Glycogen Metabolism

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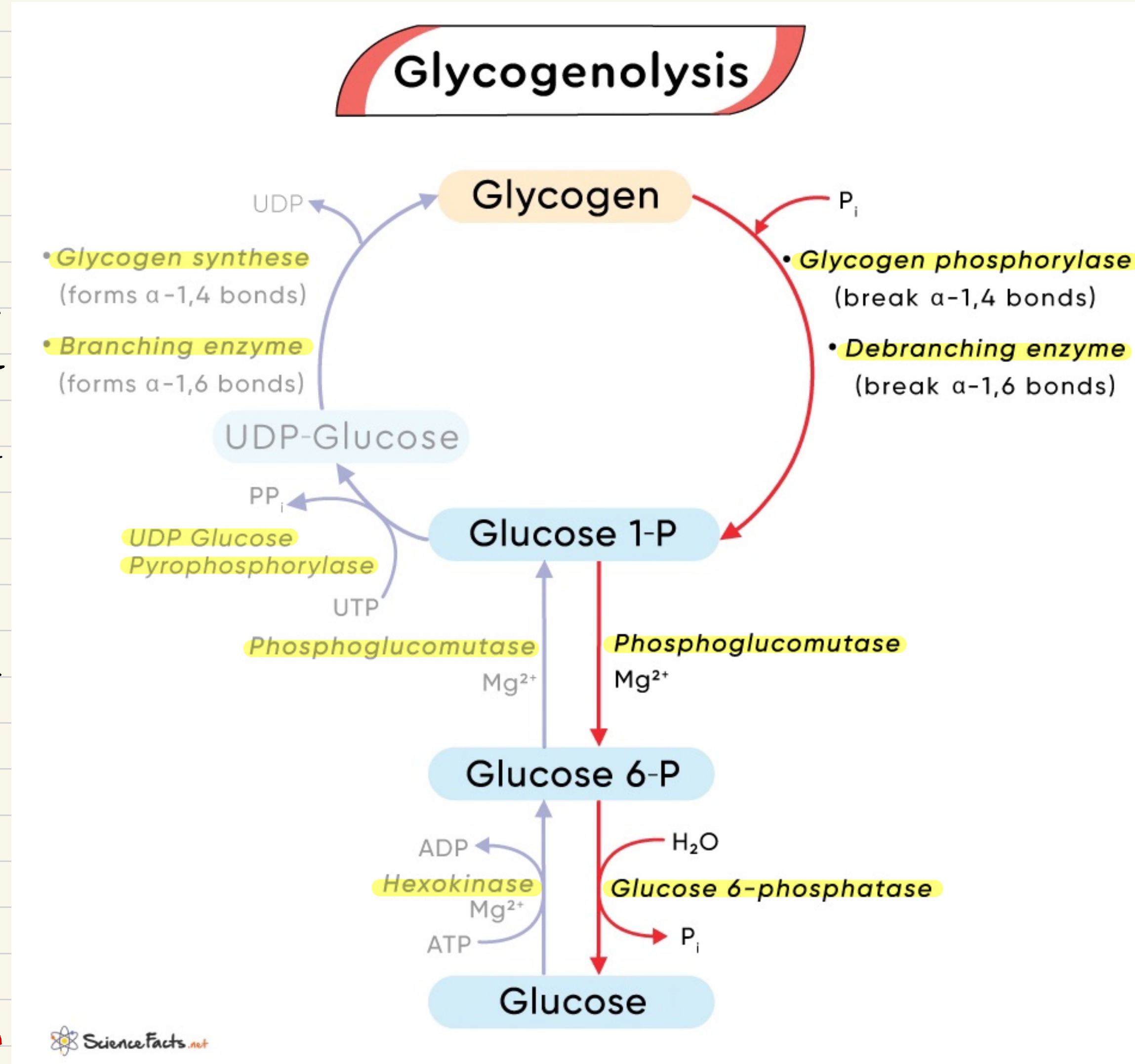
Textbook

Lippincott's Illustrated reviews: Biochemistry

المحاضرة في مودة

بما انا ذكرنا انه ال glycogen بيخزن بكميات
قليلة في liver لأسباب سبق وذكرناها
بينما كمياته اكبر في muscle ولكن
الي في muscle ل muscle لأنه بحتاجه
كمصدر طاقة to do exercise بينما الكبد
بكتفي بال fats الي عنده كمصدر طاقة
وبالتالي بحطيه ل brain and RBCs
- كمان نقطة لما ينزل مستوى glu بالجسم
تعلمنا المحاضرة الي فاتت كيف منوقف
نصنع glu من مصادر مش كارب، ونصنعه
لأنه كمية glycogen in liver is not enough
بنفس الوقت هاي العملية بدها وقت، لذلك
بنشغل حالنا بتكسير الـ glycogen ع بين ما نصنع



https://youtu.be/369E4m7GW7s?si=9fI1DnAdV4vdFoYP
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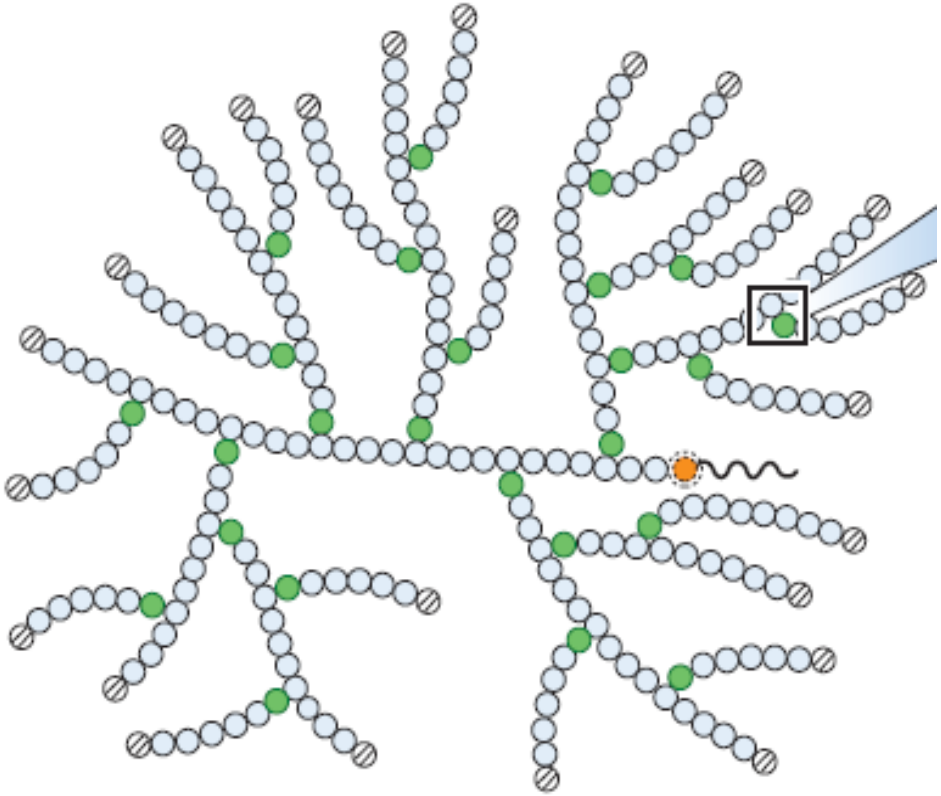
عملية البناء
عملية الهدم

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 (11 steps).
- Glycogen
  - Storage form of glucose
  - Rapid response
  - Limited amount
  - Important energy source for exercising muscle

- Quick source of glucose because of non-reducing end where breakdown of it occur resulting in glu. release

Glycogen Structure



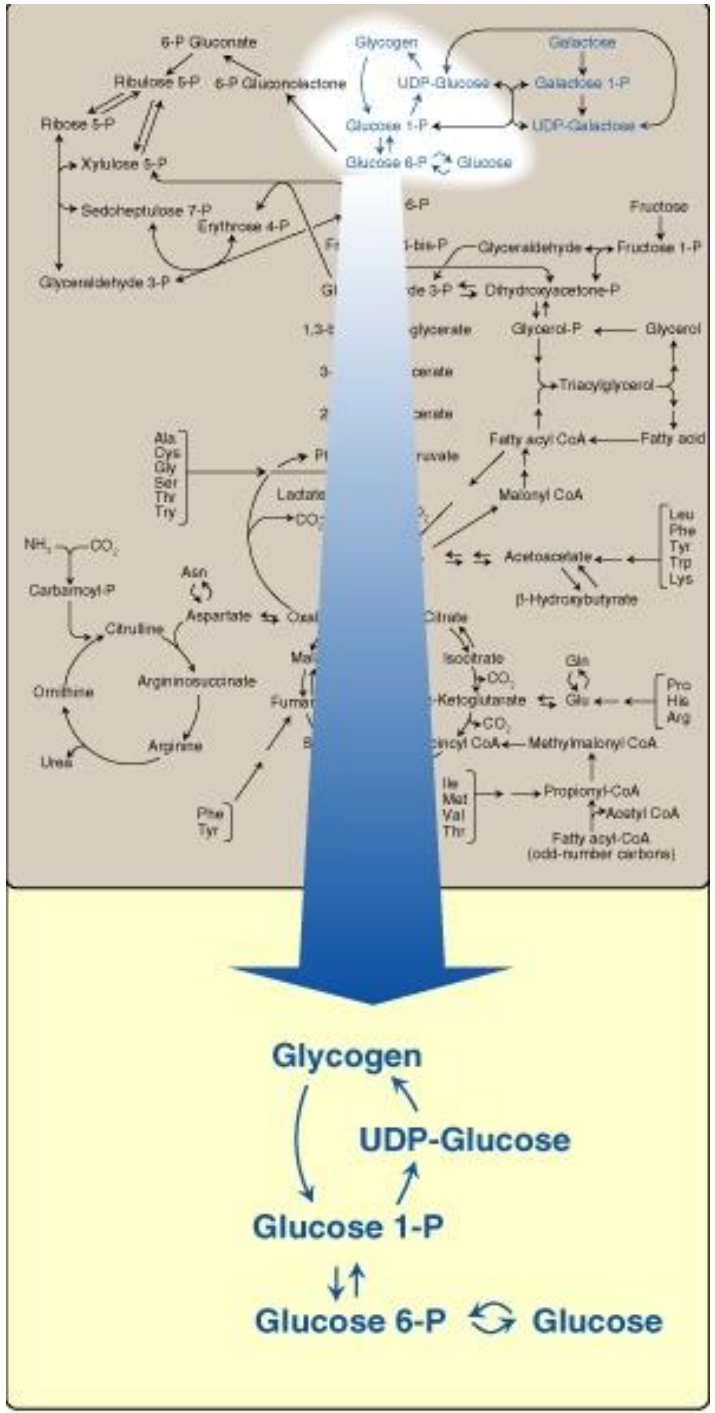
* Extensively branched homopolysaccharide

glucose residue connecting by α(1-4) while branching occure throug α(1-6)

* One molecule consists of hundreds of thousands of glucose units

– It branches every ten residue

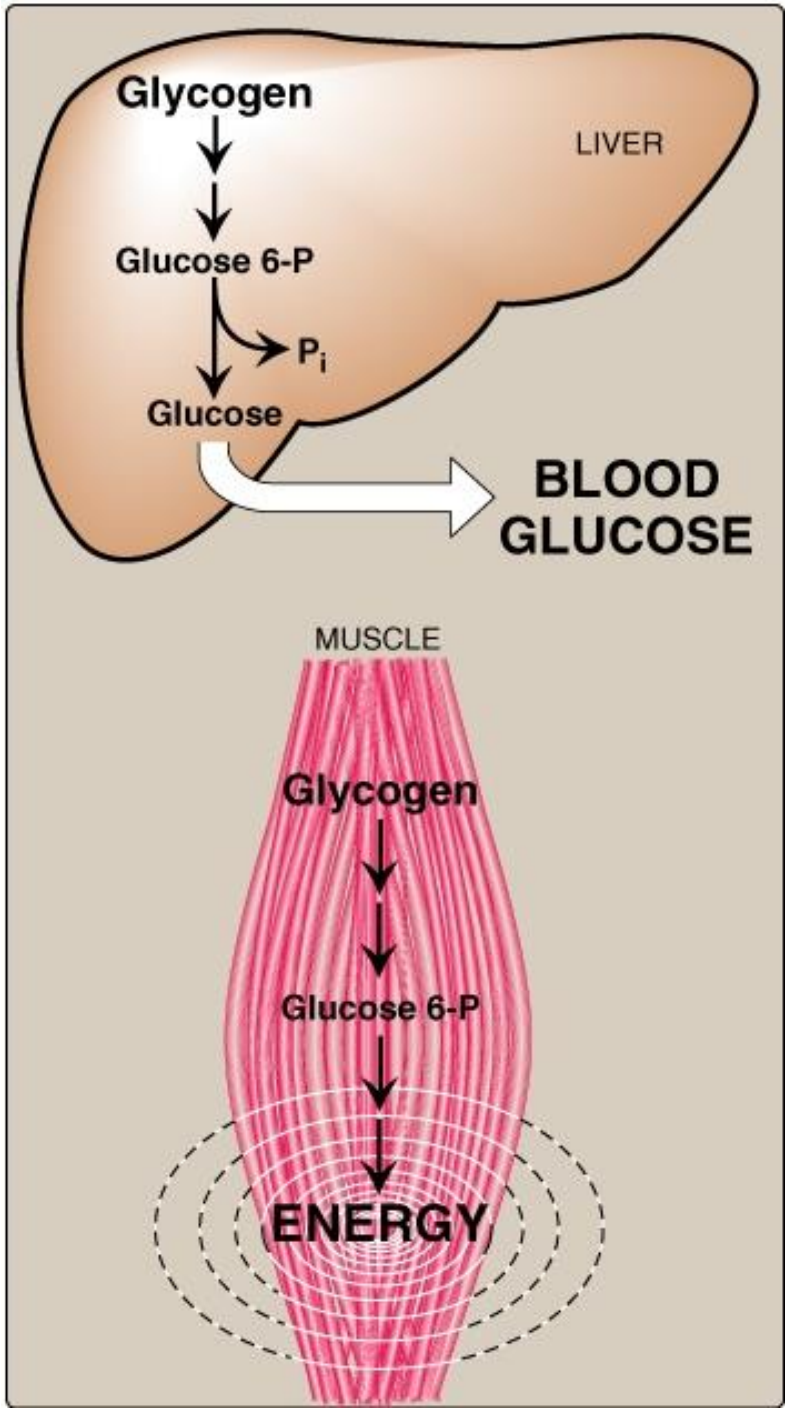
Glycogen synthesis & degradation

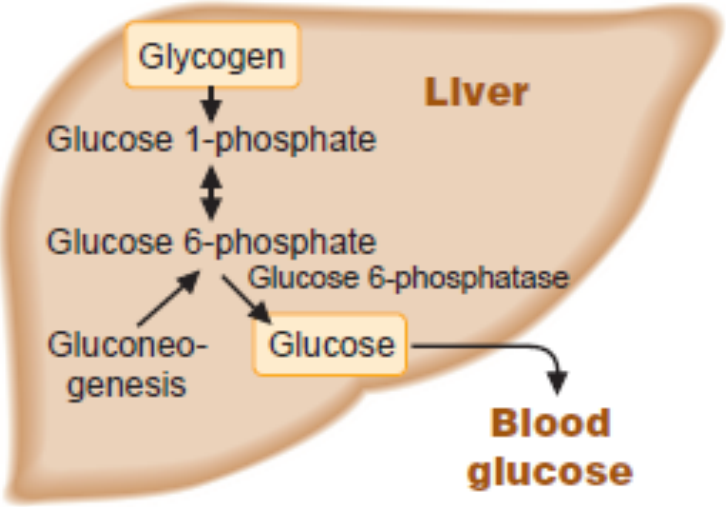


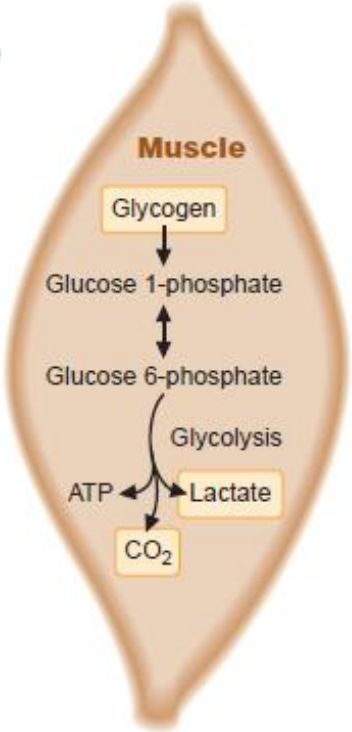
Glycogen
UDP-Glucose
Glucose 1-P
Glucose 6-P
Glucose

the degradation of glycogen occure through single step by non-reducing end resulting in glu. 1p which will be isomerized to glu. 6P ending in glu.

Fates of Glucose that results from glycogen degradation







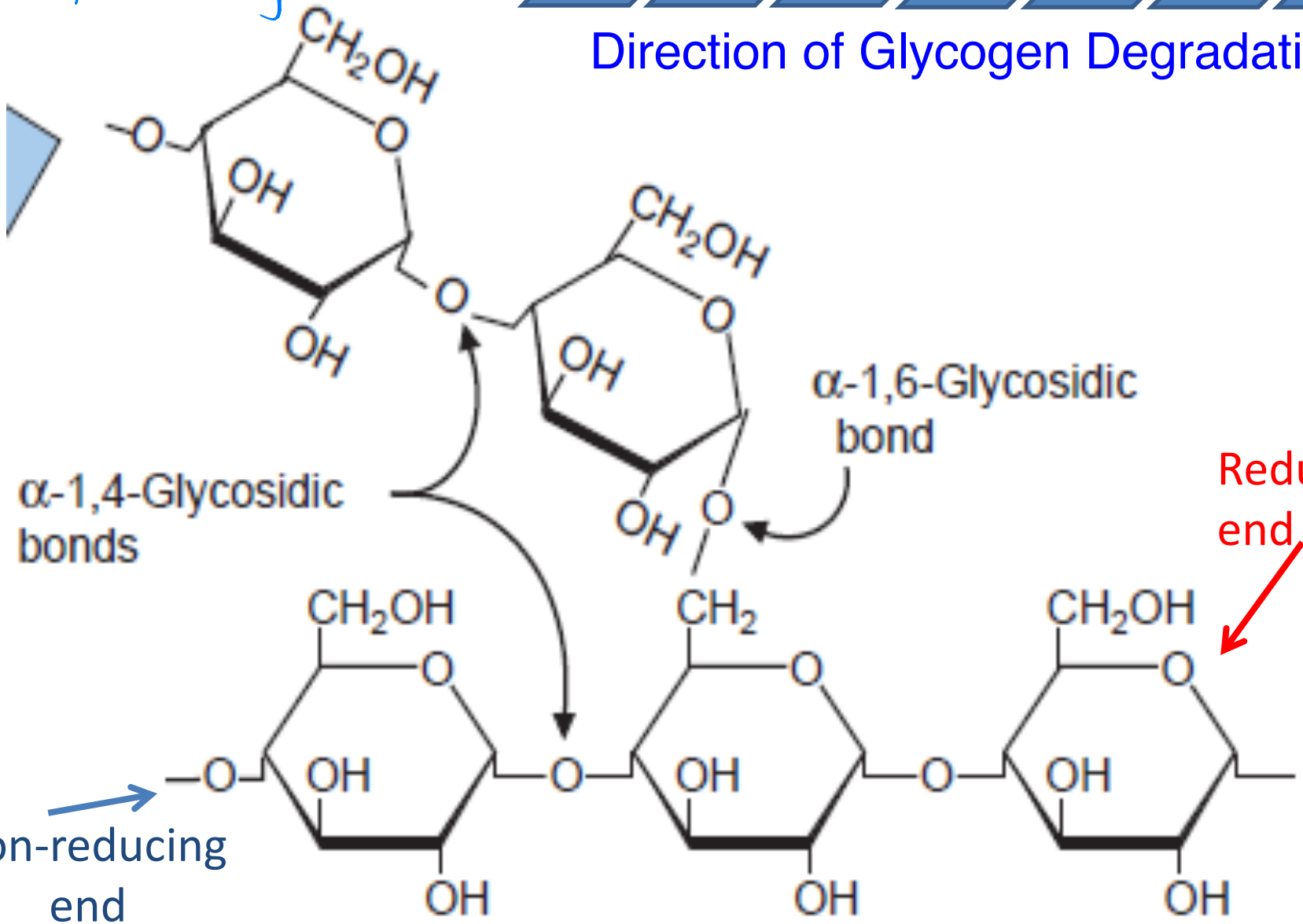
Glycogen Degradation

- 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).

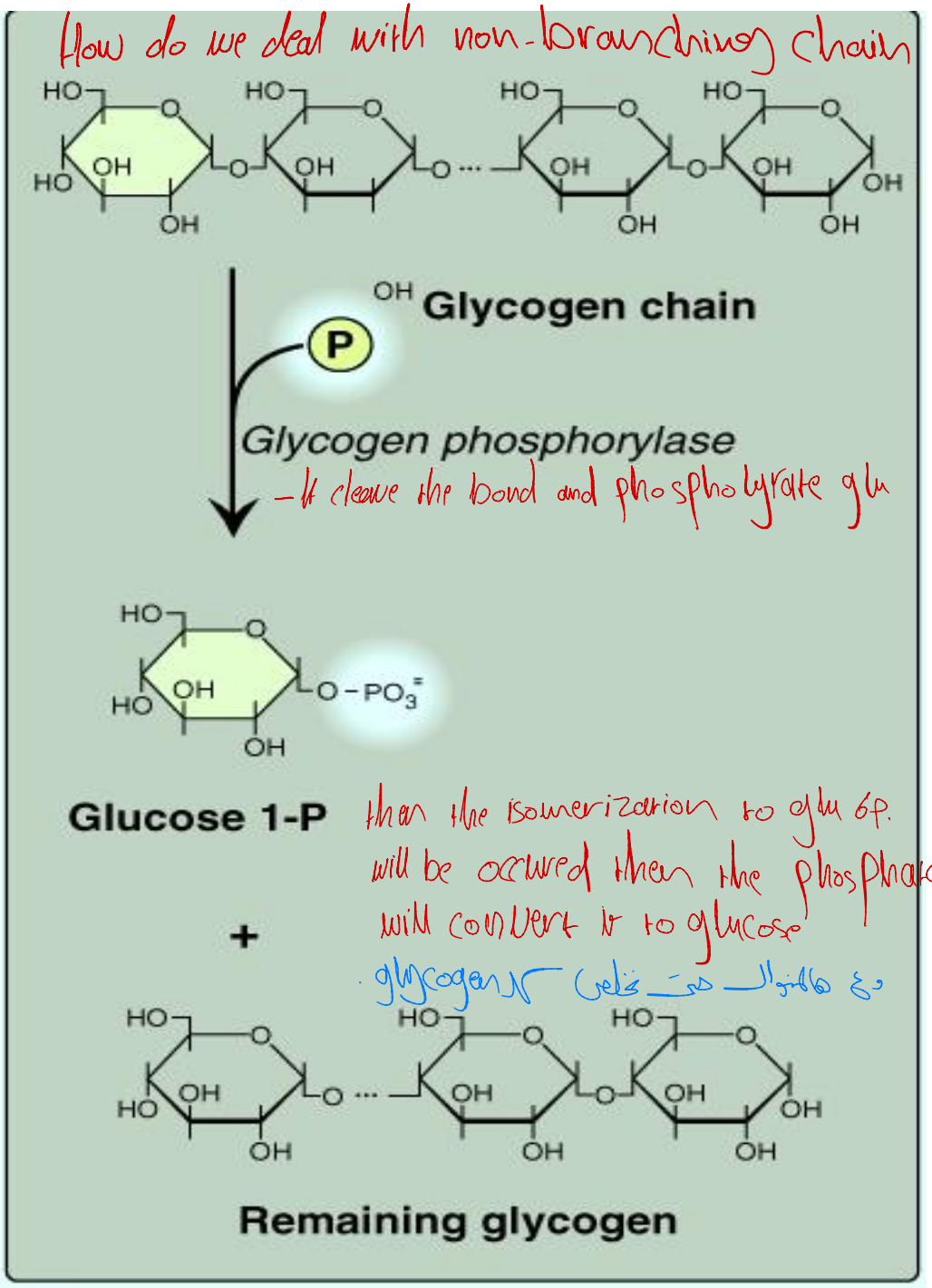
– There is no phosphatase in the muscle, so the degradation pathway will stop after we isomerization Glu1p to Glu 6.p so it could enter the glycolytic pathway and provide energy to muscle.

– In the unit time there is high Conc. of released glucose.

Direction of Glycogen Degradation



Degradation of glycogen (Glycogenolysis)



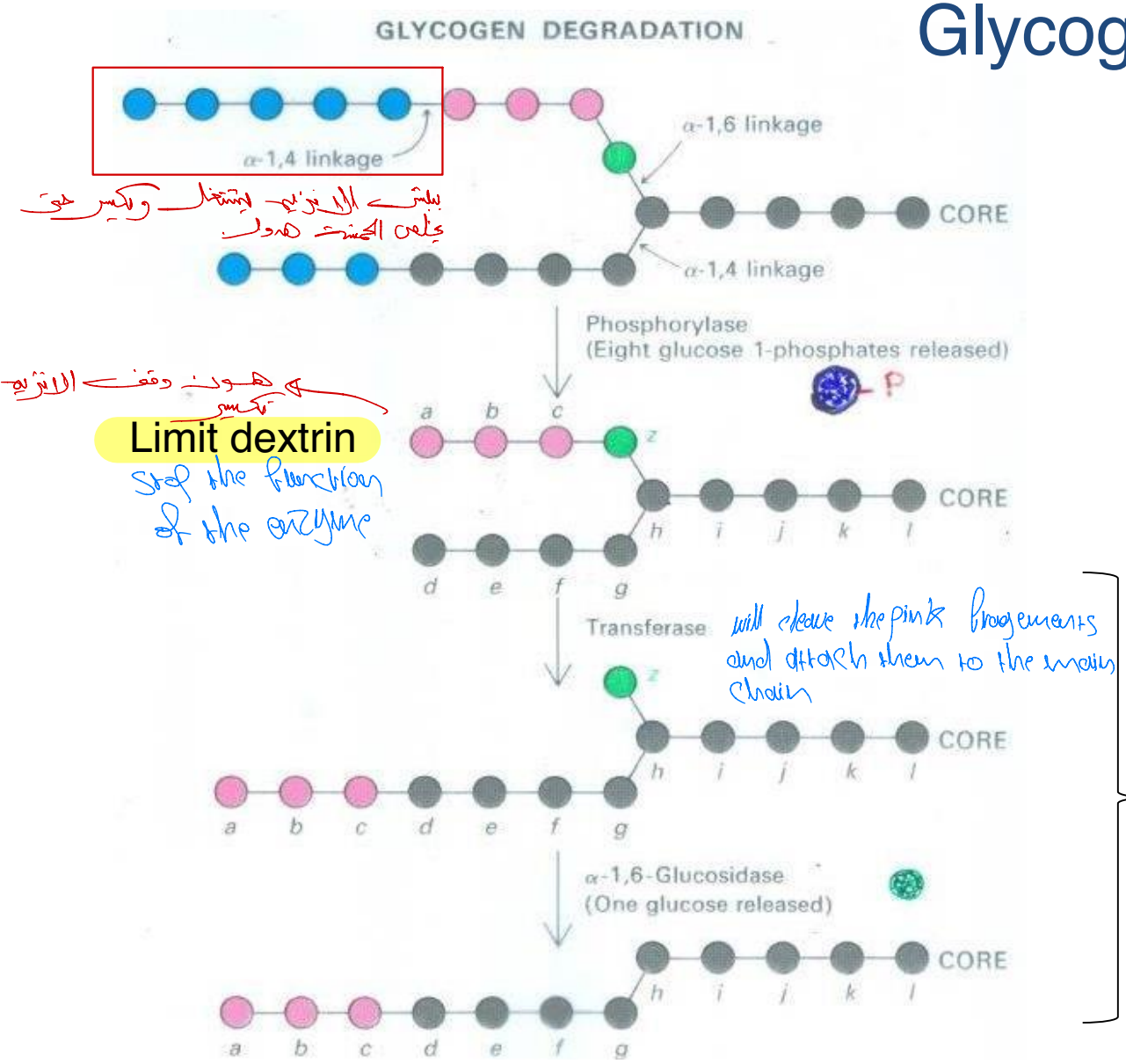
Degradation of glycogen

One glucose unit is removed at a time

Starts from the non-reducing ends

Released in the form of glucose 1-phosphate

Glycogen Degradation



Debranching enzyme

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

Another pathway for degradation.

Lysosomal degradation of glycogen

- lysosome is an acidic environment (5 pH) comparing to 7 pH cytosol, this is why the enzyme in lysosome should be work in acid environment.

- 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) glycogen Storage disorder.

- Extra info :- The glycogen is degraded in the lysosomes, an enzyme called glycogenase is used to break down glycogen.

* ع الهامش : كودة دايما بتوصيكم بالانتباه لموضوع الدهون الوراثية
ت لو كان الموضوع نادر !!

Glycogen Synthesis

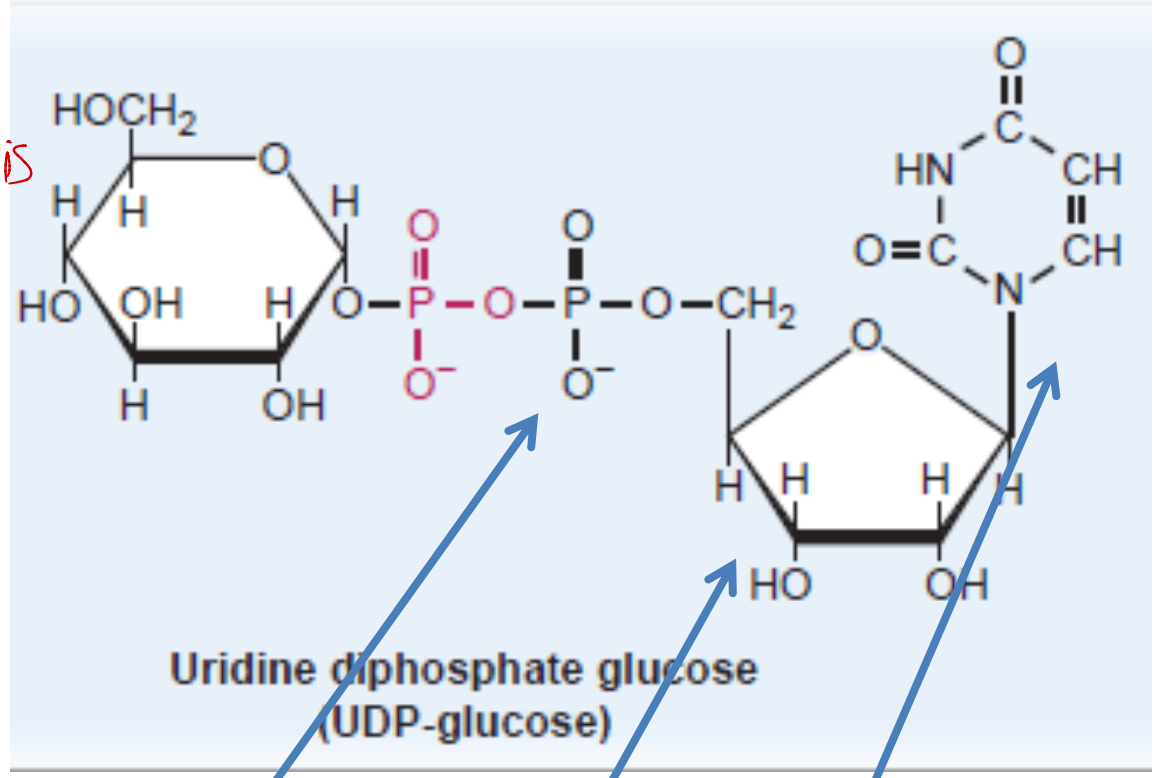
— Here we are in the well fed state, So we generate glycogen.

Glycogen is synthesized by adding glucose one by one

UDP-Glucose is the active donor of glucose units

the form of glucose which we use to synthesis Glycogen.

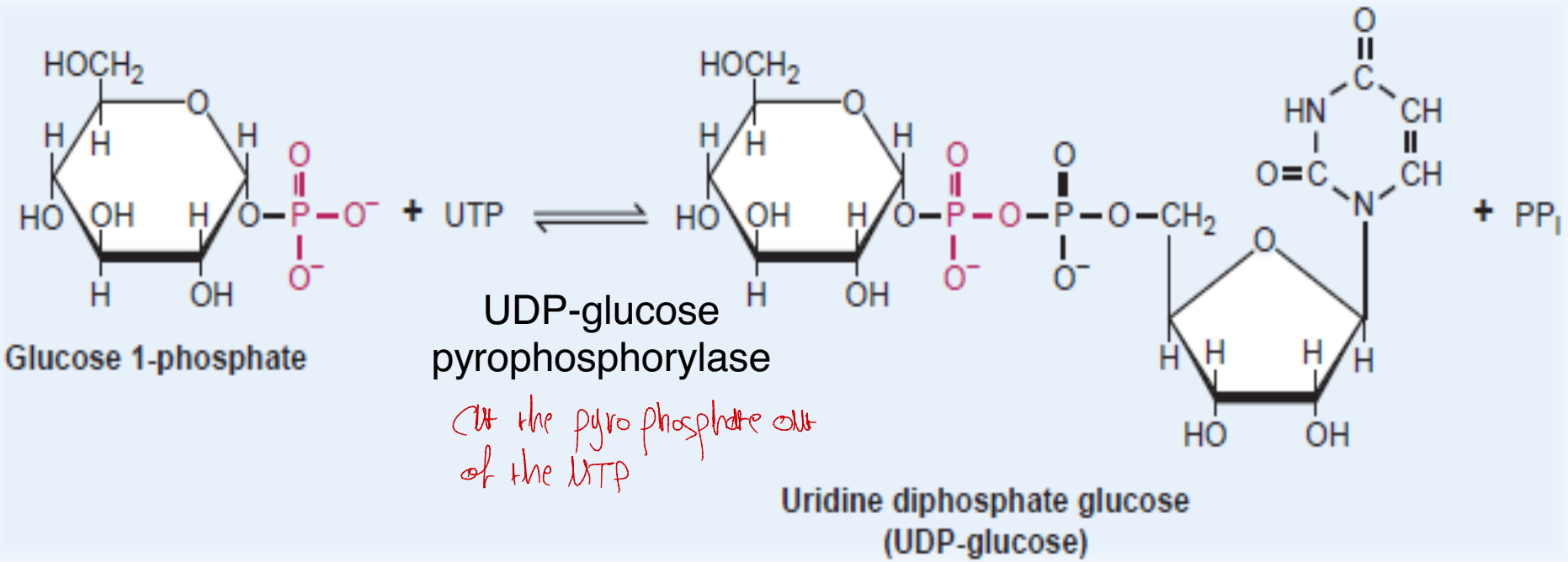
Glycogenesis



Phosphate Ribose Uracil

Formation of UDP-Glucose

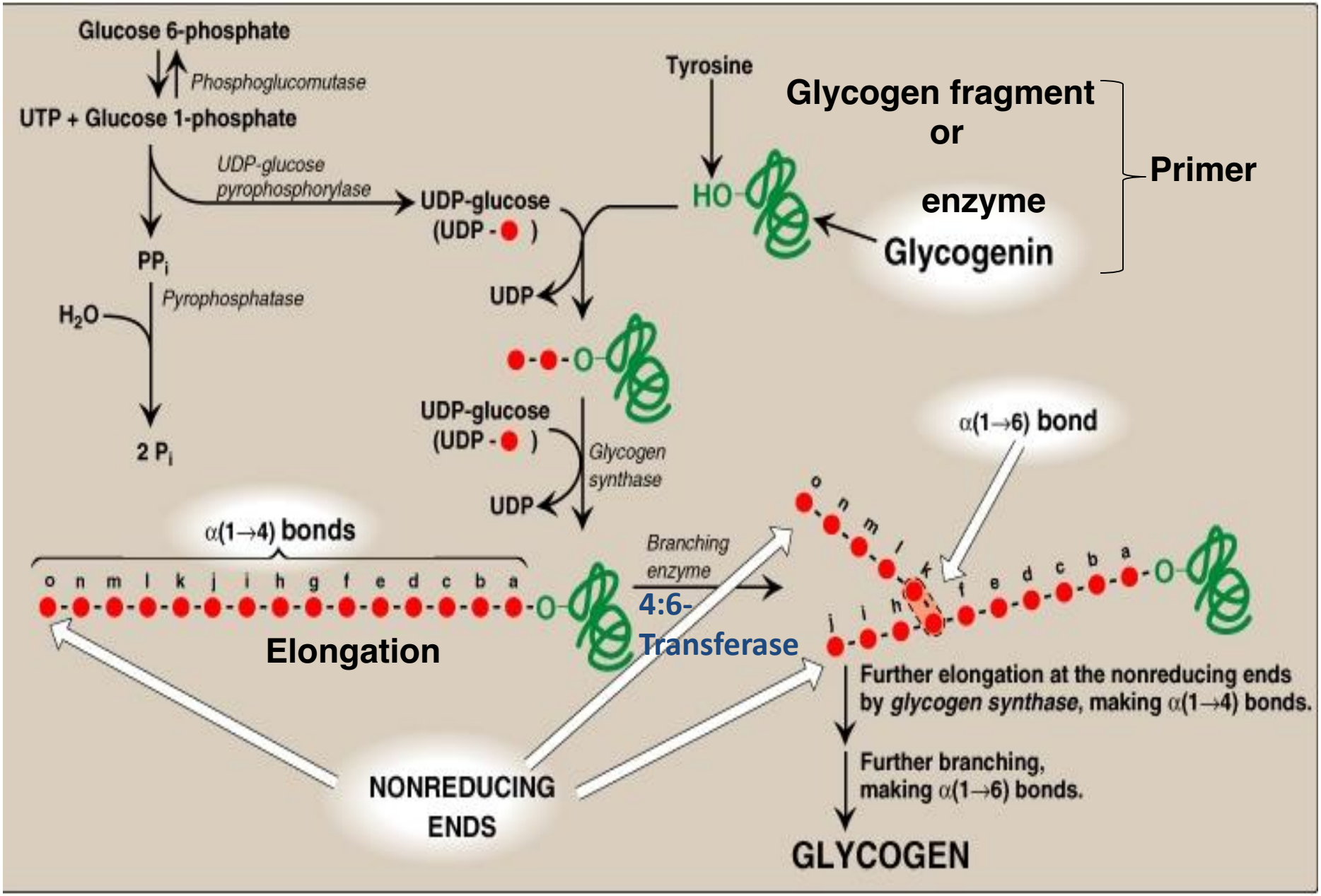
- As we know, we are in well fed state, so the Conc. of glucose is high ⇝ we will phosphorylate it either by (gluco or hexo) kinase, to become glucose 6 phosphate then it will be isomerized by mutase to be glucose 1 pho.



- Cut the pyro phosphate out of the UTP

- The glucose-1 pho. will react with UTP where it taking from UTP the suger, one phosphate group and the uridin group to attach them with phosphate on C_1. to get the UDP-glucose and releasing pyrol phosphate PP.

Glycogen Synthesis



This UDP-glucose built on the base not randomly, so we have primer which could be either a fragment of glycogen or an enzyme called glycogenin and this enzyme through its tyrosine can be connected to the first glucose to start building, and then it will be removed.

- The enzyme which going to add glucose residue on glycogen fragment called glycogen synthase.
- UDP is going to release and only glucose will be added to glycogen
- As you can see in the photo above after those steps we just have linear chain with no branching so!!

Here we will see the role of branching enzyme (4,6 transferase) in branching by transfer the fragments from 1-4 linkage to 1-6 linkage.

وبتستمر العملية 2.4 transferase بعد branching و glyc. synthase بعد بناء.

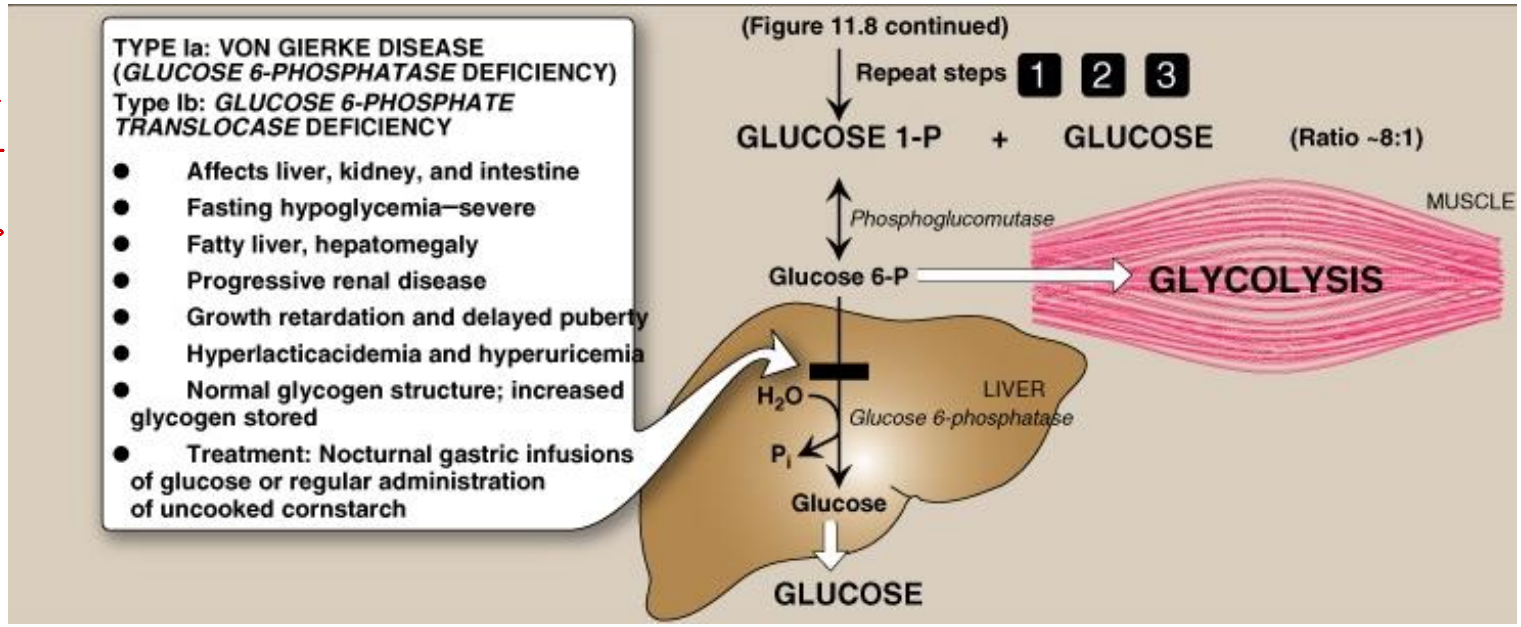
Glycogen Storage Diseases

problems maybe in synthesis or in degradation.

- 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

Glycogen Storage Diseases

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

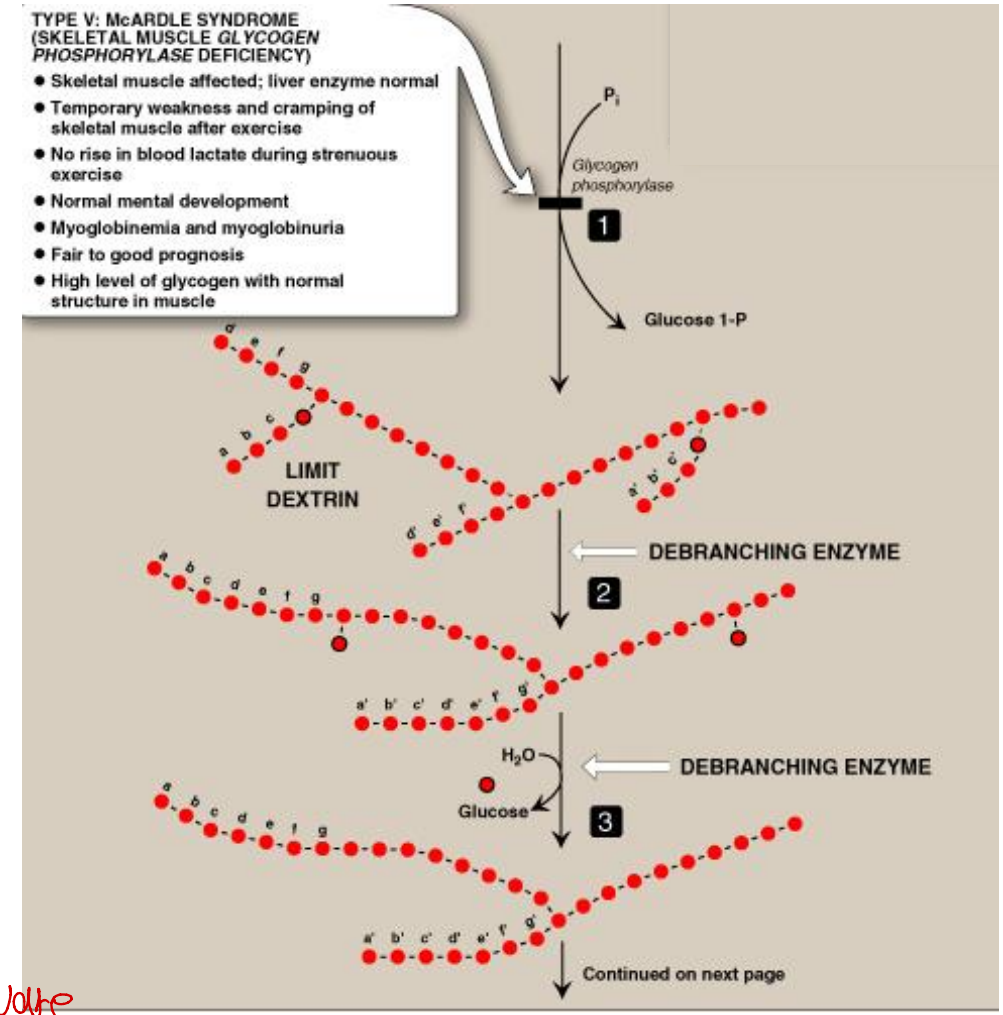


- Liver, kidney and intestine.
- Severe fasting hypoglycemia
- Hepatomegaly fatty liver.
- Normal glycogen structure.
- Progressive renal disease.
- Growth retardation.

2 Glycogen Storage Diseases

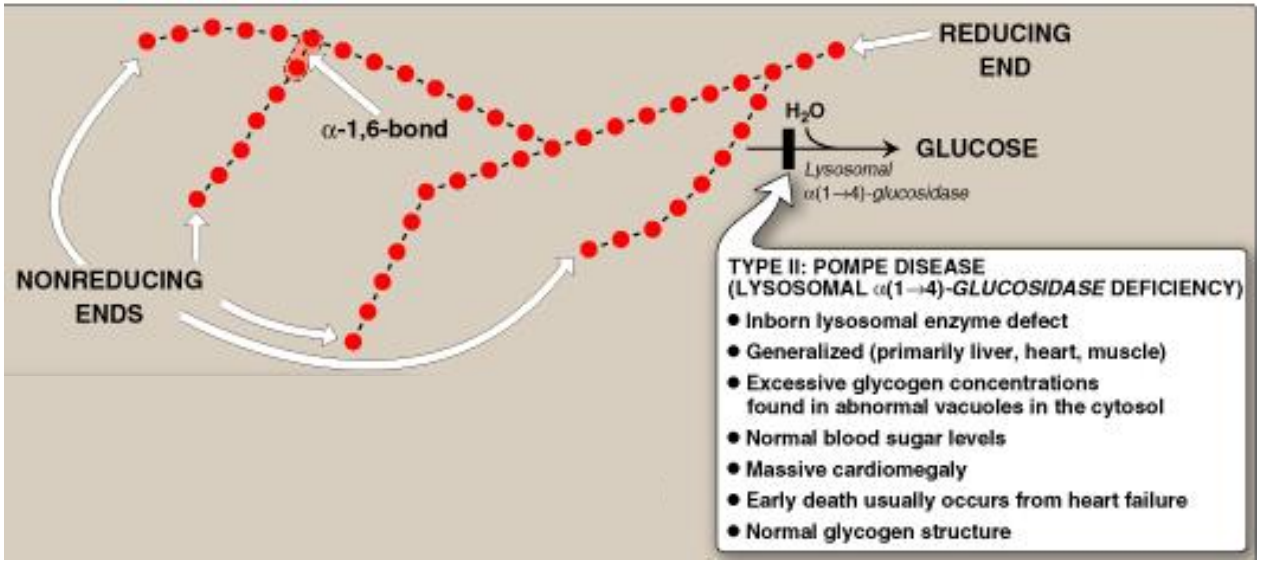
– affect the isoform of enzyme which present in the muscle only.

- 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



there is pyruvate to be converted to lactate.

3 Glycogen Storage Diseases



So many Enzymes about this pathway

- 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

Glucose + ATP ⟶ Glucose 6-phosphate + ADP

Glucose 6-phosphate ⇌ Glucose 1-phosphate

Glucose 1-phosphate + UTP ⇌ UDP-Glucose + PP_i

PP_i + H_2O ⟶ $2P_i$

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

Glc. + ATP+ UTP+ $Glycogen_{(n)}$ ⟶ ADP + UDP +$Glycogen_{(n+1}$

To add one glucose we need 2 ATP.

The net reaction in glycogen synthesis and degradation

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 + $Glycogen_{(n+1}$

In term of Glucose 1 phosphate we need one ATP molecule.

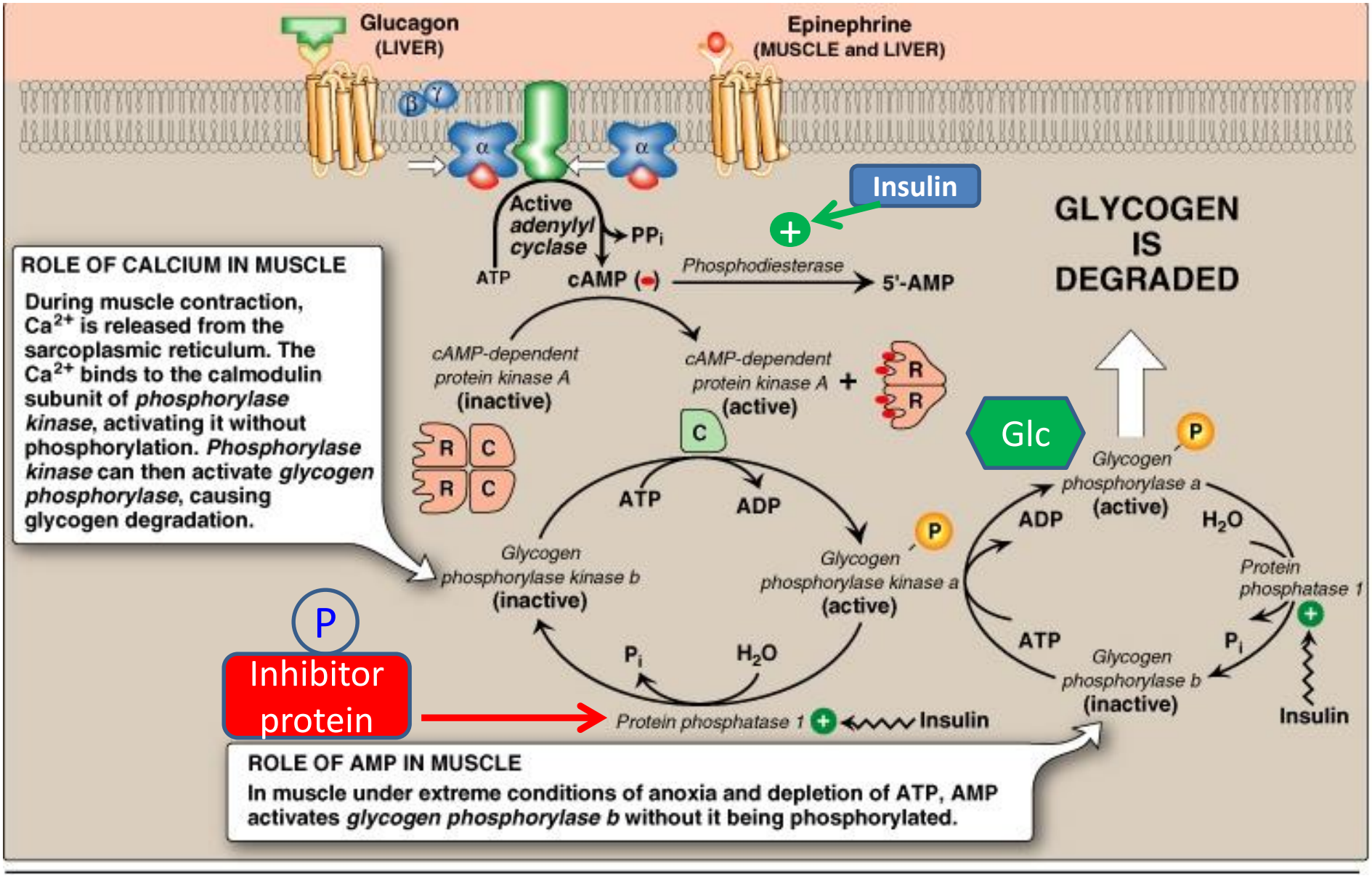
Degradation

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

https://youtu.be/2XBVUKn_I5w?si=H8ze4ADhQSb4Wdyj

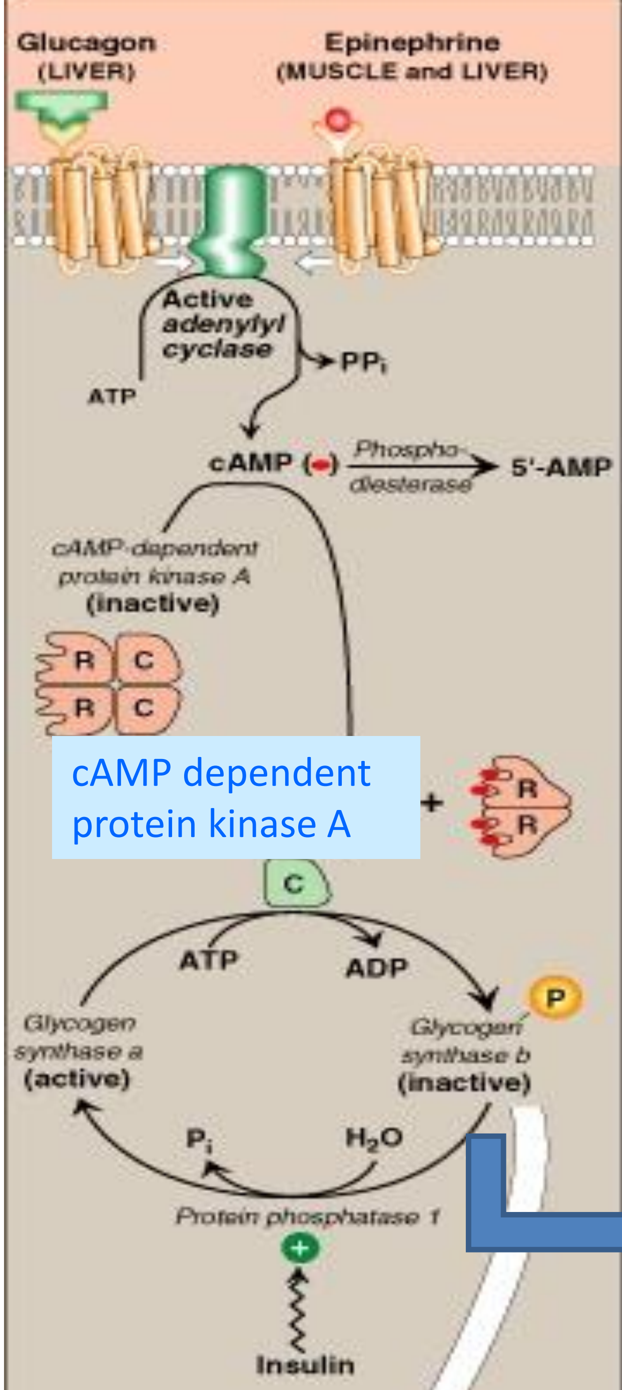
اعملوا recap لكل درسنوه من هاد الشيء للآخر.

Glycogen Metabolism Regulation



we start with degradation of glycogen what happen under fasting condition, or in fight and flight (activation of sympathetic nervous system), More epinephrin will released and bind to GPCR (Just like glucagon but each has its own receptor)
Once bound they activate α subunit, that activating adenylyl cyclase. that producing cAMP, and cAMP activate protein kinase A, which has two targets (bifunctional enzyme and pyruvate kinase), And Now we will know the third target which related to glycogen degradation (glycogen phospholyrase kinase) which is not envolve directly in the glycogen metabolism, but it is a regulatory enzyme.
So protein kinase A phospholyrate this enzyme leading to convert it into active state and then, the phosphylarate form of (glycogen phospholyrase kinase) will phosphylarate glycogen phosphatase to activate it.

- In well fed state ⟹ insulin bind to its resептor tyrosin kinase resеptor, leading to activate phosphatase in order to dephospholyration of glycogen phosphatase so glycogen degradation become inactive. - phosphodiestarase which activated by insulin convert cAMP to AMP → * يعني بوقف pathway حتى من اولها



Regulation of Glycogen Synthesis

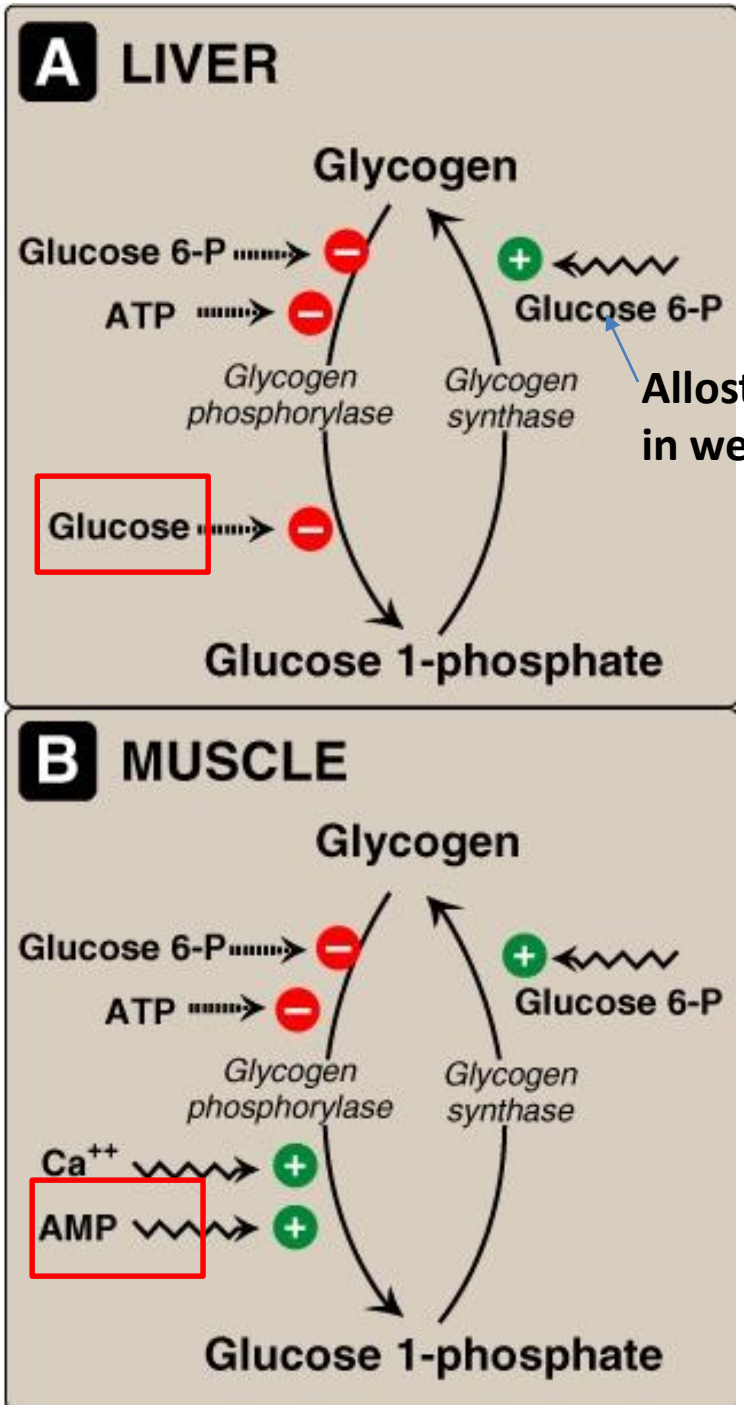
Phosphorylation at several sites

Inhibition is proportional to the degree of phosphorylation

- بـ كم تعرفوا شغلة ، عملية Phospholyration or dephosph.
ما بصير ع موقع واحد من البروتين ممكن أكثر من موقع which
leading in more inhibition or activation.

GLYCOGEN SYNTHESIS IS INHIBITED

Allosteric Regulation of Glycogen Metabolism



Allosteric activator in well-fed state

Rapid response to cell's needs

Available substrate and ATP → synthesis

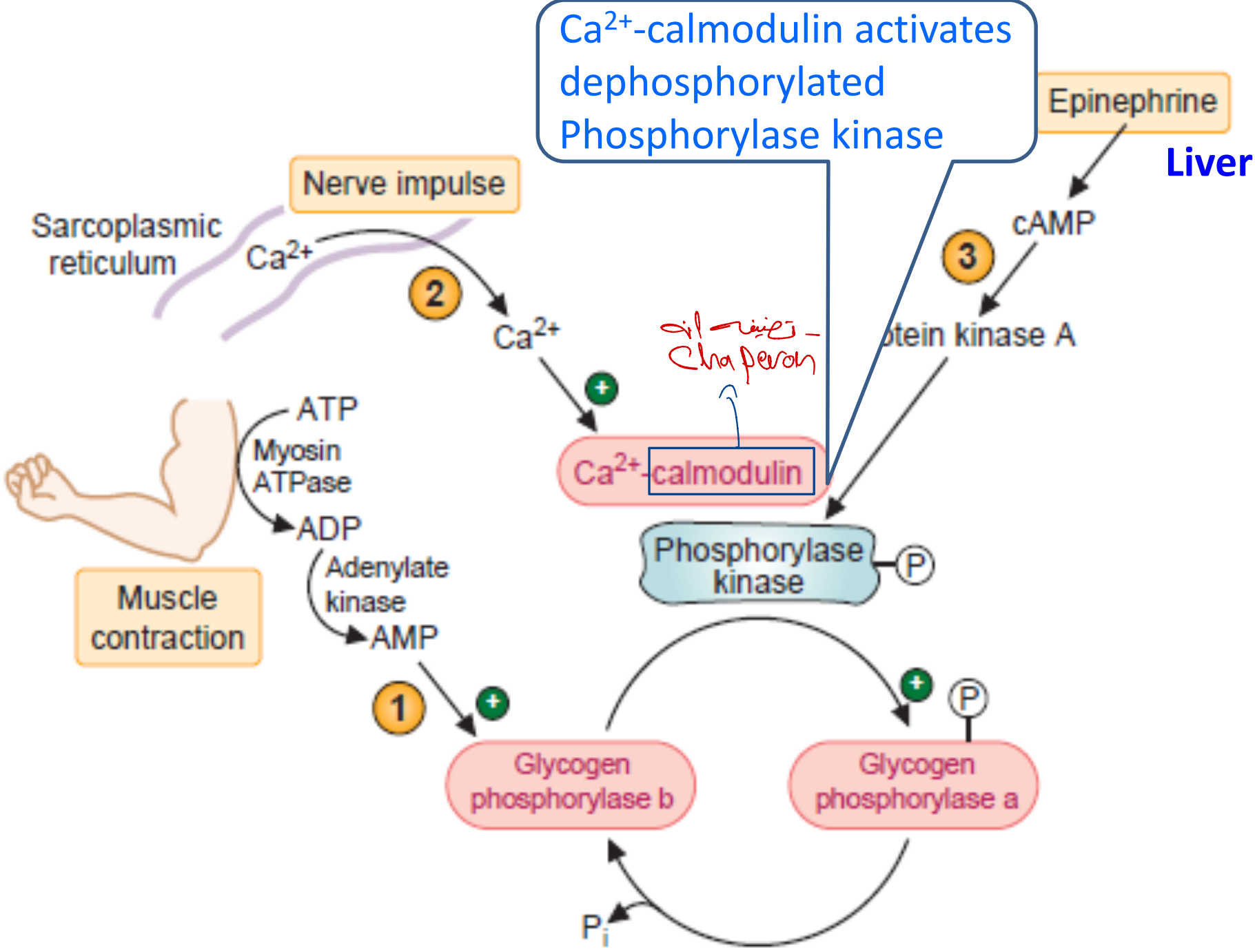
↓↓Glucose and ↓ATP → Glycogenolysis

- Glu 6 phosphate will inhibit degradation in liver and muscle because it is considered as feedback inhibition.
- ATP indicate high energy amount which mean there is no need to degrade glycogen.
- Glucose also inhibit degradation in liver just !! as we say the muscle hasn't phosphatase which converts glucose 6.p to glucose !! it has it will inhibited all time because of glucose.
- Muscles have Ca^+ and AMP as activators which they absent in liver, why? because the Ca^+ released in contraction (So it is indicate need of energy) (muscle is active) and AMP indicate low energy, but why the liver doesn't use AMP as an indicator? liver has not any problem in term of energy (it is provided by fatty acid and it is even larger in amount than producing it from glucose)

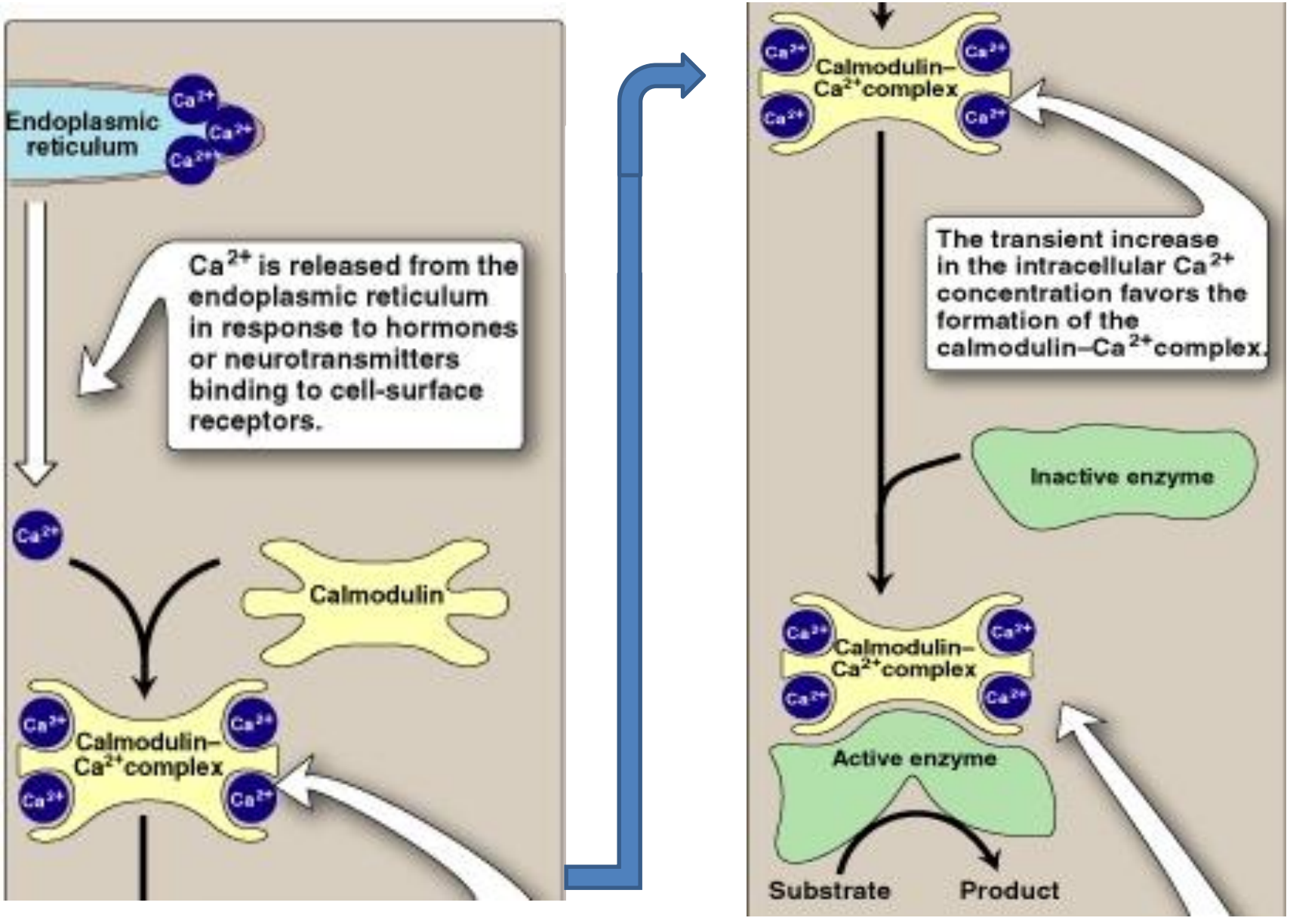
يعني زي ما حكينا هي بأمن على الطاقة (مؤقتاً).

while in muscles we need ATP for contraction.

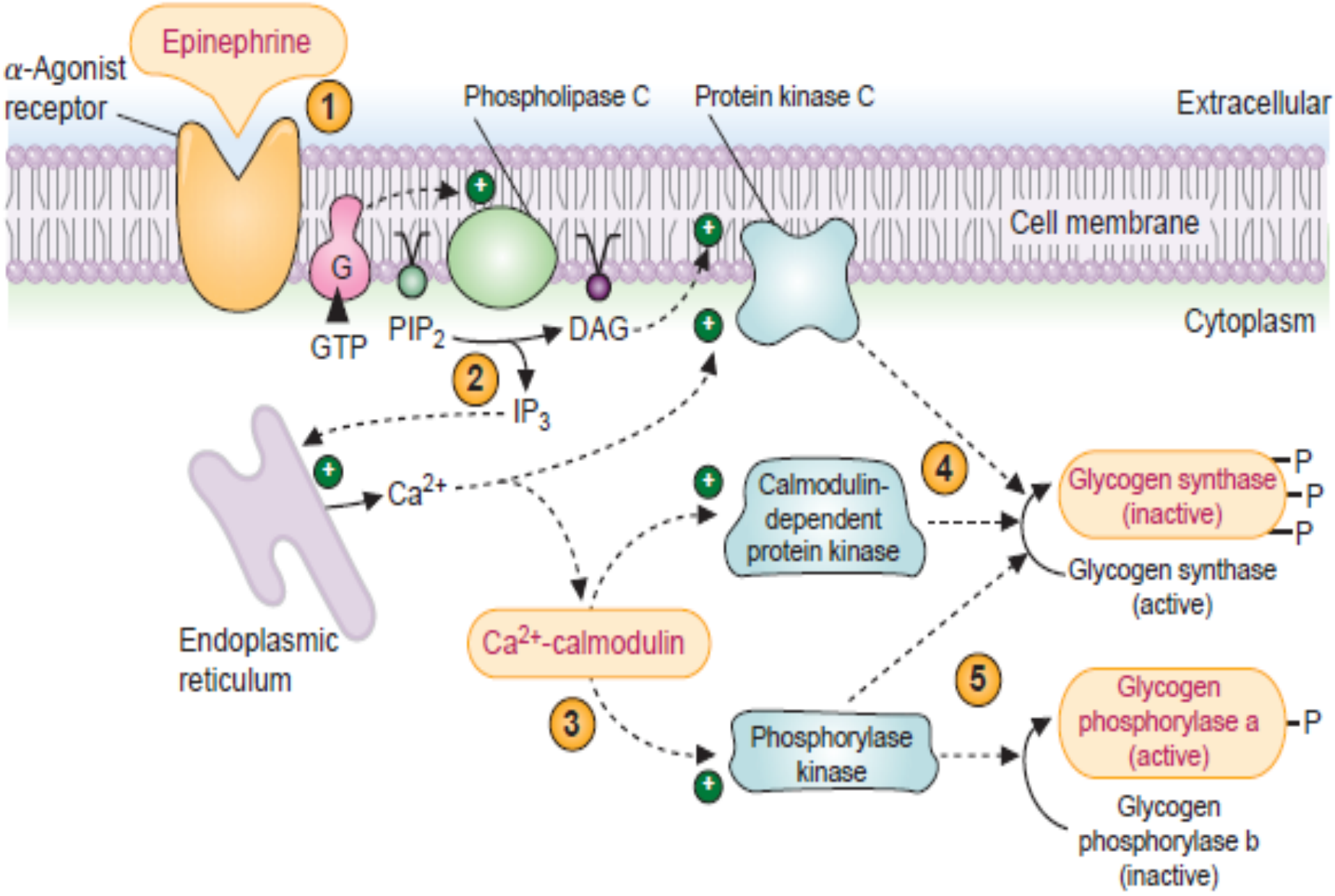
Lujain


Ca2+-calmodulin activates dephosphorylated Phosphorylase kinase
Epinephrine
Liver
Nerve impulse
Sarcoplasmic reticulum
Ca2+
2
Ca2+
cAMP
3
Protein kinase A
Chaperon
ATP
Myosin ATPase
ADP
Ca2+-calmodulin
Phosphorylase kinase
P
Muscle contraction
Adenylate kinase
AMP
1
Glycogen phosphorylase b
Glycogen phosphorylase a
P
Pi

Ca^{+2} -Calmodulin Complex Function



Calcium Activation of liver phosphorylase Kinase



once Ca^{+} released out of cytoplasmic reticulum it bind to protein called Calamodulin
So its Conformation will be Changed to activate other protein by binding to them
the Calmodulin - Ca^{+2} complex will bind to glycogen phospholyrase kinase → دهاي ثاني إشارة تنشيط توصل
So it is an active to start phospholyration.

How signaling occur under these Conditions (under need GPCR), So we have types of second messenger produced ⟹ 1) IP_3 ⇝ G protein under need GPCR activate Phospholipase C (enzyme that degrade membrane lipids) it degrade specificly PIP_2 releasing it into form of IP_3 and DAG stays attach to the membrane (hydrophobic) while the hydrophilic IP_3 will leave to the cytosol as a second messenger where it bind to gates of channels of Ca^{+} in the ER (open it resulting in Ca^{+2} releasing)

Lujain Ahmad

في بالرسمة أدوار لل Ca^{+} - Calmodulin و كتار منهم.

لا تنسوني من الدعاء.