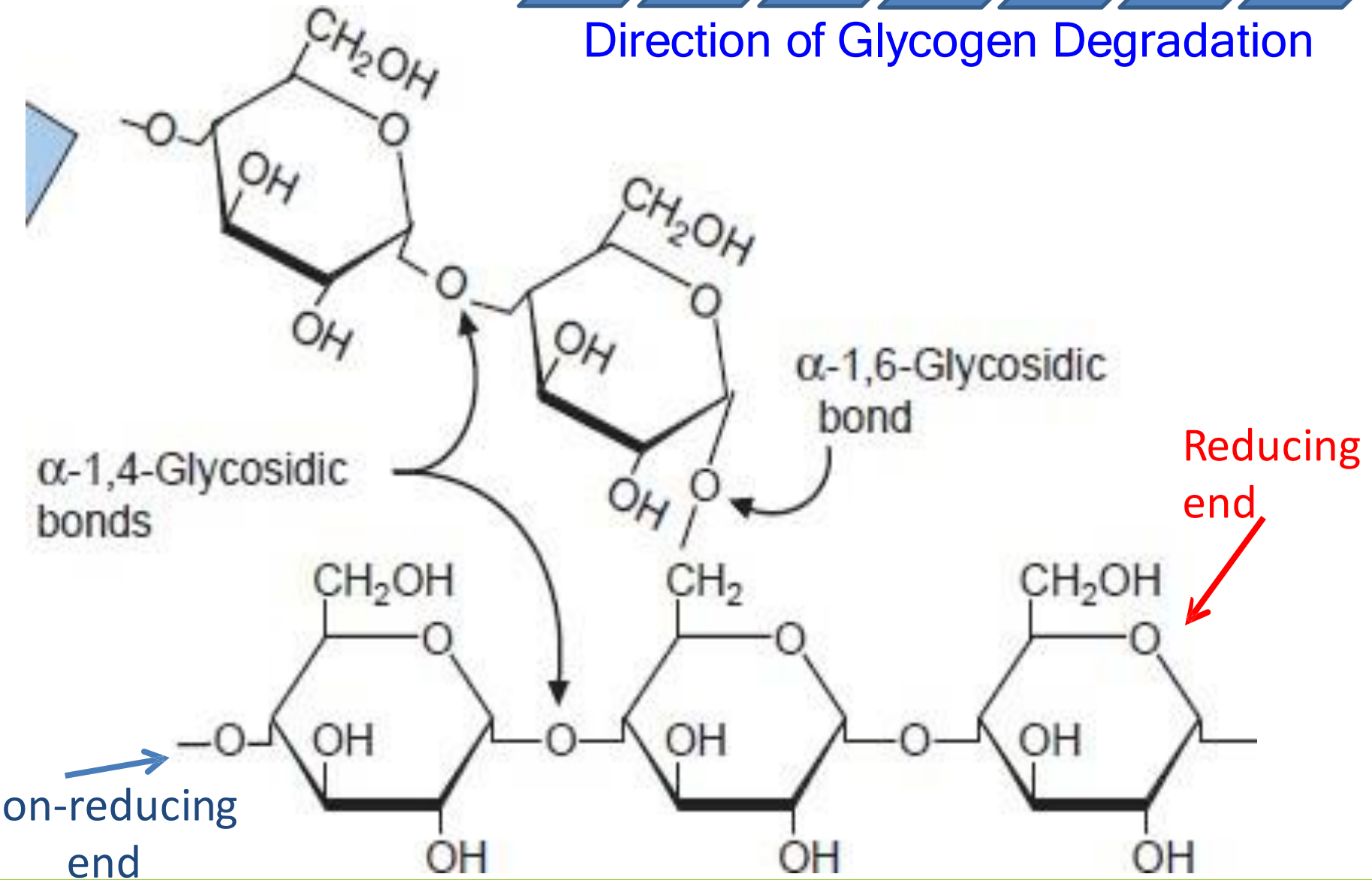
NOTE: The mechanism of glycogen degradation to produce energy (in muscles) :

The glycogen breaks down into glucose1-p after that glucose1-p is converted into glucose6-p and gets stuck but why?? because in the muscles there is no glucose-6-phosphatase enzyme, so glycolysis begins

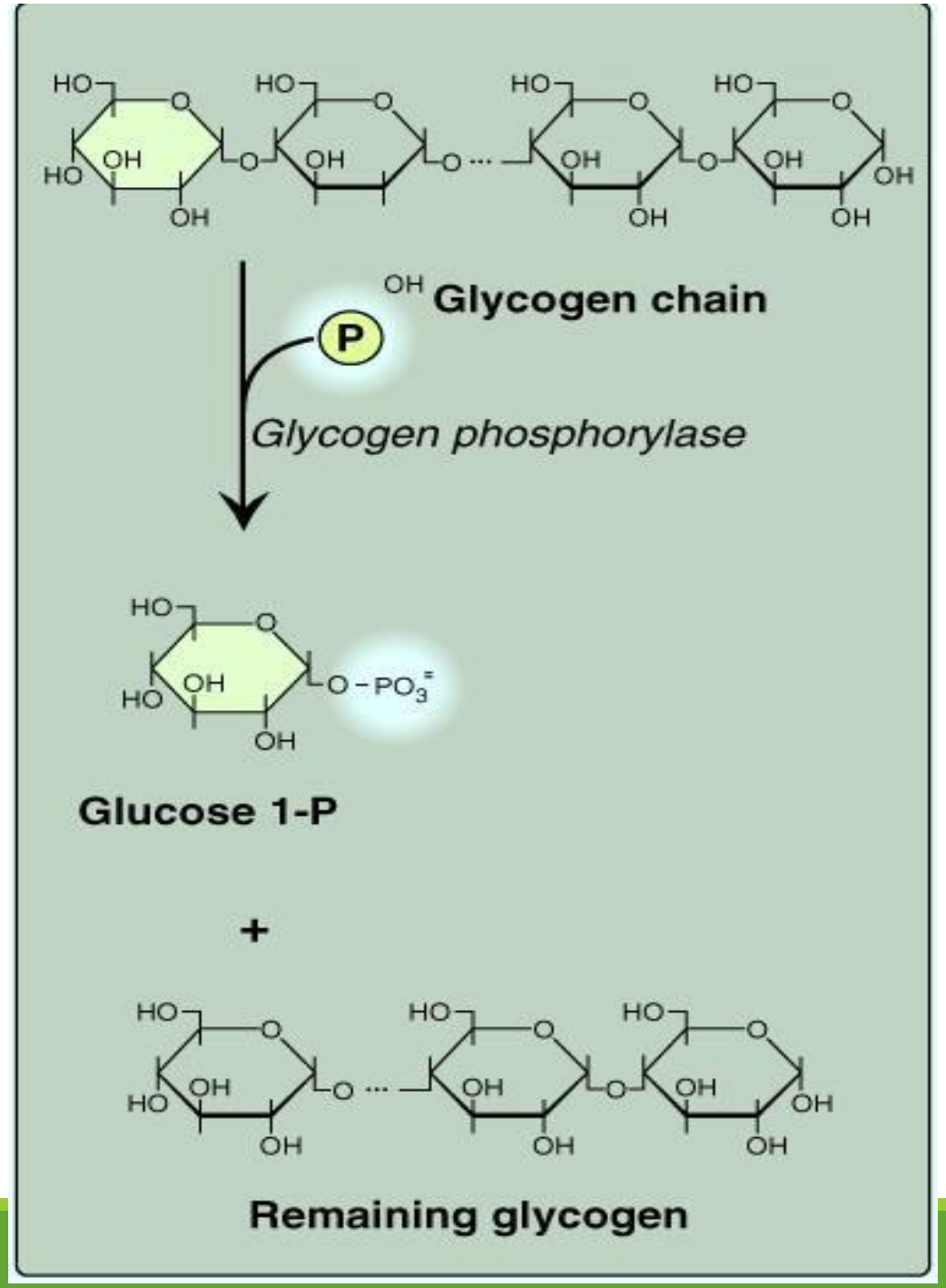
Glycogen Degradation

- Liver glycogen stores increase during the well-fed state and are depleted during fasting
- Muscle glycogen is not affected by short periods of fasting (a few days) and is only moderately decreased in prolonged fasting (weeks).

Direction of Glycogen Degradation



Degradation of glycogen (Glycogenolysis)

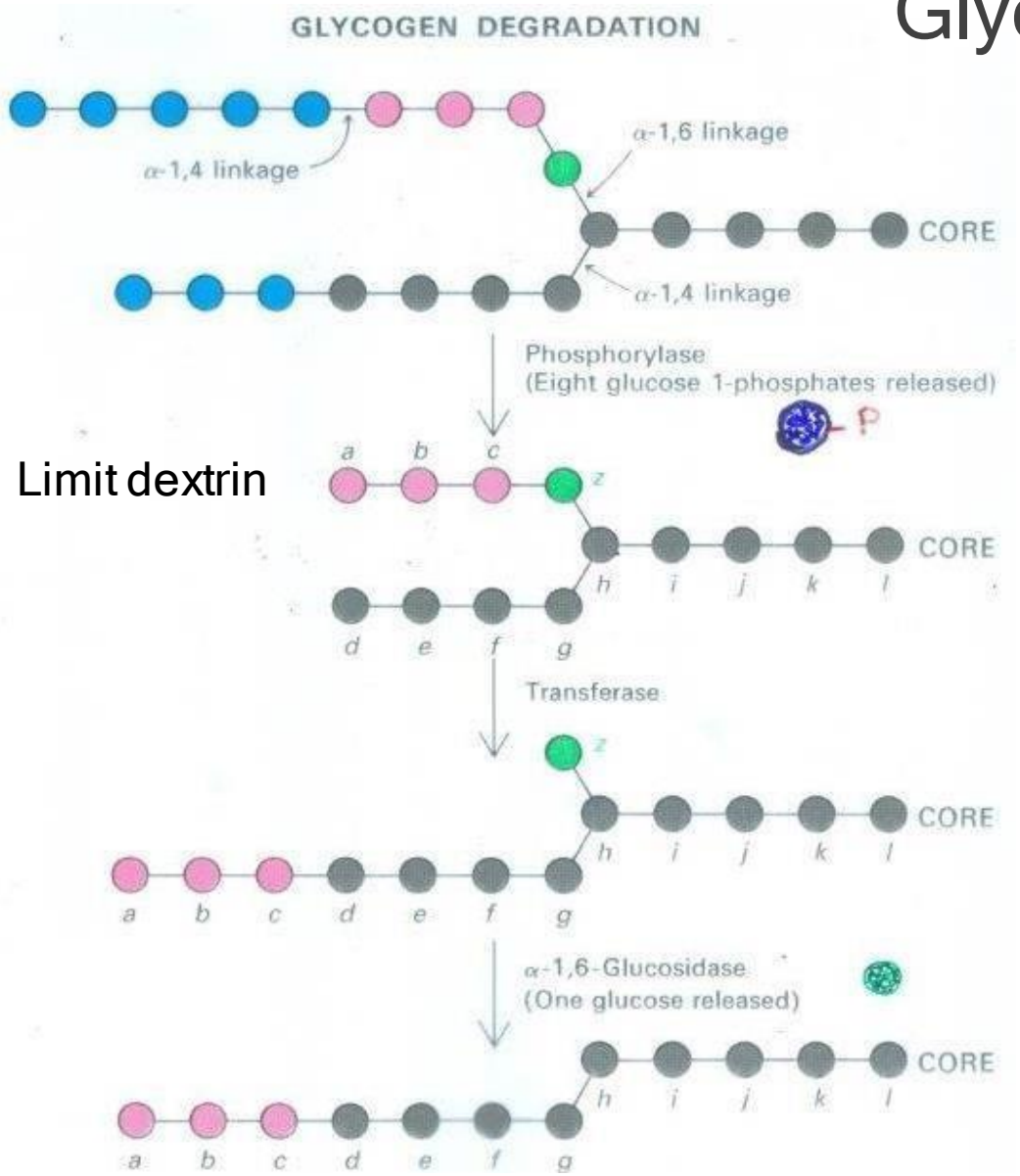


Degradation of glycogen
One glucose unit is removed at a time

Starts from the non-reducing ends

Released in the form of glucose 1-phosphate

Glycogen Degradation



NOTE: This is the main degradative pathway of glycogen

Debranching enzyme

G-1-P is converted in the cytosol to G-6-P by phosphoglucomutase

The complement in this slide: the enzyme that cuts the A (1,4) bond call glycogen phosphorylase it breaks down glycogen to glucose then add phosphate to it so it becomes glucose-1-p, when the phosphorylase enzyme becomes close about 4 glucose residues to A (1,6) bond at (branching point) it will stop (due to steric hindrance)and remain short chain of glucose this chain is called (limit dextrin) the remained 3 glucoses will transfer to another main chain by enzyme call (de-branching enzyme)
this enzyme also breaks down A (1,6)

NOTE: It is called a (limit) dextrin because it stops the activity of the enzyme (glycogen phosphorylase)

NOTE: In conclusion the de-branching enzyme have two functions (transferase, A (1,6) glycosidase)

Lysosomal degradation of glycogen

- A small amount (1-3%) of glycogen is degraded by the lysosomal enzyme, α(1–4)-glucosidase (acid maltase).
- The purpose of this pathway is unknown.
- A deficiency of this enzyme causes accumulation of glycogen in vacuoles in the lysosomes (Type II: Pompe disease)

NOTE: The minor degradative pathway of glycogen , important in muscles, heart and liver

Glycogen Synthesis

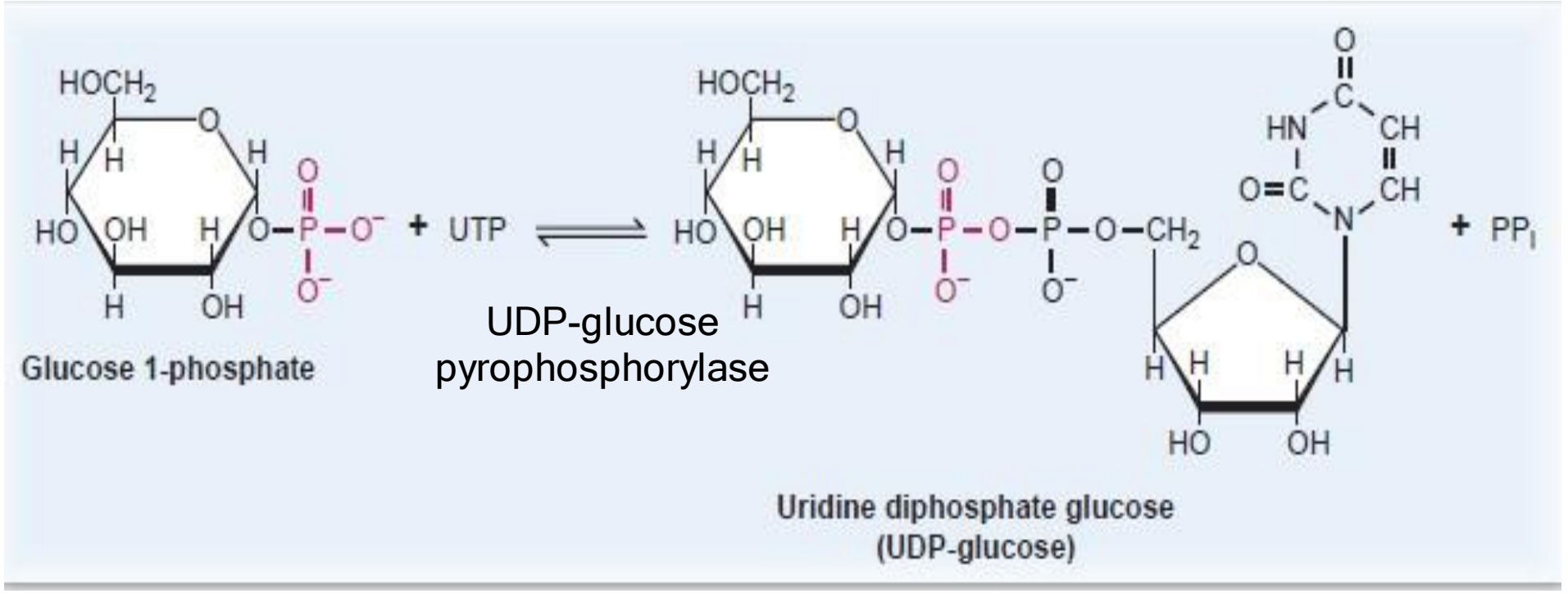
Glycogen is synthesized by adding glucose one by one
UDP-Glucose is the active donor of glucose units

Glycogenesis

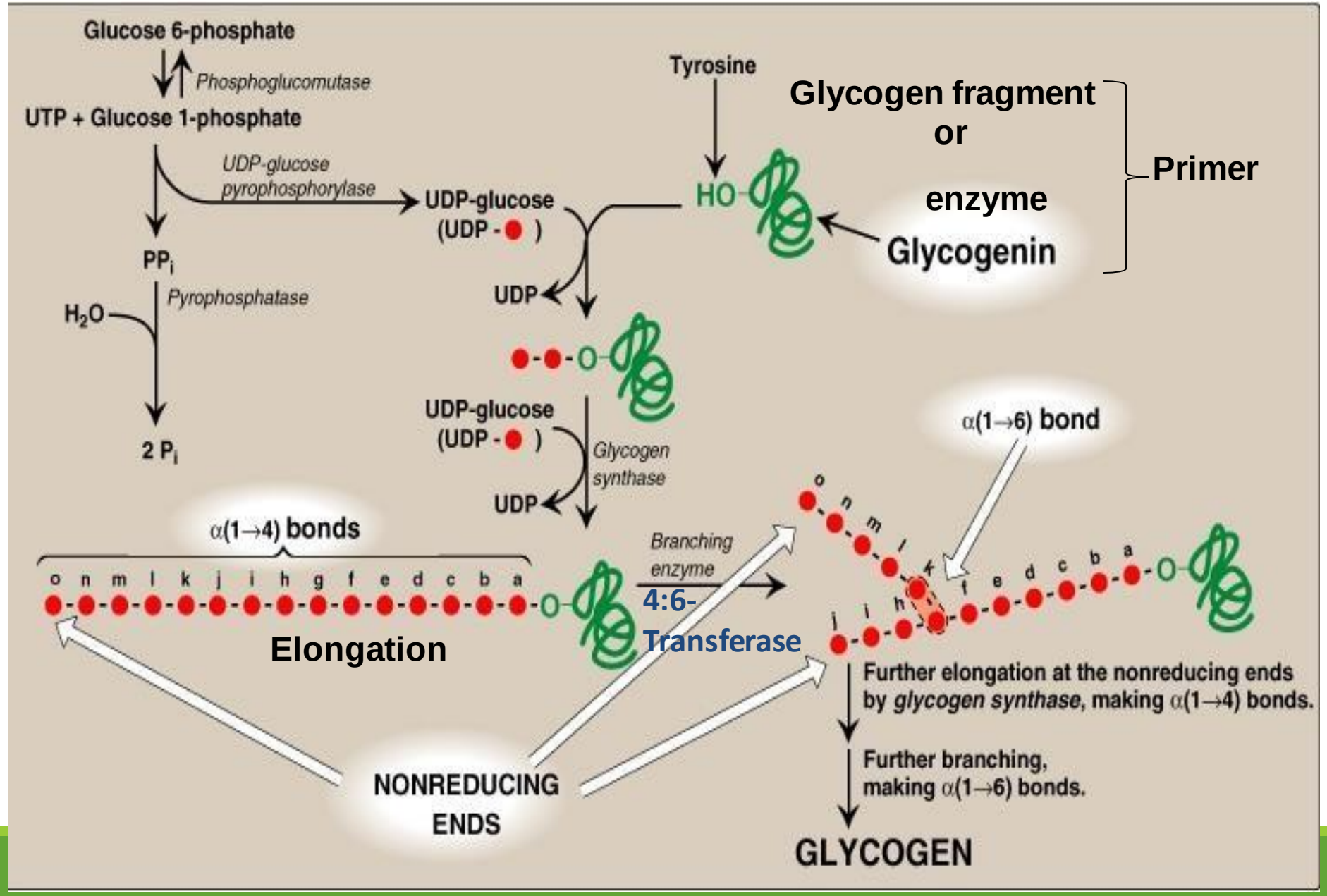
NOTE: now we are in the well fed state

Phosphate Ribose Uracil

Formation of UDP-Glucose



Glycogen Synthesis



The complement in this slide: Again, in well fed state , we will have a large amount of glucose that entered the cell and get phosphorylated into glucose6-p and convert into glucose1-p by (phosphoglucomutase) and then glucose1-p combines with UTP to produce UDP-glucose by (UDP-glucose pyrophosphorylase) then it combines with residue of glycogen fragment (by a primer) it could be either a glycogen fragment or enzyme called (glycogenin) this enzyme contain terminal tyrosine to react with glucose by hydroxyl group after this UDP will be released by first carbon
Then another UDP-glucose binds by (glycogen synthase) and UDP is released, and this process is repeated to consist long chain but not branched (elongation)

- **The complement in this slide:** Now how do branches form? by enzyme called (branching enzyme or 4:6-transferase) this enzyme will cut down part of this long chain then add this part to the main chain and now we have two non-reducing ends and the process is repeated to form glycogen as we see in The previous picture

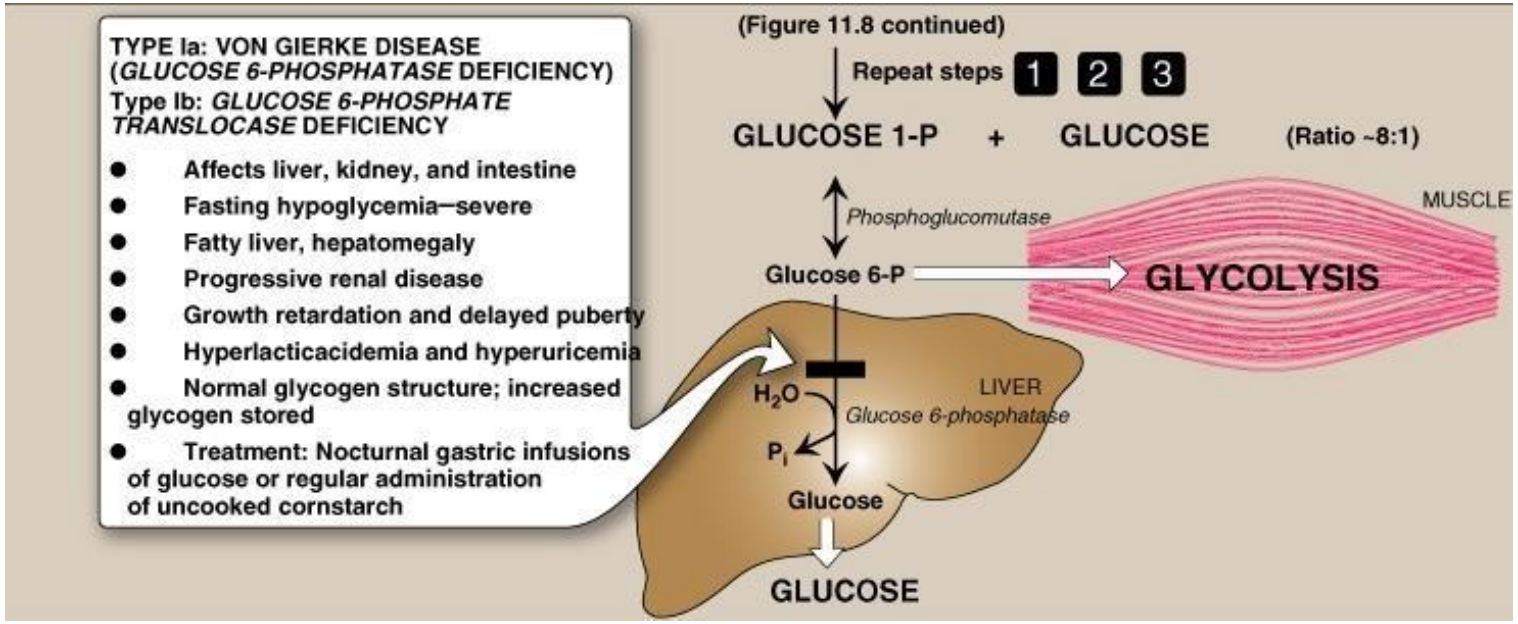
Glycogen Storage Diseases

- Genetic diseases
- Defect in an enzyme required for synthesis or degradation ➔
- Accumulation of excessive amount of abnormal glycogen (synthesis) or normal glycogen (degradation)
- In one or more tissue
- Severity: FATAL in Infancy……. Mild disorder

NOTE: **If we have problem in enzymes involved in synthesis of glycogen it leads to synthesis abnormal glycogen (abnormal structure)but when we have problem in enzymes that involved in degradation it leads to accumulation of glycogen**

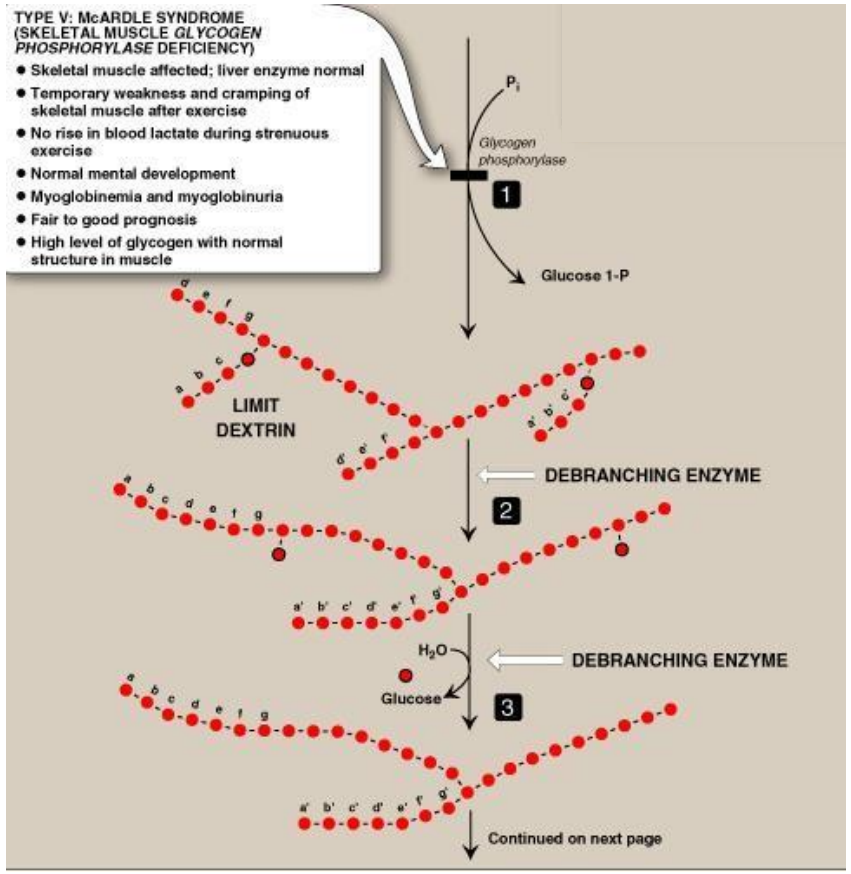
Glycogen Storage Diseases

- I Glucose-6-phosphatase (von Gierke disease)



- Liver, kidney and intestine.
- Severe fasting hypoglycemia
- Hepatomegaly fatty liver.
- Normal glycogen structure.
- Progressive renal disease.
- Growth retardation.

NOTE: Hepatomegaly (enlarge the size of the liver)…liver enlarges itself trying to compensate for the loss of function but without actually correcting it



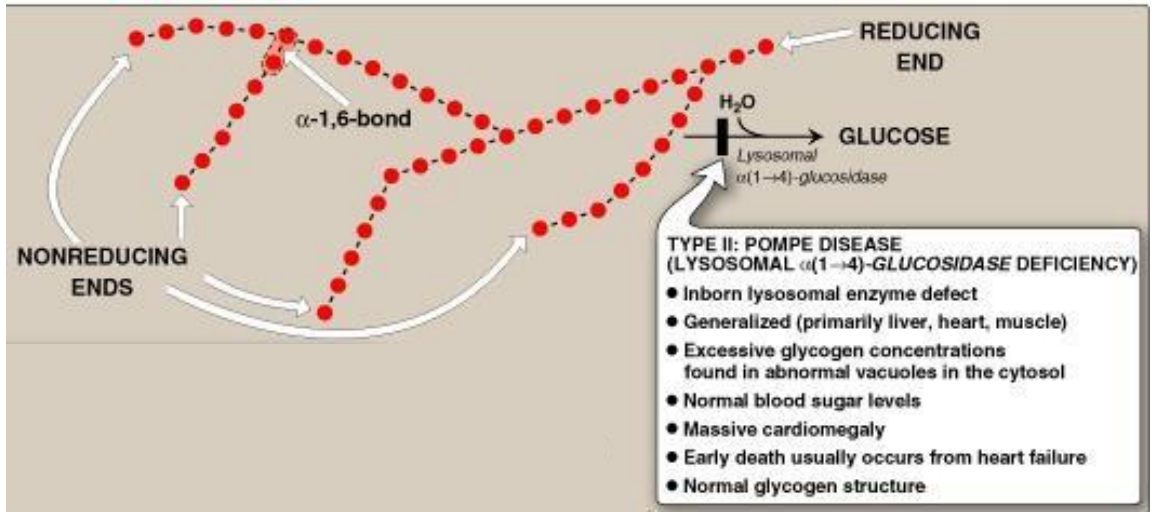
Glycogen Storage Diseases

- V Muscle glycogen phosphorylase (McArdle syndrome)
- Skeletal muscle glycogen phosphorylase deficiency
  - Only muscle is affected;
  - Weakness and cramping of muscle after exercise
  - no increase in [lactate] during exercise

NOTE: Only the glycogen phosphorylase (in the muscle) isn't functioning , It is normal in the liver

NOTE: lactate level does not affected

Glycogen Storage Diseases

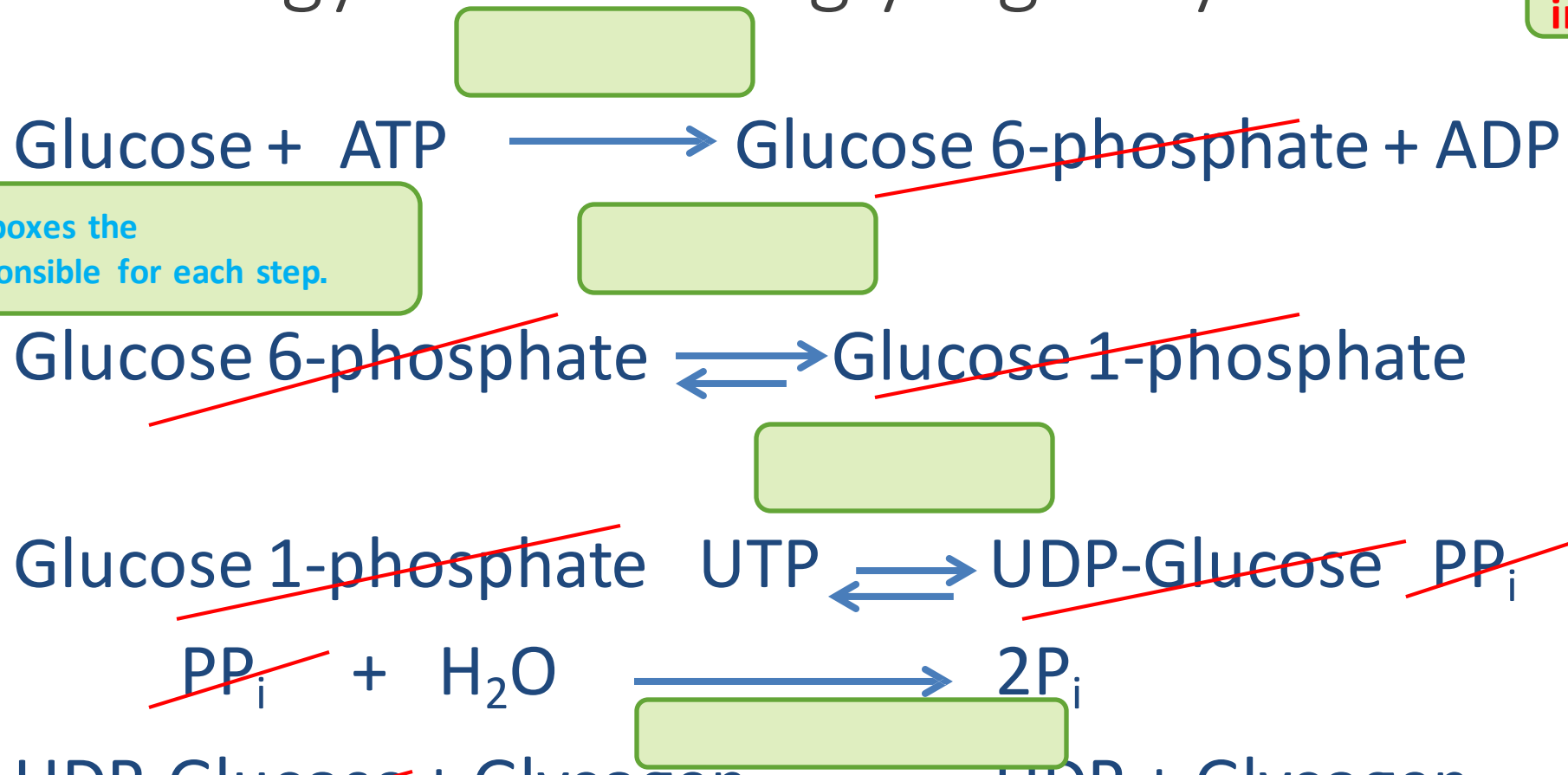


- II Lysosomes α (1→4) glucosidase → POMPE Disease
- Degradation of glycogen in the lysosomes
- ≈ 3% of glycogen is degraded in the lysosomes
- Affects liver, heart and muscle
- Excessive glycogen in abnormal vacuoles in the lysosomes
- Massive cardiomegaly
- Normal blood sugar, normal glycogen structure
- Early death from heart failure.

Energy needed for glycogen synthesis

Read the picture important!!

Write in the boxes the enzyme responsible for each step.



$$\text{Glc.} + \text{ATP} + \text{UTP} + \text{Glycogen}_{(n)} \rightarrow \text{ADP} + \text{UDP} + 2\text{Pi} + \text{Glycogen}_{(n+1}$$

- **Note:** Approximately 2 ATP molecules are consumed for every glucose molecule added to glycogen.

The net reaction in glycogen synthesis and degradation

NOTE: here we assumed that we have G6P from glycolysis so after the isomerization:

Glucose 1-phosphate + UTP $\rightleftharpoons$ UDP-Glucose + PP_i

$PP_i + H_2O \longrightarrow 2P_i$

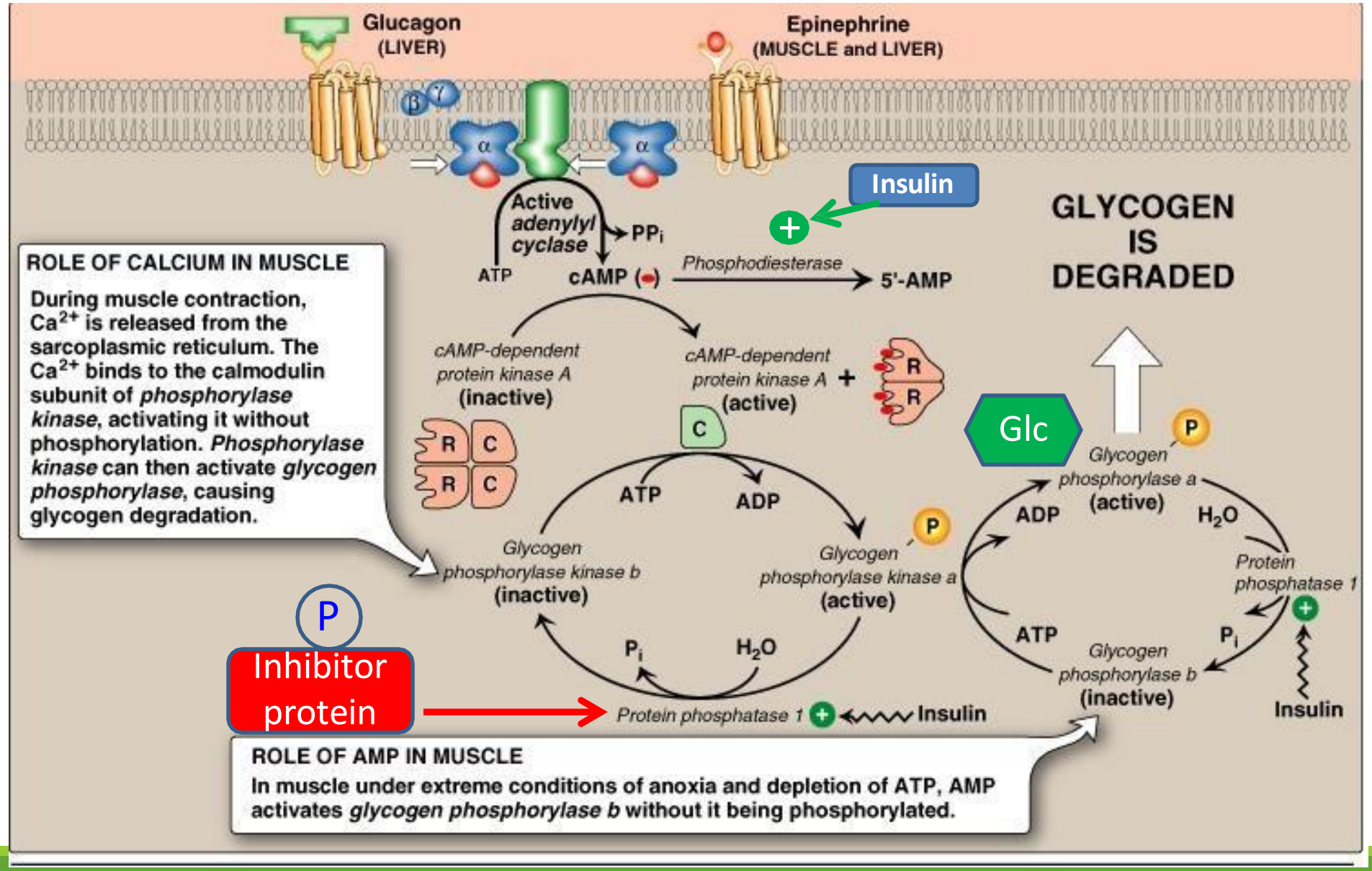
UDP-Glucose + $Glycogen_{(n)}$ $\rightleftharpoons$ UDP + $Glycogen_{(n+1)}$

Glc. 1-phosph. + UTP+$Glycogen_{(n)}$ $\longrightarrow$ UDP + 2Pi +$Glycogen_{(n+1}$

Degradation

$Glycogen_{(n)}$ + P_i $\rightleftharpoons$ $Glycogen_{(n-1)}$ +Glc. 1-phosphate

Glycogen Metabolism Regulation

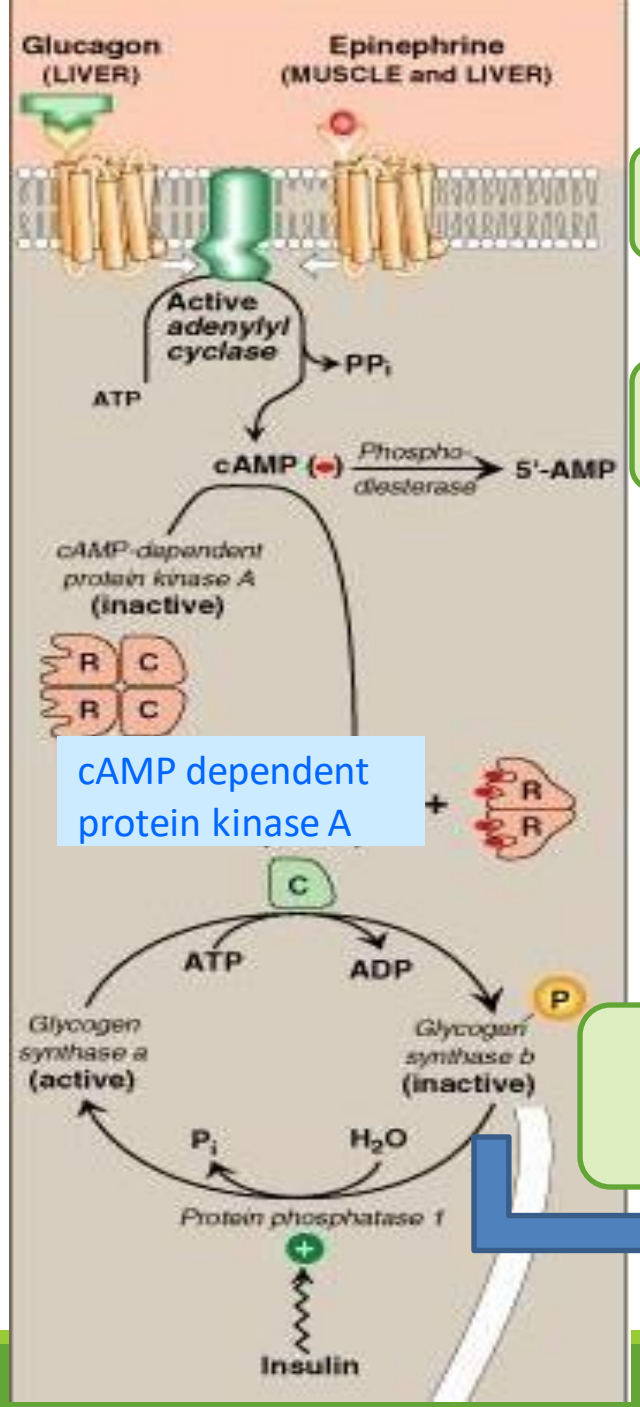


- **The complement in this slide:** When we say glycogen synthesis (feeding state) we expect to see active hormones such as insulin , in degradation(fasting state) we expect to see glucagon and epinephrine(Emergency situation--->we have sympathetic system activated)

We are talking now about regulation of glycogen degradation:

- Now in fasting condition(Degradation of glycogen) : Glucagon concentration is high.
- So we have epinephrine and glucagon and both can bind to same surface of the GPCR (g protein coupled receptors), but each one of them has specific receptor to distinguish between them.
- When they bind of the GPCR then the receptor get activated , g-proteins get activated by exchanging GDP by GTP at the alpha subunit , then the alpha subunit become active and dissociate out of the complex(separate form beta & gamma subunit) , beta & gamma subunit stay attached to membrane and alpha subunit go on a several pathways.
- One of these pathways is the activation of adenylyl cyclase to produce cAMP then cAMP attach to the regulatory subunits of the protein kinase A
- Protein kinase A targets : 1- bifunctional enzyme 2- pyruvate kinase
  3- glycogen phosphorylase kinase 4- glycogen synthase .

- **The complement in this slide:** glycogen phosphorylase kinase (which is regulatory enzyme for glycogen phosphorylase) will phosphorylate **glycogen phosphorylase-b (inactive form)** to **glycogen phosphorylase-a (active form)**
- When **glycogen phosphorylase** become active it starts/activates glycogen degradation.
- (in this process the phosphorylation process is an activation process , pyruvate kinase phosphorylation process is inhibitory)



Regulation of Glycogen Synthesis

- **NOTE:** look at the picture, then proceed to the next slide, and then return to this slide

Phosphorylation at several sites

- **NOTE: phosphorylation of glycogen synthase inactivates it**

Inhibition is proportional to the degree of phosphorylation

- **NOTE:** important thing to know about phosphorylation process is : I might have more than one site for phosphorylation regardless if it happens by the same enzyme or by multiple enzymes, and the more phosphorylation that occurs the more effect on the activity of the enzyme.

يعني لو عنا انزيم (فسفرته بتعمل تنشيط اله) ممكن افسفره في ثلاث مواقع ومرة فسفرته في موقعين ومرة في ثلاث, المرة الي فسفرته فيها في ثلاث مواقع هيكون اكثر فاعلية

GLYCOGEN SYNTHESIS IS INHIBITED

- We are talking now about regulation of glycogen synthesis:
- In well fed state(synthesis of glycogen): insulin concentration is high.
- We have insulin which bind on the receptor type C kinase
- Insulin affect so many proteins **indirectly**:

1- activation of **phosphodiesterase** enzyme : which degrades **cAMP to 5'-AMP** so the second messenger which activates the protein kinase A will be inhibited so there is no activation of glycogen degradation.

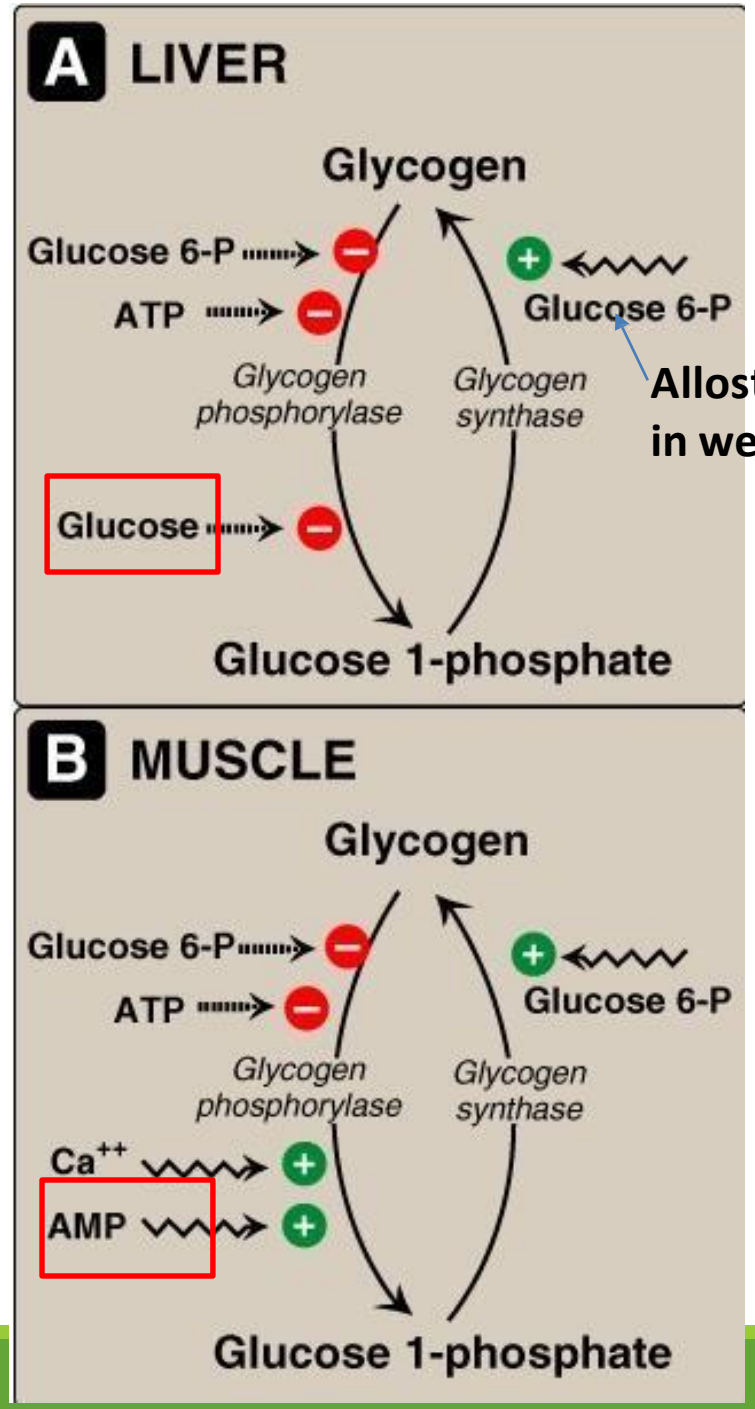
2- Activation of **protein phosphatase** results in the **dephosphorylation** of **glycogen phosphorylase kinase** and **glycogen phosphorylase**, making them **inactive**. This leads to the inhibition of glycogen degradation.

3- the 4th target of Protein kinase A **glycogen synthase** (the enzyme responsible for the synthesis of glycogen) : **dephosphorylation of this enzyme will activate it.**

(back to the previous slide now to understand)

(don't forget to read the picture it's important !!!!!)

Allosteric Regulation of Glycogen Metabolism



Allosteric activator in well-fed state

Rapid response to cell's needs Available substrate and ATP➔

synthesis

↓↓Glucose and ↓ATP ➔

Glycogenolysis

- **The complement in this slide:** Allosteric regulators bind to the enzymes Directly and change their activity.
- We are going to talk about glycogen metabolism (degradation and synthesis) in muscle and liver).

- **In the Liver:**
- When we talk about Liver in the degradation of Glycogen to glucose 1- phosphate this process can be inhibited by glucose 6-p because we use **glucose 6-p** to produce energy then we have large amount of glucose 6-p we don't need to degrade glycogen, so **G6P** work as inhibitor for degradation of glycogen and as an activator for glycogen synthase.
- **Glucose** work as inhibitor (of glycogen degradation) in the liver because it is the final product of glycogen degradation (feedback inhibition).
- ATP works as universal inhibitor(it means that ATP ,regardless of its source ,indicates a high state of energy, so it's going to inhibit any degradative/catabolic pathway)

- **In the Muscle:**
- **G6P** work as inhibitor for degradation of glycogen and as an activator for glycogen synthase.
- ATP functions as an inhibitor for the same reasons we mentioned earlier.

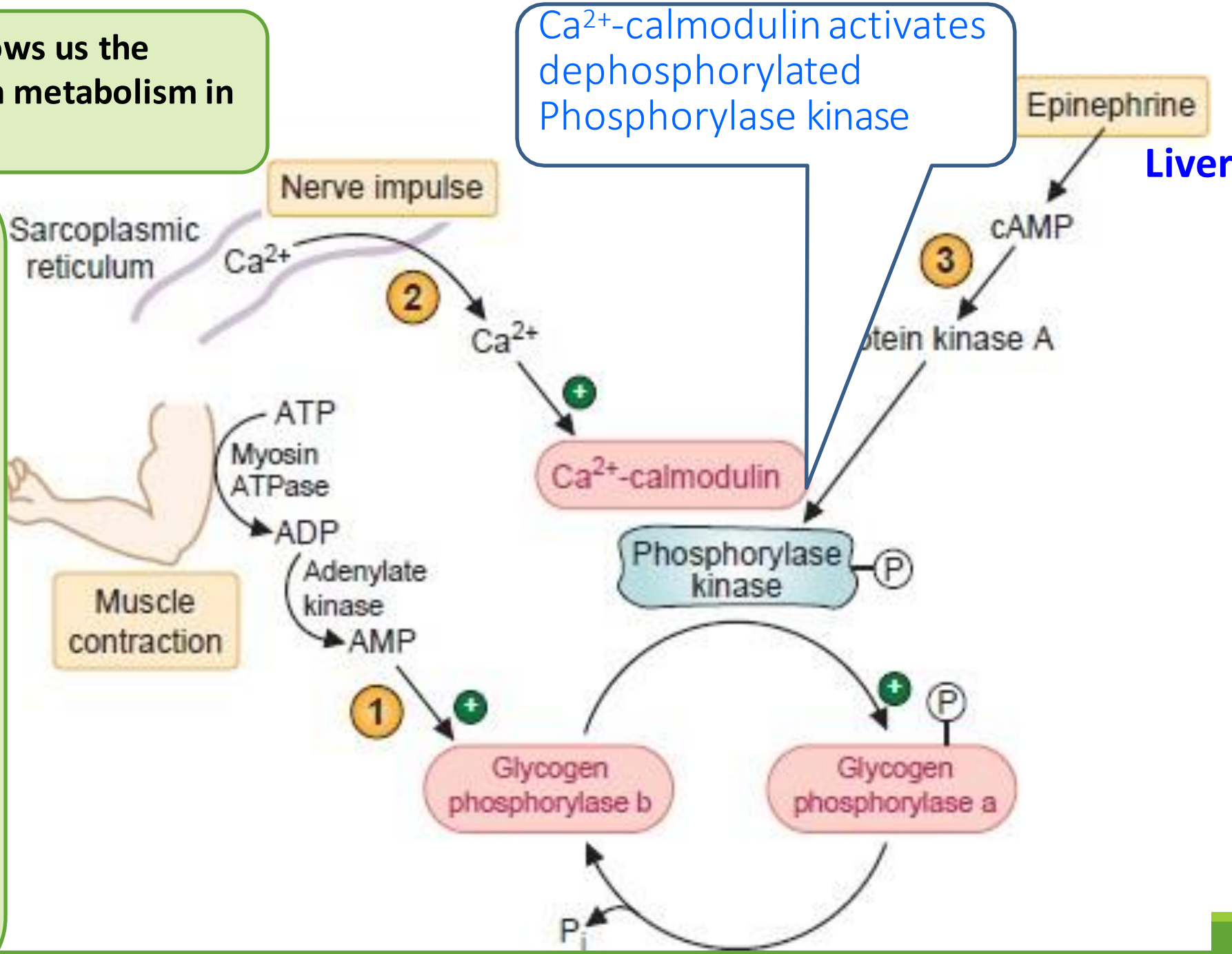
- **Ca+2**: during muscles contraction Ca+2 is released from sarcoplasmic reticulum then Ca+2 increased in the cytosol then this means the cell is highly active and need energy, so we **degrade glycogen**.
- **AMP**: when we have large amounts of AMP then we have small amount of energy, so we need to degrade more amounts of glycogen, so it activates degradative of glycogen.

Why AMP found in muscle and not in liver?? Because the glucose that produced in liver it's not for degradation in liver it will go to blood stream that's why we have a glucose 6-phosphotase in liver and no in muscle then we have a lot of AMP in muscle that activate muscle.

- **NOTE: this picture shows us the regulation of glycogen metabolism in the muscle.**

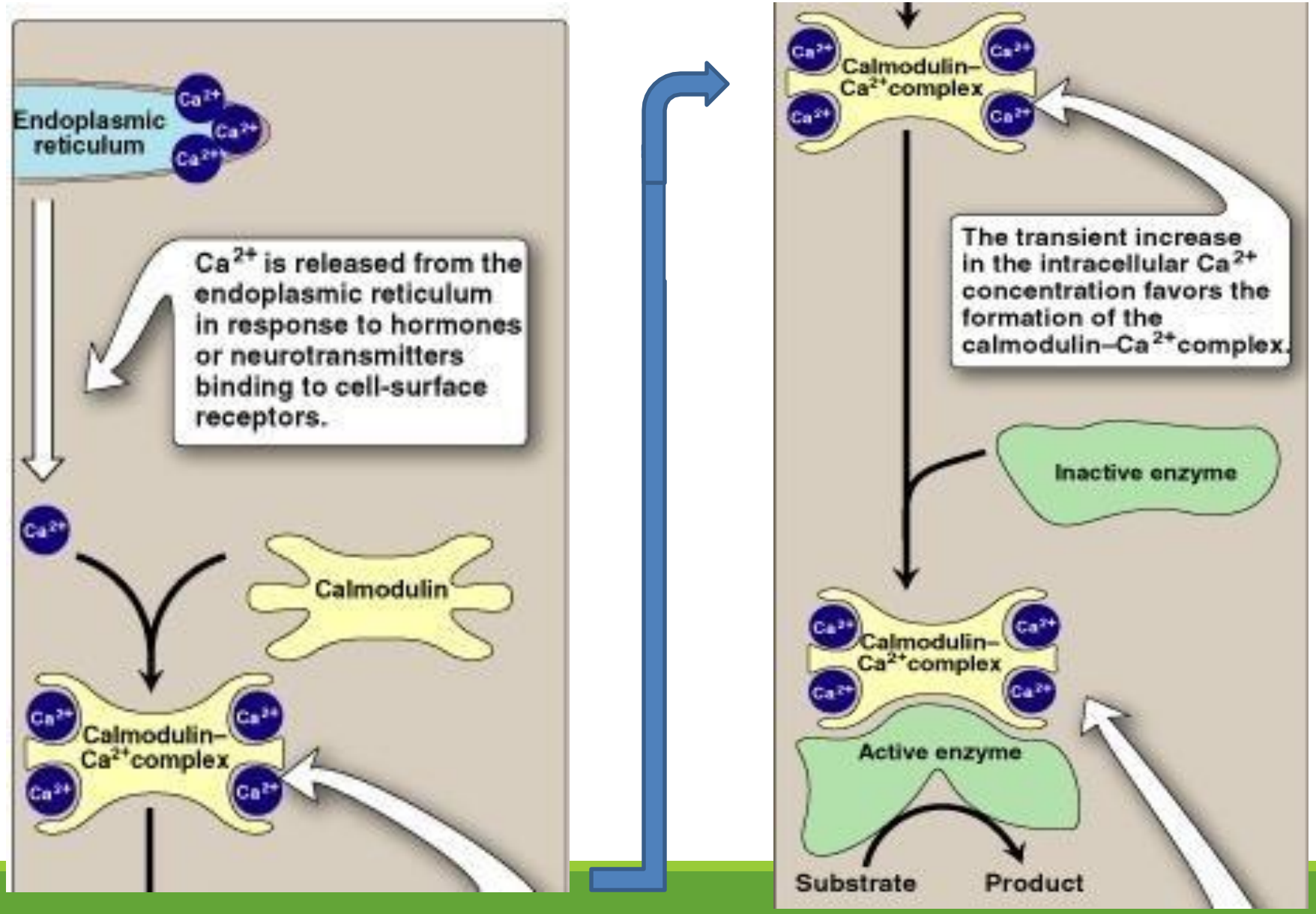
- **Muscle's contraction need ATP so it will hydrolyse to ADP, increase in concentration of ADP will activate Enzyme called Adenylate kinase]AMP] increase**

And as we see before it is allosteric regulator of glycogen phosphorylase and it is activates more degredation of glycogen in the muscle.

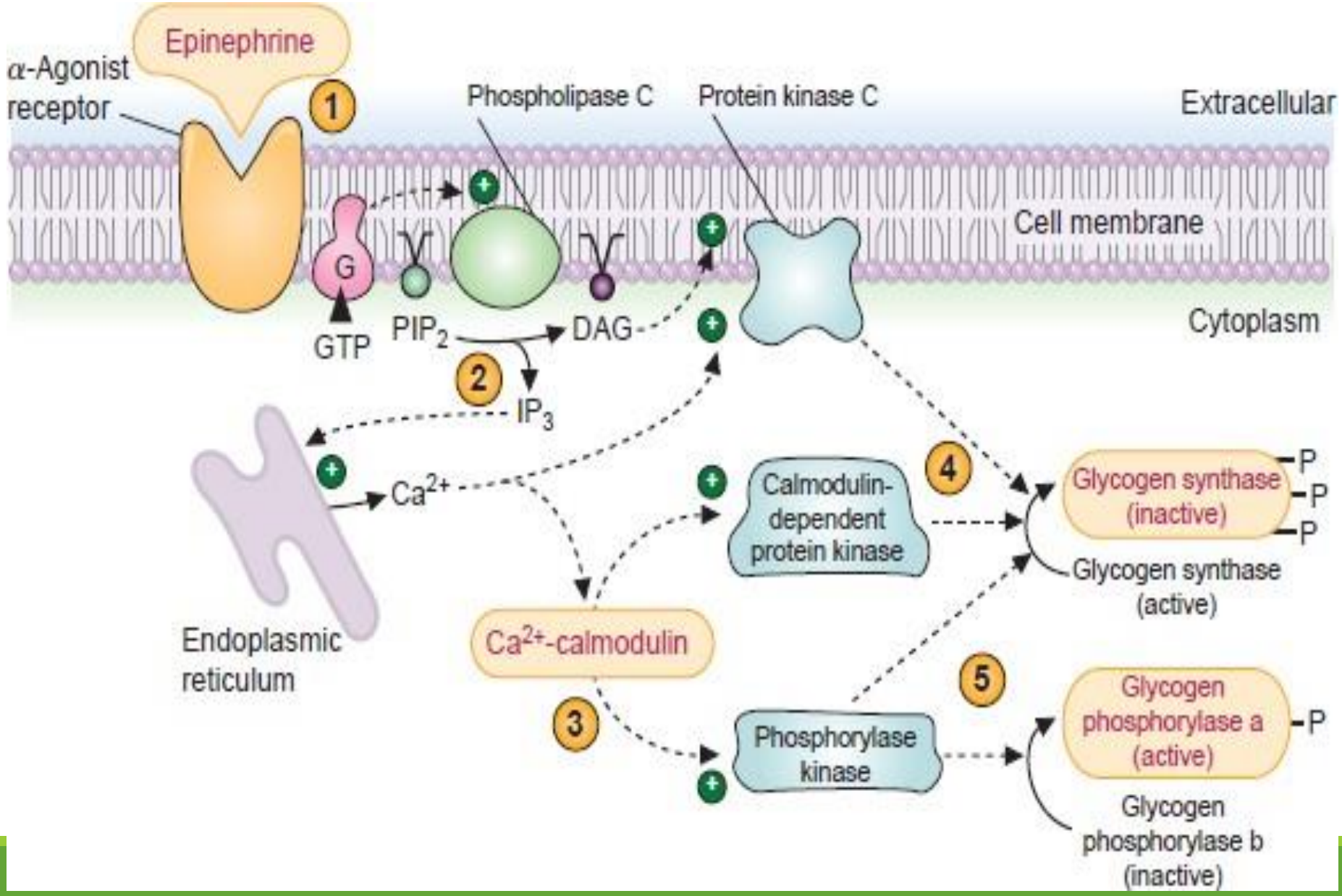


- **The complement in this slide:** When the nerve impulses reach the muscles , then the muscle contract and calcium is going to released out the sarcoplasmic reticulum (as we said before) , calcium is an allosteric regulator which bind to the glycogen phosphorylase and activate it , another pathway that calcium bind to another protein called calmodulin (cal means bind to calcium)
- Once the calcium ions are released they bind to calmodulin changing its conformation to the active state and it's bind to some inactive enzymes in the cell, and they turn them on.
- What happen here is Ca+2-calmodulin complex bind to glycogen phosphorylase kinase and this binding changes this regulatory protein into the active state.

Ca^{+2} -Calmodulin Complex Function



phosphorylase KinaseCalcium Activation of liver



- Under neath GPCR: 1- activates the formation of the cAMP second messenger

2- it may also activate the formation of another type of second messenger like IP3.

- we have another pathway which start when alpha subunit activates enzyme called phospholipase C , this enzyme involved in the metabolism of phospholipids and degrades phosphatidylinositol bisphosphate (PIP2) to diacylglycerol (DAG)(have hydrophobic part so it stays in the membrane) and IP3(goes out because it is hydrophilic) (look at the picture to understand)
- IP3 it's a second messenger and can leave into intracellular part and it bind with IP3 gated calcium channel of the sarcoplasmic reticulum --->opens them----> releases calcium make Ca+2-calmodulin complex as we said before.
- Also, this complex binds to calmodulin Dependent protein kinase activating it which will phosphorylate glycogen synthase inactivating it.
- By the effect of calcium ,protein kinase c can Phosphorylate glycogen synthase So inactive it.

- NOTE: Phosphorylation of glycogen synthase can be regulated by the following:

- 1glucagon or epinephrine
- 2protein kinase A
- 3calmodulin Dependent protein kinase
-4by the effect of calcuim protein kinase C get activated

تم بحمد الله تعالى

جرحاهم وتقبل شاف,اللهم كن مع اخوتنا في غزة

شهدائهم وانصر على عدوهم

اللهم عليك بمن خذل هذا الدين

اللهم احفظ أرواح المجاهدين في فلسطين، وردهم إلى أهلهم مردًا كريمًا آمنًا.

V2: slide 29

Targets instead of has 4 subunits