

METABOLISM

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ



MID – Lecture 14

- 1) From Pyruvate to Acetyl-CoA
- 2) Glycogen Metabolism

وَإِن تَوَلَّوْاْ يَسْتَبَدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَلَكُمْ

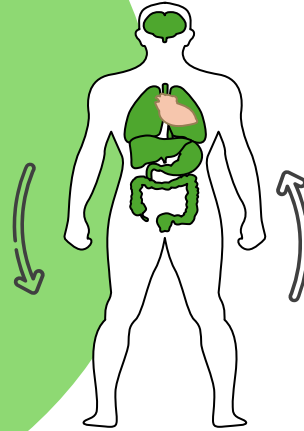
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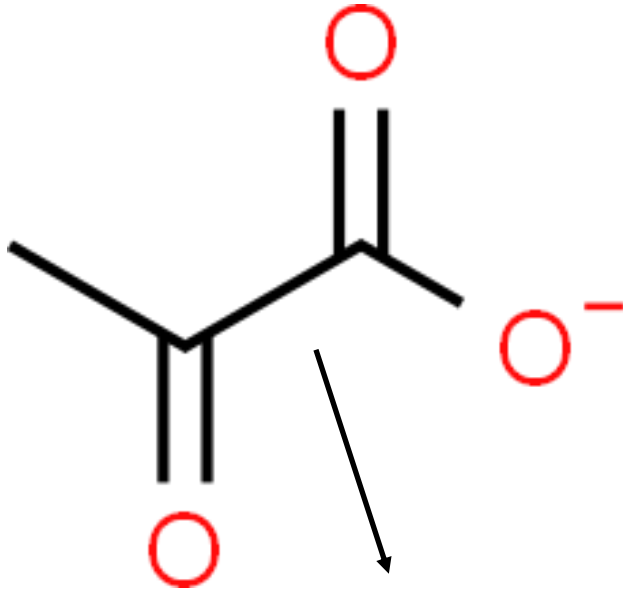
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Short Quiz on Lecture 13

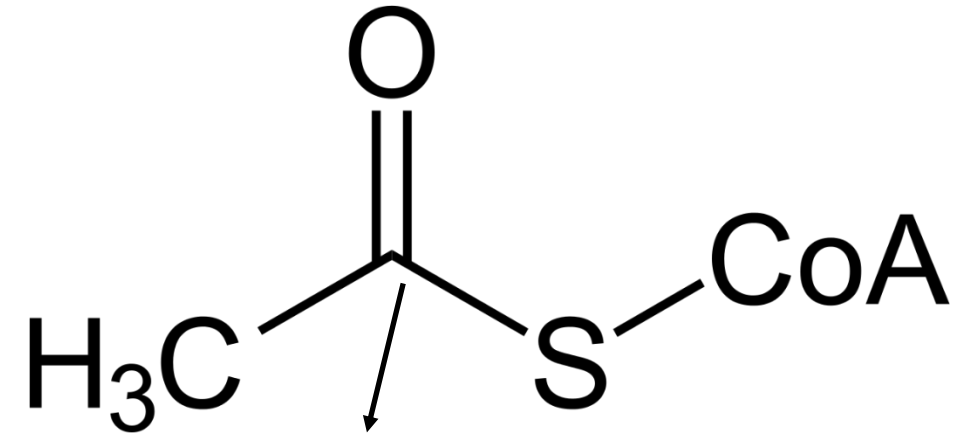
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Pyruvate is a 3 carbon molecule that has carboxyl, carbonyl and methyl groups

Pyruvate \rightarrow Acetyl-CoA

by PDH complex



This Acetyl-CoA contains carbonyl and methyl. The carboxyl group is removed, making this an oxidative decarboxylation reaction catalyzed by the PDH complex.

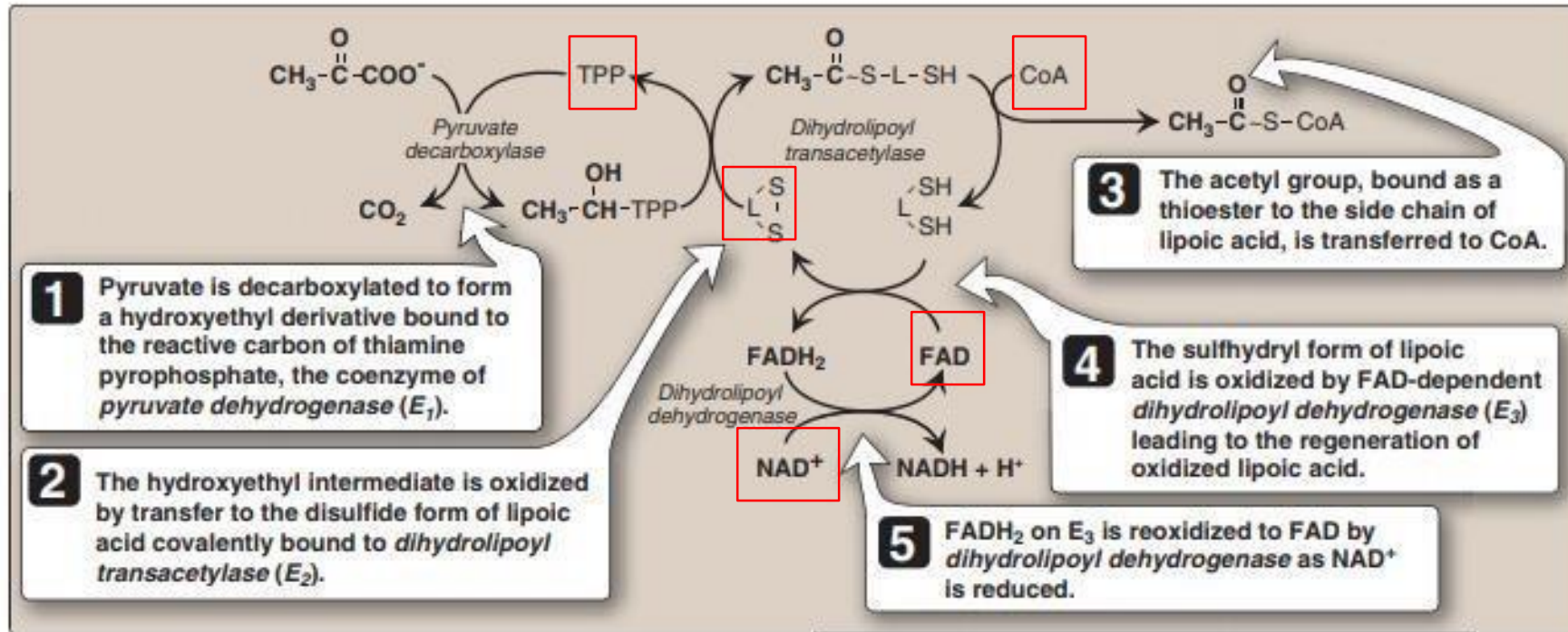
After Glycolysis: From Pyruvate to Acetyl-CoA

Dr. Diala Abu-Hassan, DDS, PhD

From Pyruvate to Acetyl-CoA

Oxidative decarboxylation of pyruvate

- ✓ Pyruvate is produced in the cytosol and needs to be transported to the mitochondria by a specific pyruvate transporter
- ✓ Once in the matrix, pyruvate is converted to acetyl CoA by the pyruvate dehydrogenase (PDH) complex, which is a multienzyme complex made of 3 enzymes, E1 (decarboxylase), dihydrolipoyl transacetylase (E2), and dihydrolipoyl dehydrogenase (E3).



1

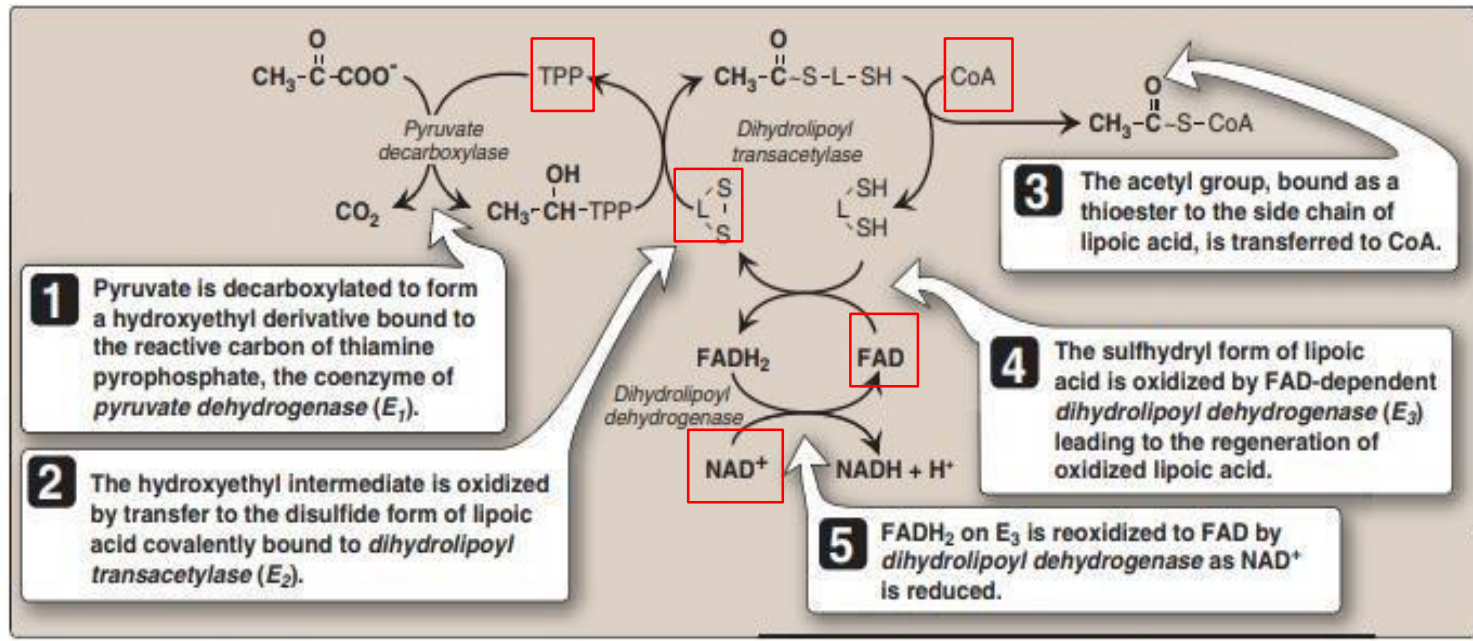
The first enzyme, pyruvate decarboxylase, removes the carboxyl group, releasing it as CO₂. The carbonyl is reduced, and the remaining two-carbon fragment binds to the coenzyme TPP.

2

After TPP dissociates, the two-carbon unit attaches to a second coenzyme, lipoic acid which must be in its oxidized state (forming a disulfide bridge). When lipoic acid reacts with the hydroxyethyl intermediate, it will become acetyl due to oxidation, and lipoic acid structure will open and be reduced (one sulfur atom becomes reduced, and the two-carbon unit binds to the other sulfur atom). E2, then catalyzes the transfer of the acetyl group to CoA, replacing the lipoic acid.

3

E2 transfers the acetyl group to CoA, completing the production of acetyl-CoA. Acetyl-CoA is now ready, and lipoic acid is released in its reduced form (SH-L-SH), also known as dihydrolipoic acid



4 + 5

To recycle lipoic acid back to its oxidized state to reuse it, the third enzyme, E3 (dihydrolipoyl dehydrogenase), catalyzes an oxidation-reduction reaction. During this process, two hydrogens are removed, restoring the disulfide bridge in lipoic acid and preparing it for another reaction. FAD is reduced to FADH₂ and then re-oxidized back to FAD, while NAD⁺ is simultaneously reduced to NADH by E3

Regulation of PDH Complex

The enzyme complex (PDH) is quite large, making it highly regulated. Regulation occurs through;

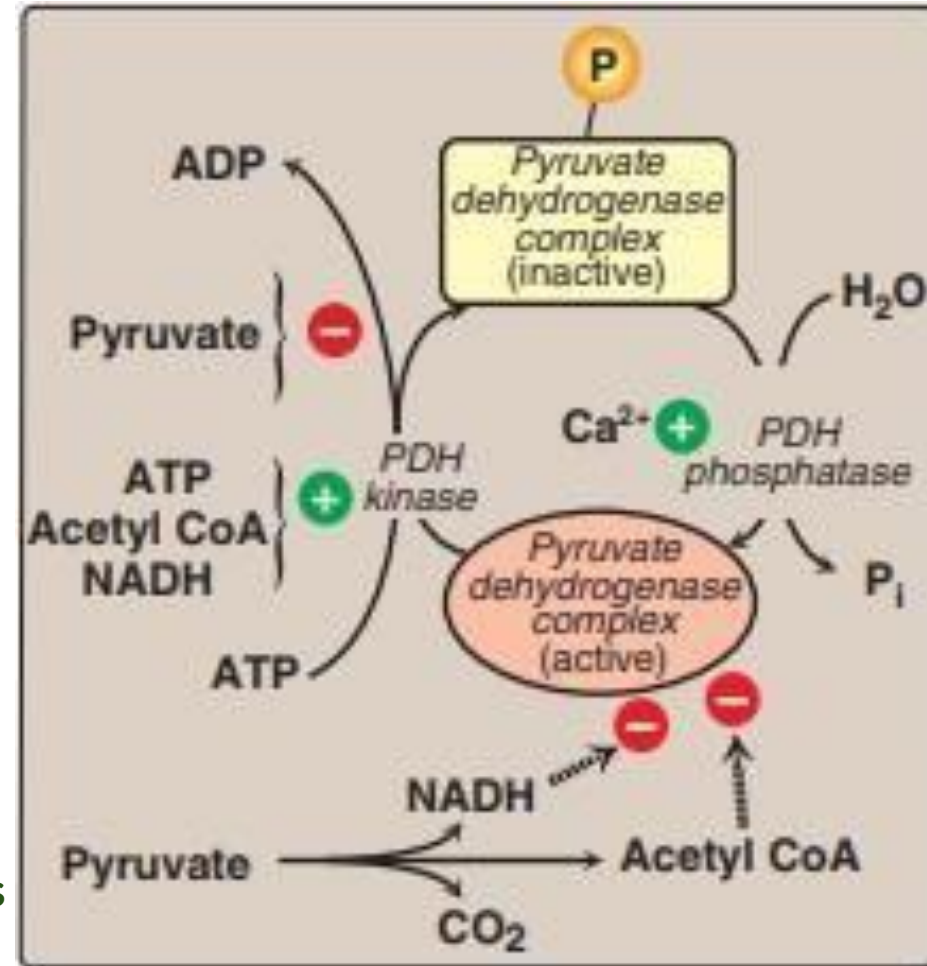
- allosteric regulators
- regulatory enzymes.

Allosteric regulators bind directly to the enzyme complex modifying its activity. Important regulators that inhibits the complex when present ---> acetyl-CoA, NADH

NADH acts as an inhibitor because the reaction requires its oxidized form. If NADH levels are high, the reaction cannot proceed, signaling that the Krebs cycle, which requires NAD^+ , is also stalled. So, this causes inhibition of both the Krebs cycle and the enzyme complex.

✓ **The complex also contains two tightly bound regulatory enzymes, PDH kinase and PDH phosphatase**

There are two main regulatory enzymes: PDH kinase which phosphorylates and inactivates pyruvate dehydrogenase, and PDH phosphatase, which dephosphorylates and activates it. These enzymes also have their own allosteric regulators.



❖ allosteric regulators of Regulatory enzymes:

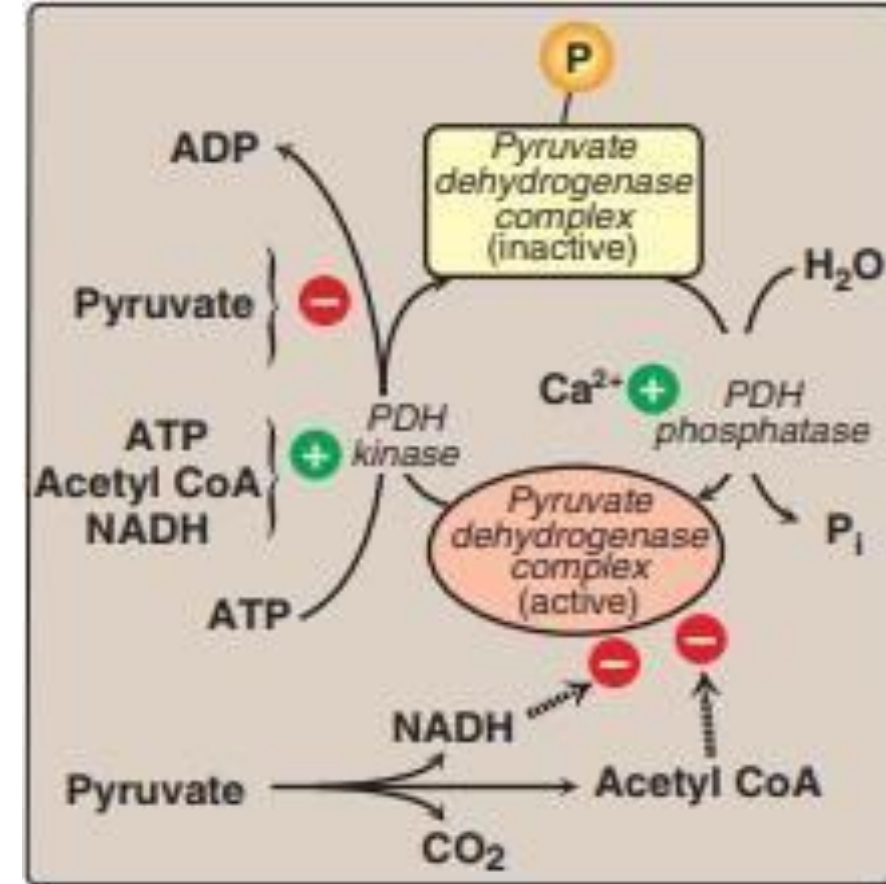
□ PDH kinase

- **PDH kinase**, which phosphorylates and inactivates PDH, is activated by ATP, signaling a high-energy state. This activation switches off PDH to prevent unnecessary acetyl-CoA production when energy is abundant. Acetyl-CoA and NADH both also activate the kinase, leading to PDH complex inactivation through phosphorylation. These regulations prevent excess energy production.

- Pyruvate acts differently by inhibiting the kinase, which keeps PDH active. When pyruvate levels are high, it needs to be converted to acetyl-CoA to enter the Krebs cycle, rather than accumulating and undergoing conversion to lactate in anaerobic conditions

□ PDH phosphatase

- Calcium serves as a positive allosteric regulator of **PDH phosphatase**. In muscle cells, high calcium levels indicate increased activity and a higher demand for ATP. Calcium ions bind to phosphatase, activating it, which then dephosphorylates and activates pyruvate dehydrogenase (PDH). As a result, acetyl-CoA can enter the Krebs cycle (TCA cycle) to produce energy.

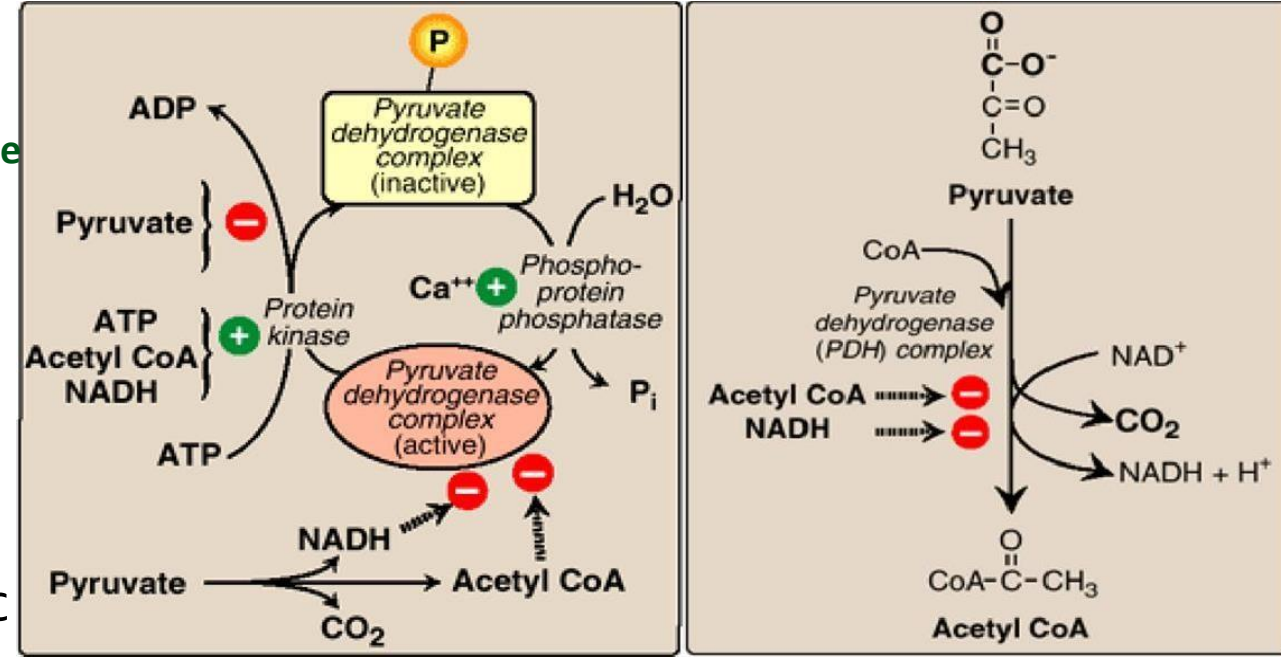


Clinical Application: PDH deficiency

The enzyme most affected by the genetic mutation that leads to deficiency is E1.

- Component enzymes
- Coenzymes
- Regulation of the pyruvate dehydrogenase complex

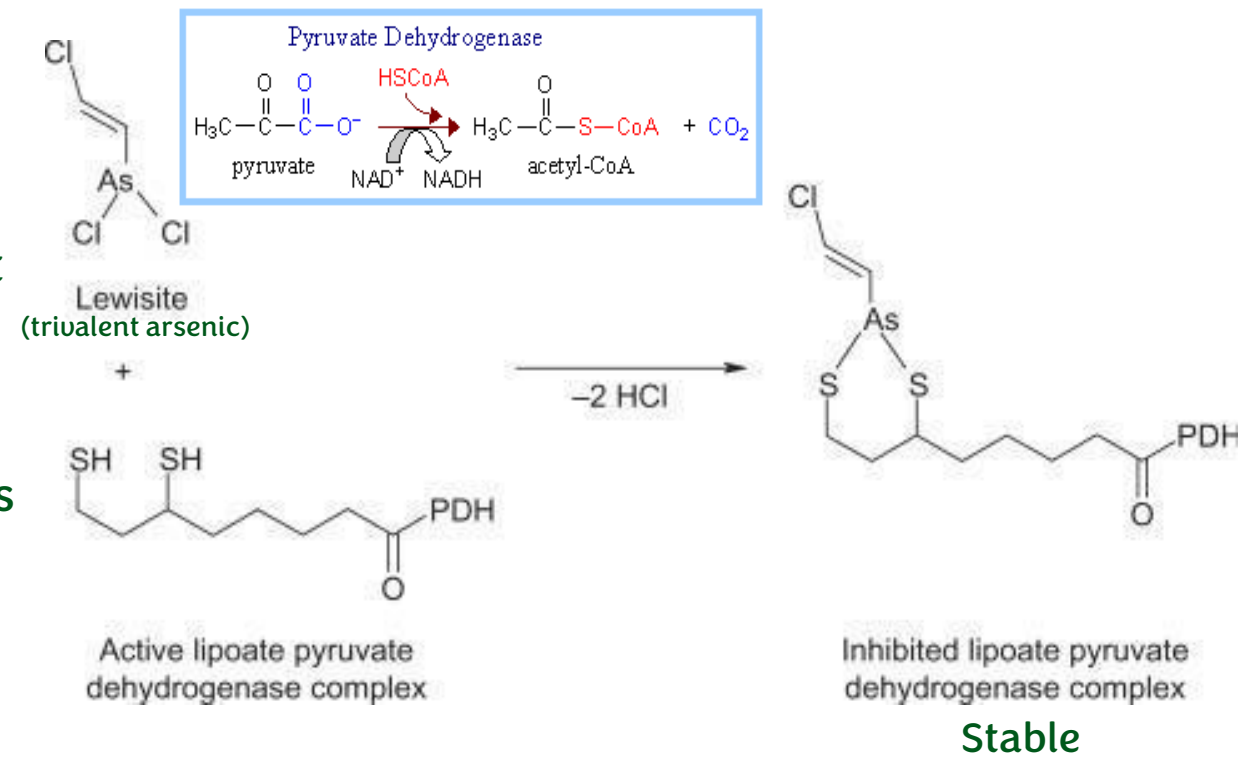
- Pyruvate dehydrogenase deficiency: A deficiency in E₁ component is the most common biochemical cause of congenital lactic acidosis (X-linked, no treatment)
- ✓ Affected tissues: brain, relies on the TCA cycle for most of its energy, and is sensitive to acidosis. (those that rely exclusively on glucose for energy)
- ✓ Symptoms are variable and include neurodegeneration, muscle spasticity and, in the neonatal onset form, early death.
- ✓ Dietary restriction of carbohydrate and supplementation with TPP may reduce symptoms in select patients.



- The gene for (E1) is present in the X chromosome. It's X-linked, so males are more susceptible to this kind of problem. Since Males have a single X chromosome and since the mutation is X-linked recessive
- When there is a deficiency in the PDH complex due to an E1 subunit mutation, pyruvate accumulates. This accumulation activates alternate metabolic pathways, such as the conversion of pyruvate to lactate, leading to lactic acidosis. **Lactic acidosis is the most congenital consequence of this metabolic imbalance.** Pyruvate cannot be converted to oxaloacetate in this context, as oxaloacetate formation occurs in gluconeogenesis, and ethanol production is not relevant to human metabolism.

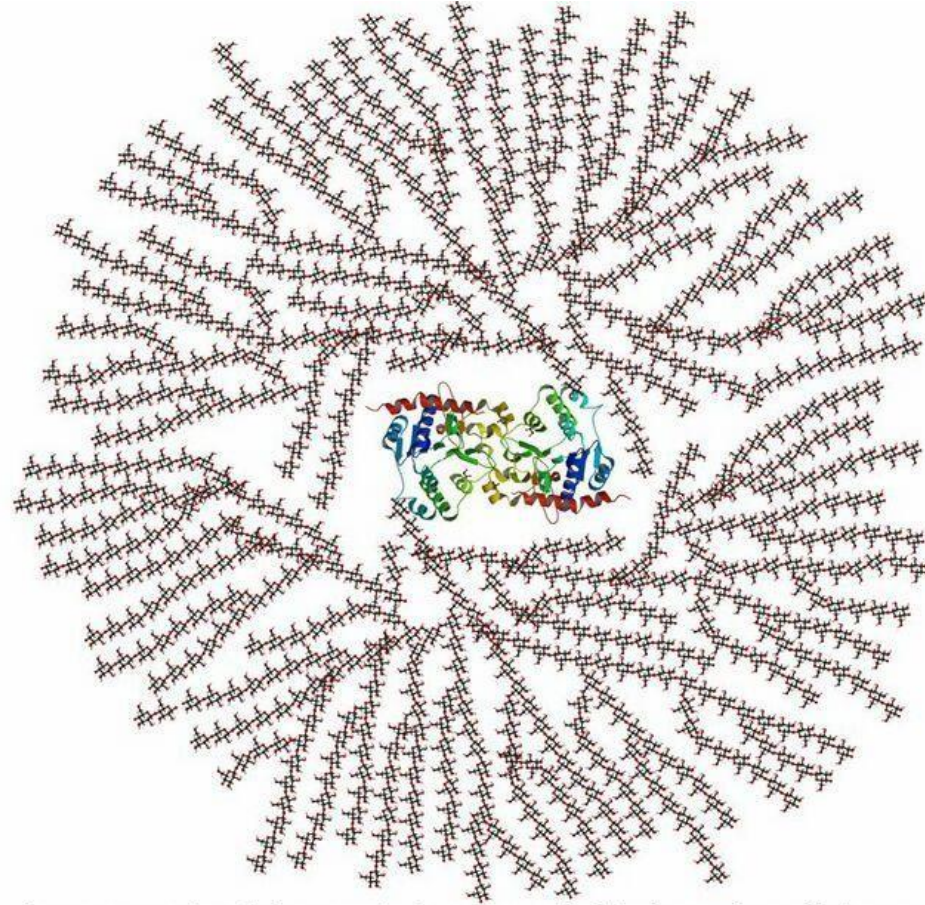
■ Mechanism of arsenic poisoning

Arsenic has two main toxic forms: pentavalent and trivalent. Pentavalent arsenic inhibits glycolysis directly, while trivalent arsenic disrupts complexes that require lipoic acid. Specifically, trivalent arsenic binds to the thiol groups of lipoic acid, forming a stable complex and inhibiting the PDH complex and alpha-ketoglutarate dehydrogenase complex. As expected this inhibition further impairs energy metabolism.



Glycogen Metabolism

Dr. Diala Abu-Hassan

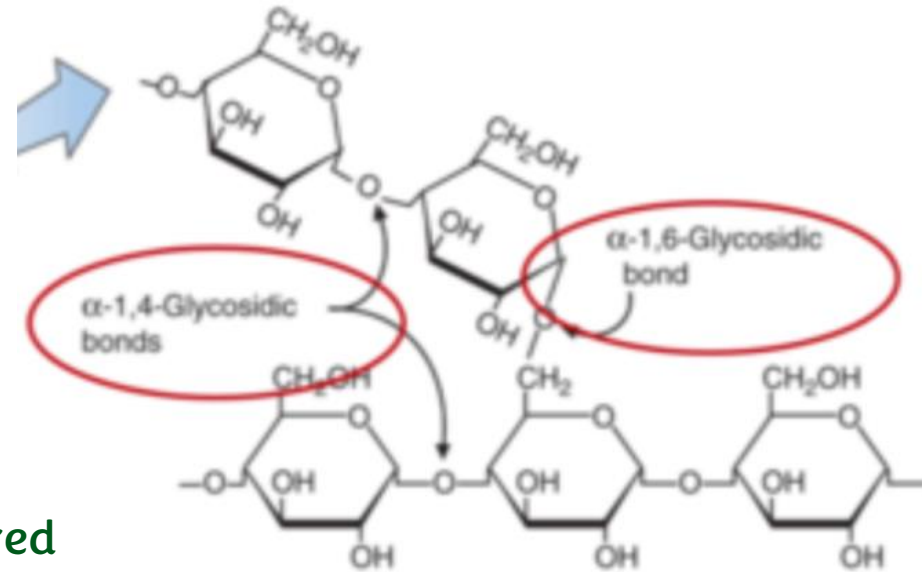


A core protein of glycogenin is surrounded by branches of glucose units.
The entire globular complex may contain approximately 30,000 glucose units.

صَلُّوا عَلَى الْحَبِيبِ

Introduction

- ❖ After consuming a meal, blood sugar levels peak within two hours following digestion and absorption. Insulin is then released, promoting glucose uptake by cells and lowering blood sugar back to fasting levels. If this regulation fails, it may indicate diabetes.
- ❖ Once inside the cells, glucose can be used for energy production, stored as glycogen, or utilized in various biosynthetic pathways, such as pentose sugar formation for nucleotide synthesis, **Lactose production, which is used by nursing mothers, or for the synthesis of glycosaminoglycans in the extracellular matrix, modified lactose is involved in the latter case.**
- ❖ Although glycogen can be stored in most cell types, the largest reserves are found in muscle tissue. Despite this, the total glycogen storage in the human body is limited to approximately 500 grams, around 75 grams are stored in the liver, 400 grams in the muscles, and about 20-25 grams in the extracellular matrix, lasting only 12 to 18 hours during fasting.



Also known as animal starch, glycogen serves as the storage form of glucose in animal and human cells.

Remember: Fatty acids give more energy, however they are slower in their metabolism

Sources of Blood Glucose

- **Diet** (primary source of glucose)
 - Starch, mono and disaccharides, glucose
 - Sporadic, depend on diet
- **Glycogen** (secondary source of glucose) during fasting state it's 1st source
 - Storage form of glucose
 - Rapid response
 - Limited amount
 - Important energy source for exercising muscle
- **Gluconeogenesis** (the sustained source of glucose for prolonged fasting)
 - Sustained synthesis
 - Slow in responding to falling blood glucose level

The key advantage of glycogen as a glucose source is its rapid availability, as glucose can be quickly released one molecule at a time, unlike starch which needs time.

gluconeogenesis uses non-carbohydrate precursors to synthesize glucose, since sugars are unavailable.

Gluconeogenesis, the opposite of glycolysis, occurs primarily in the liver and to a lesser extent in the kidneys. It provides a steady glucose supply over extended periods, enabling survival even in prolonged fasting states, such as 60 days without food, these individuals who fast for long durations can still have their **essential** body functions maintained.

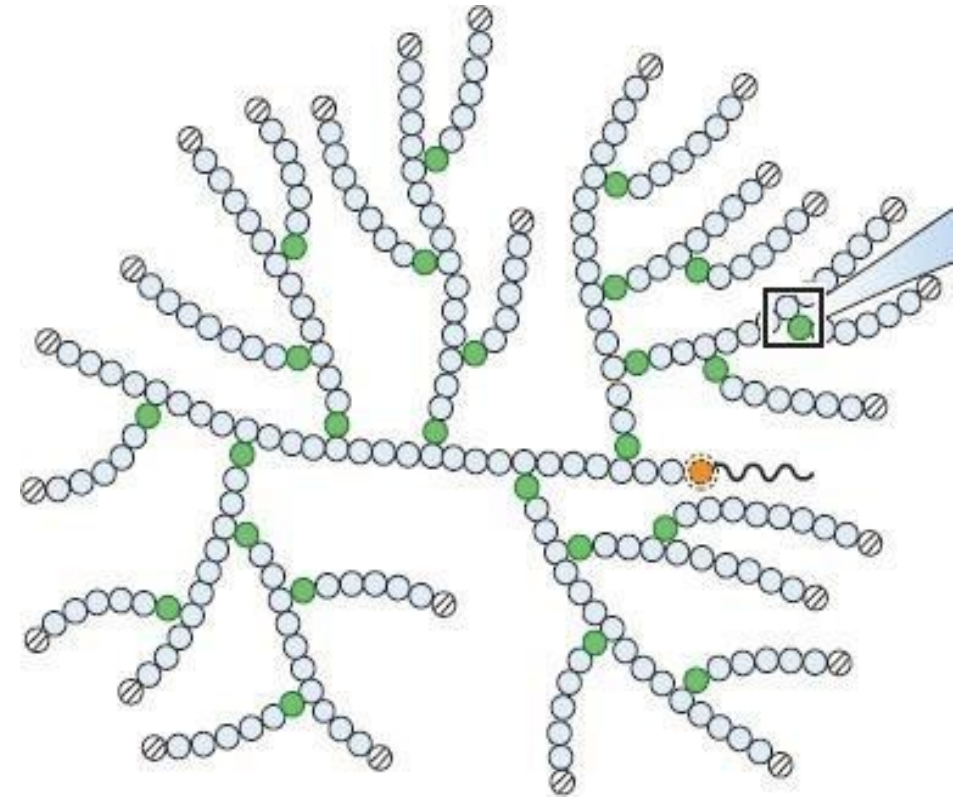
Gluconeogenesis is a long-term glucose supply, unlike **glycogen, which only provides energy for a short duration.**

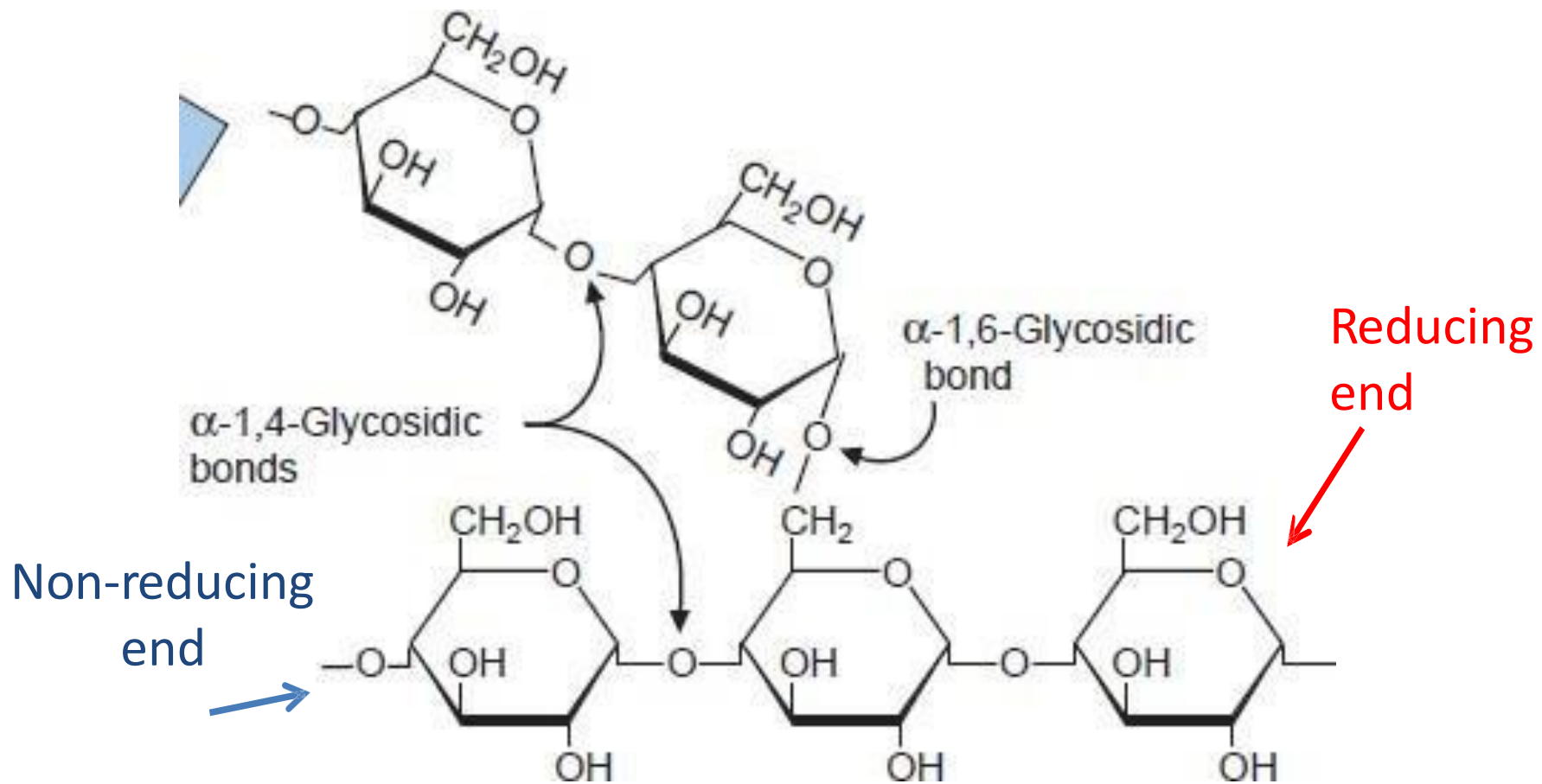
Glycogen Structure

*Extensively branched homopolysaccharide

*One molecule consists of hundreds of thousands of glucose units

- ❖ Glycogen is a homopolysaccharide composed of glucose residues linked by alpha-1,4 glycosidic bonds in the linear chains and alpha-1,6 glycosidic bonds at the branch **points**.
- ❖ Glycogen is stored in the form of granules within the cytoplasm of cells.

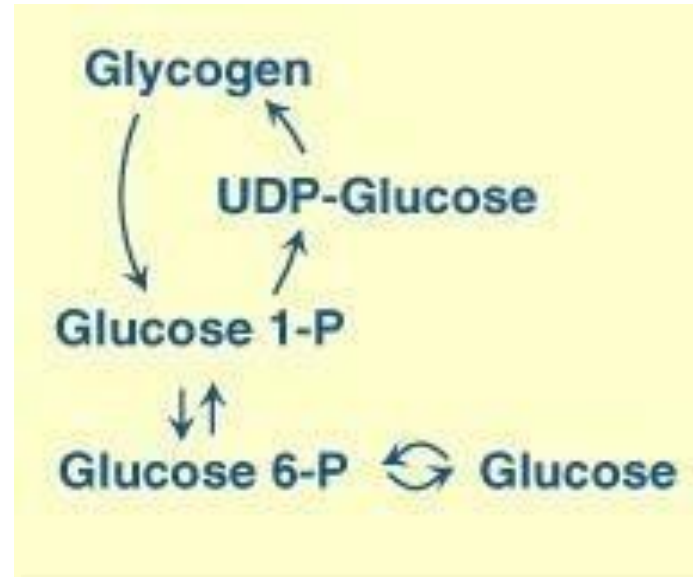




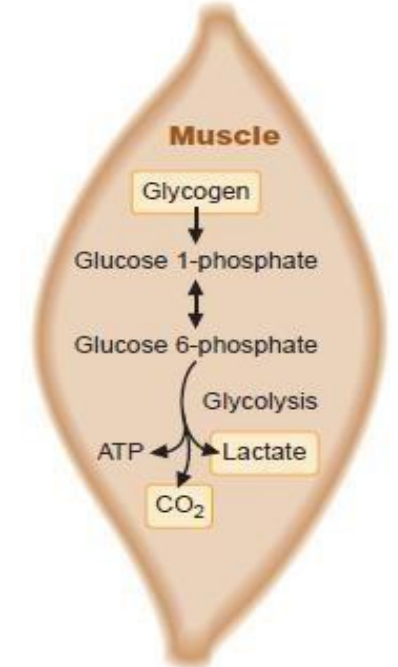
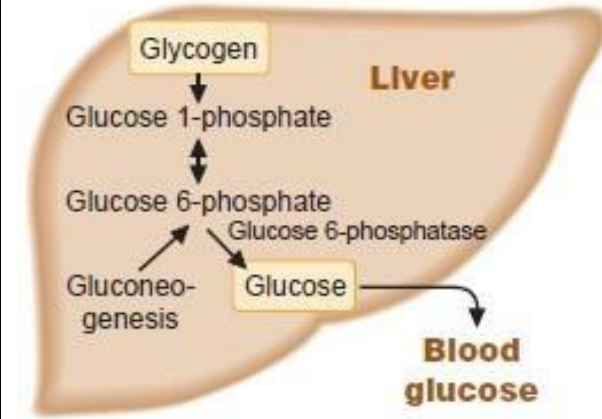
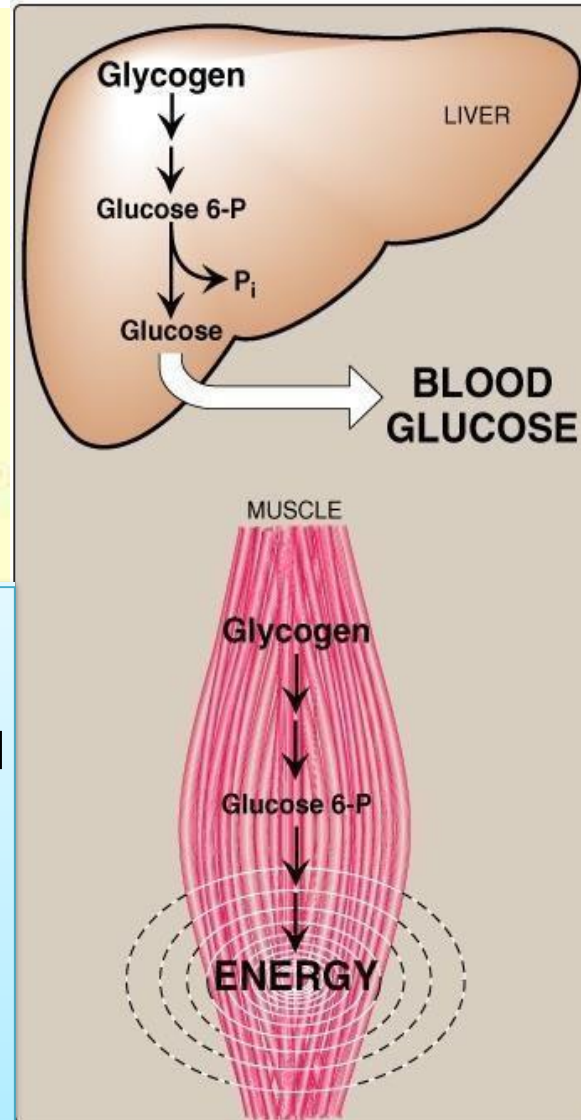
- Almost all ends of glycogen molecules are non-reducing ends. This is because the free carbon at these ends is carbon number 4 of the glucose residues, and the anomeric carbons (carbon number 1) are engaged in glycosidic bonds, making them unable to act as reducing agents. Only the very first glucose unit in the main chain retains a reducing end, but overall, glycogen primarily features non-reducing ends.

Glycogen synthesis & degradation

Notice that both the glycogen synthesis and degradation pathways involve only a few enzymes and steps, with many of the steps being repetitive.



- 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).



Fates of Glucose that results from glycogen degradation

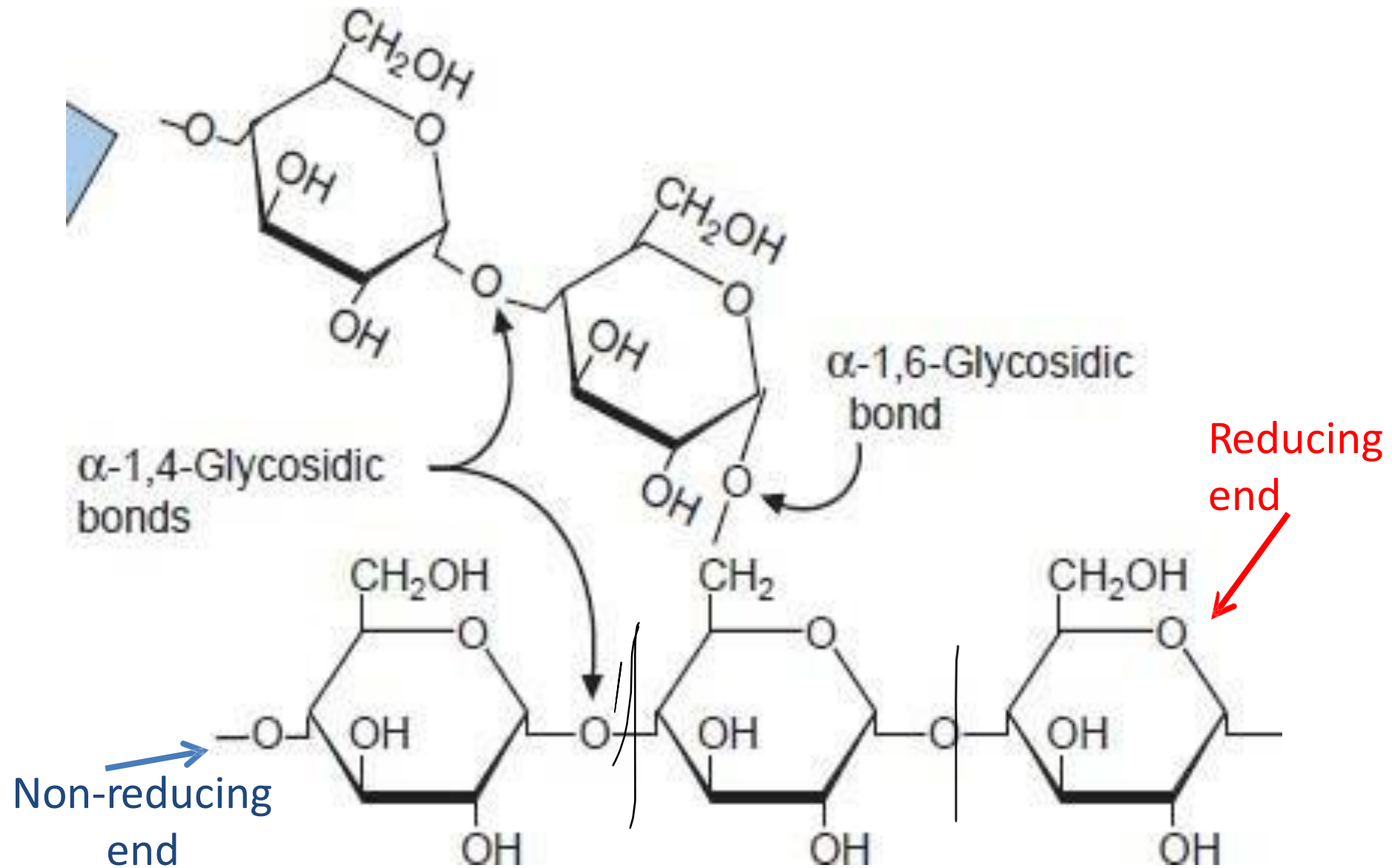
Explanation of the previous slide:

- ❖ Glycogen degradation involves repeating the same series of steps. Each time the reaction occurs, a glucose residue is released (cleaved from a non-reducing end) and immediately phosphorylated to glucose-1-phosphate. Glucose-1-phosphate is then isomerized to glucose-6-phosphate, which can either be dephosphorylated to release free glucose (in liver cells) or stay as is (in muscle cells)
- ❖ **In a well-fed state**, high glucose levels in the cell lead to phosphorylation of glucose to glucose-6-phosphate, trapping it inside the cell. This glucose-6-phosphate can either progress through glycolysis, enter the pentose phosphate pathway, or be converted to glucose-1-phosphate for glycogen synthesis. The glucose-1-phosphate is activated by attaching it to a nucleotide, forming UDP-glucose, which is used to add glucose residues to the growing glycogen chain, releasing UDP in the process.

IMPORTANT

- ❖ In hepatocytes, glucose generated from glycogen degradation (glycogen → glucose-1-phosphate → glucose-6-phosphate → glucose) is exported to the bloodstream through GLUT transporters, rather than using it themselves. This glucose supplies tissues that rely exclusively on glucose for energy, such as the brain, adrenal medulla, and red blood cells, helping to maintain blood glucose levels.
- ❖ Hepatocytes use fatty acids to supply themselves with energy since it's very active and needs a lot of energy.
- ❖ However in muscle cells, glycogen degradation only proceeds to glucose-6-phosphate. Muscles lack the enzyme glucose-6-phosphatase, so glucose-6-phosphate cannot be converted to free glucose and it's stuck inside the cell and is instead used internally for energy production through glycolysis. Muscle glycogen provides a longer-lasting energy source for muscular activity (unlike liver glycogen (only 75 grams)), with the duration depending on the level of physical exertion .

Direction of Glycogen Degradation



Explanation of the previous slide:

- ❖ Glycogen degradation, or regeneration, begins at the non-reducing ends of the molecule. Each time the reaction occurs, a glucose residue is released. However, this release does not happen automatically; it must have a certain enzyme to cut it, glycogen phosphorylase, is needed to cleave the alpha-1,4 glycosidic bonds. This enzyme-mediated cleavage occurs step-by-step, moving from the non-reducing ends toward the reducing end along the main chain or toward the branching points at alpha-1,6 linkages.

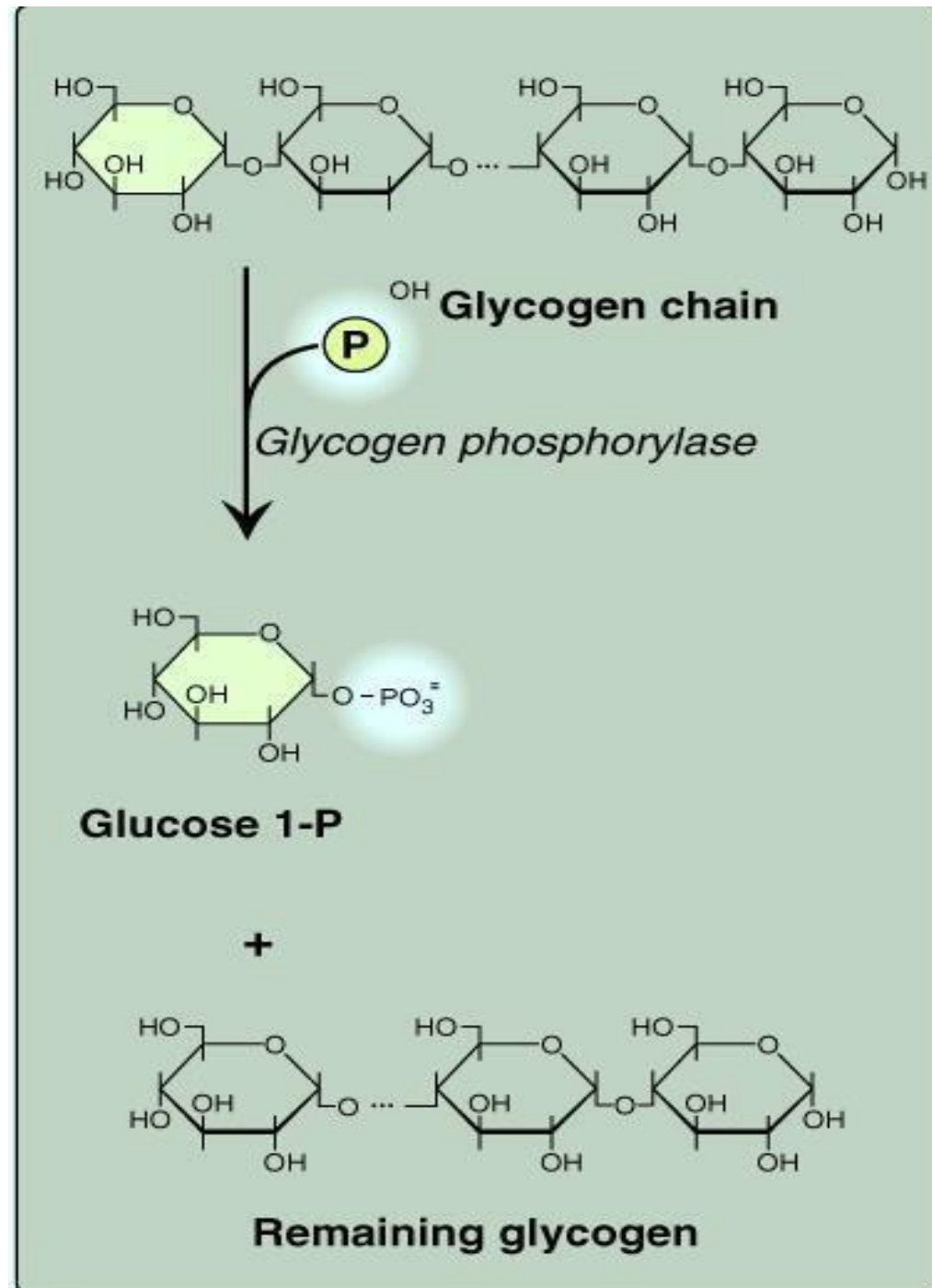
Degradation of glycogen (Glycogenolysis)

Major pathway

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



- The enzyme glycogen phosphorylase begins at the non-reducing end, breaking the α -1,4 glycosidic bonds and immediately phosphorylating glucose, releasing glucose-1-phosphate.

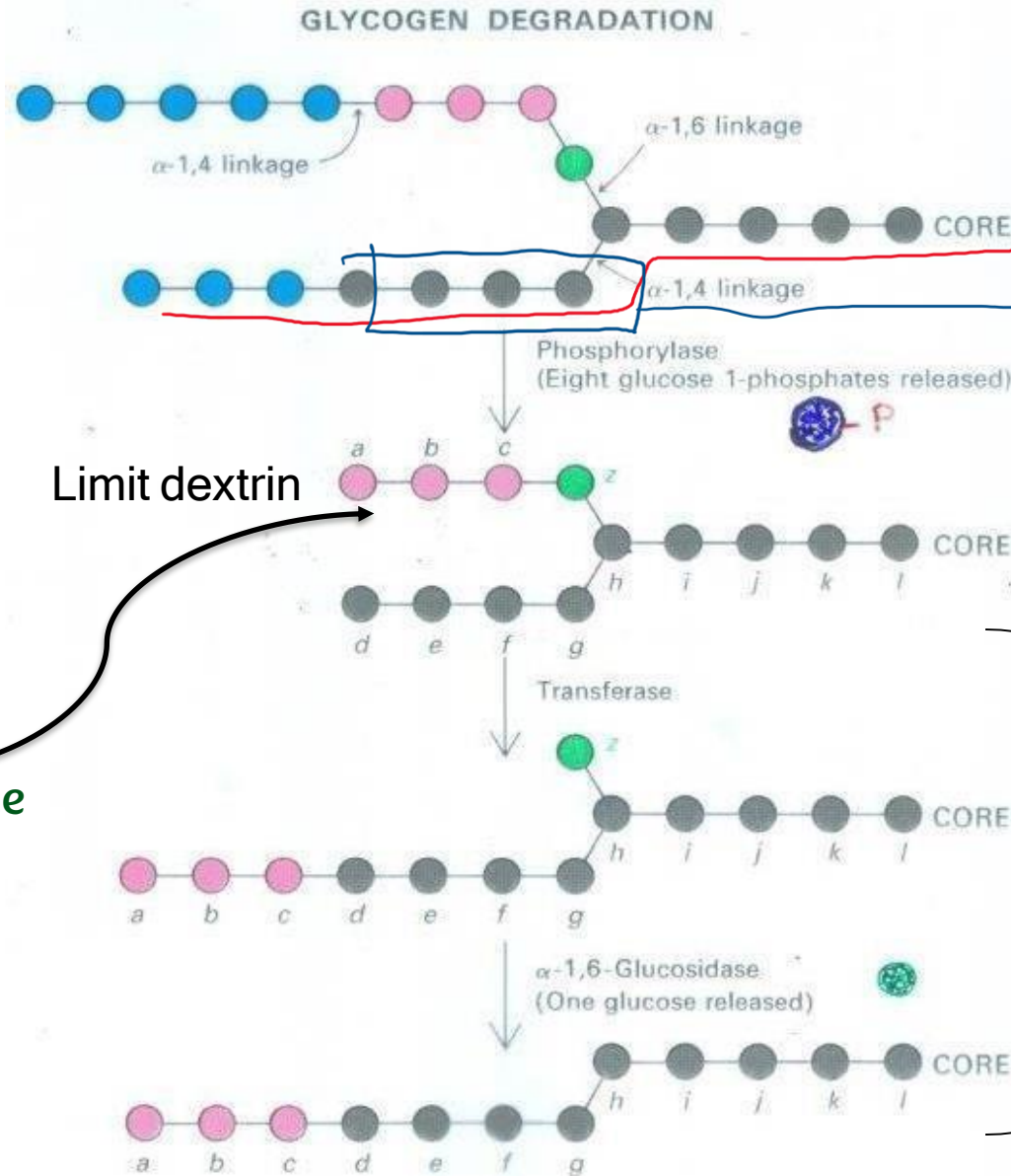
Glycogen Degradation

- When the enzyme (glycogen phosphorylase) reaches a point where only four glucose residues remain near a branch (these last residues are known as a "limit dextrin"), it stops. This **limit dextrin** acts as a barrier that glycogen phosphorylase cannot bypass.

- To handle these branches, another enzyme called the debranching enzyme is required. The debranching enzyme has two main functions:

1. **Transferase Activity:** It transfers three of the four remaining glucose residues from the branch to the main chain, making it a straight chain.

2. **Alpha-1,6 Glucosidase Activity:** It then cleaves the alpha-1,6 glycosidic bond of the last glucose residue, releasing it as free glucose (not glucose-1-phosphate).



Red line represents The main chain (not a branch)

Even though these four glucose residues are part of the main chain, they are positioned too close to the α -1,6 branch point for phosphorylase to remove them directly when the branch is there, requiring the involvement of debranching enzymes to complete their degradation if needed.

Debranching enzyme

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



- ❖ Once the branches are removed, glycogen phosphorylase can resume its activity on the straight chain. The released glucose-1-phosphate is then isomerized to glucose-6-phosphate by **phosphoglucomutase**. In the liver, glucose-6-phosphate is dephosphorylated to free glucose for release into the bloodstream, whereas in muscle cells, glucose-6-phosphate is used internally for energy production via glycolysis.

Lysosomal degradation of glycogen

It's a minor degradative pathway occur in lysosomes, as glycogenolysis is the major one. It occurs in the lysosomes (the digestive system of the cell)

- A small amount (1-3%) of glycogen is degraded by the lysosomal enzyme, $\alpha(1-4)$ -glucosidase (**acid maltase**) .

Lysosomes have an acidic environment (PH=5, while it's 7 in cytosol; 100-fold of H⁺ concentration difference!), so they have their own enzymes.

- The purpose of this pathway is unknown.
- **Despite that it's a minor pathway**, a deficiency of this enzyme causes accumulation of glycogen in vacuoles in the lysosomes (Type II: **Pompe disease**) *Very rare disease*
50 in the whole world! , no treatment

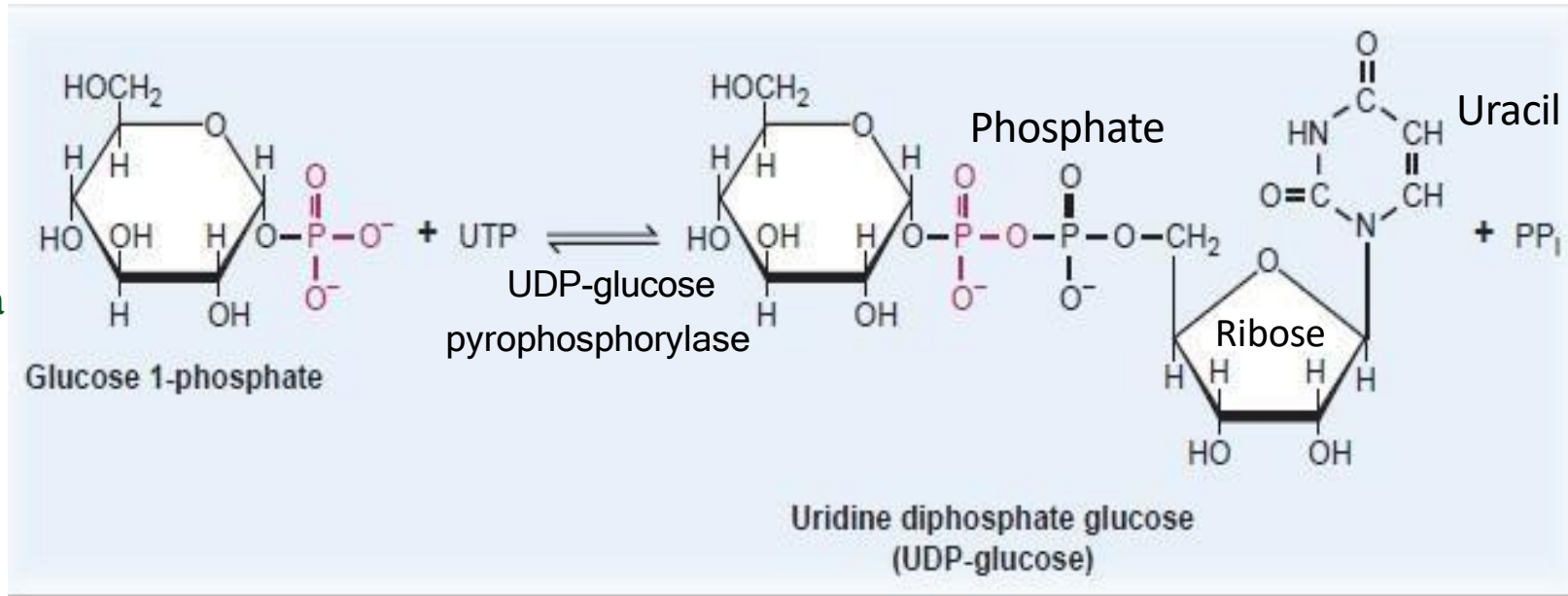
Glycogen Synthesis (glycogenesis)

Generation

Glycogenesis-Glycogen synthesis

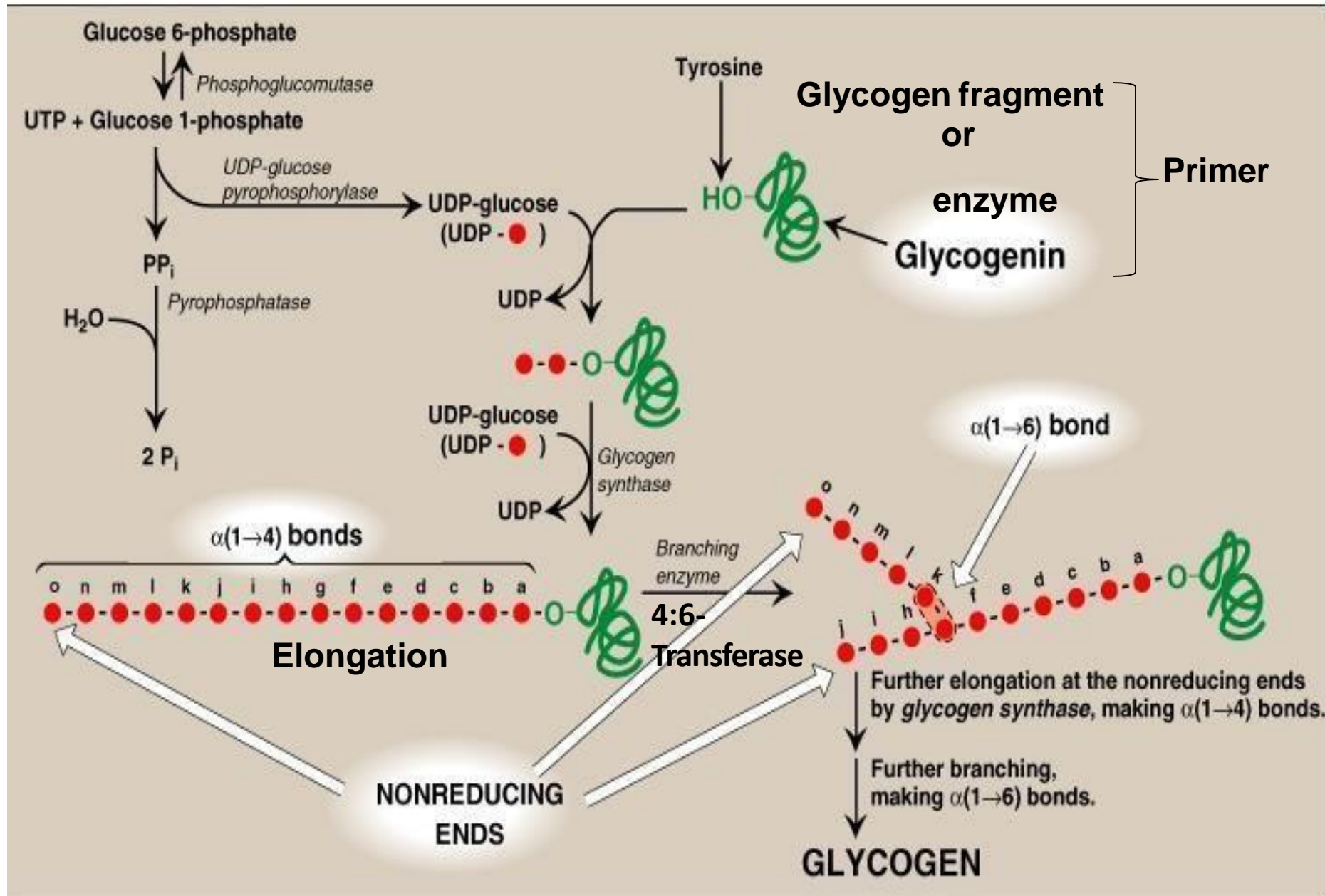
Glycogen is synthesized by adding glucose one by one.
UDP-Glucose is the active donor of glucose units.

Glucose is phosphorylated to Glucose 6-phosphate, via glucokinase or hexokinase (via help of glycolysis) then isomerized to make Glucose 1-phosphate



Formation of UDP-Glucose

Glycogen Synthesis



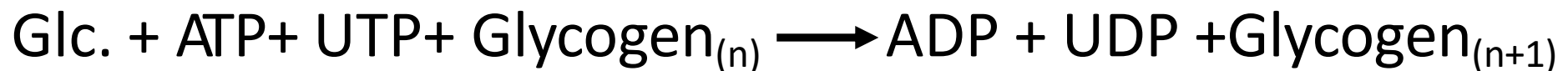
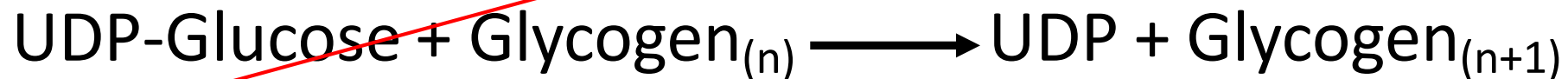
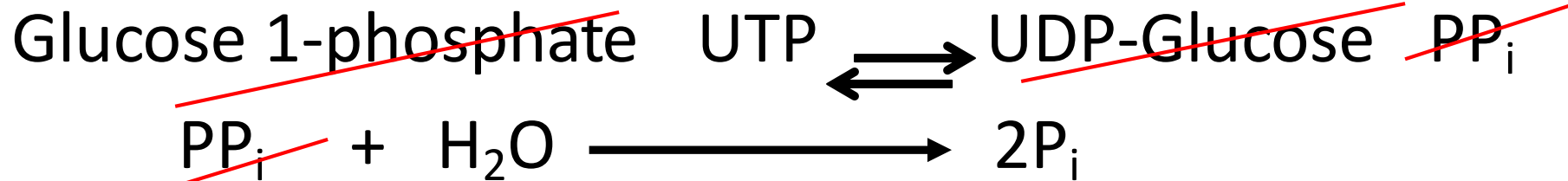
Explanation of the pic

To form UDP-glucose, **phosphoglucomutase** converts glucose 6-phosphate into glucose 1-phosphate. Then UDP-glucose pyrophosphorylase forms UDP-glucose & pyrophosphate which is hydrolyzed to 2 inorganic phosphates.

The construction of a glycogen structure involves starting with a base, which could either be glycogen fragments or the enzyme glycogenin. Glucose residues are added, with glycogen synthase facilitating this process to form a linear chain without branches. To introduce branching points, another enzyme called the branching enzyme (4,6- transferase) is used. It breaks the $\alpha(1-4)$ in the main chain and binds it to another residue via $\alpha(1-6)$ bond. As branching occurs, the process alternates between using glycogen synthase to elongate the main and branched chain(s) and the branching enzyme to introduce more branches. This pattern repeats until the structure has multiple branches, allowing it to reach 13 layers of branching.

Energy needed for glycogen synthesis

As it's a synthetic (anabolic) reaction, it needs energy.
Every glucose addition needs energy equal to 2 ATP (1 ATP and 1 UTP)

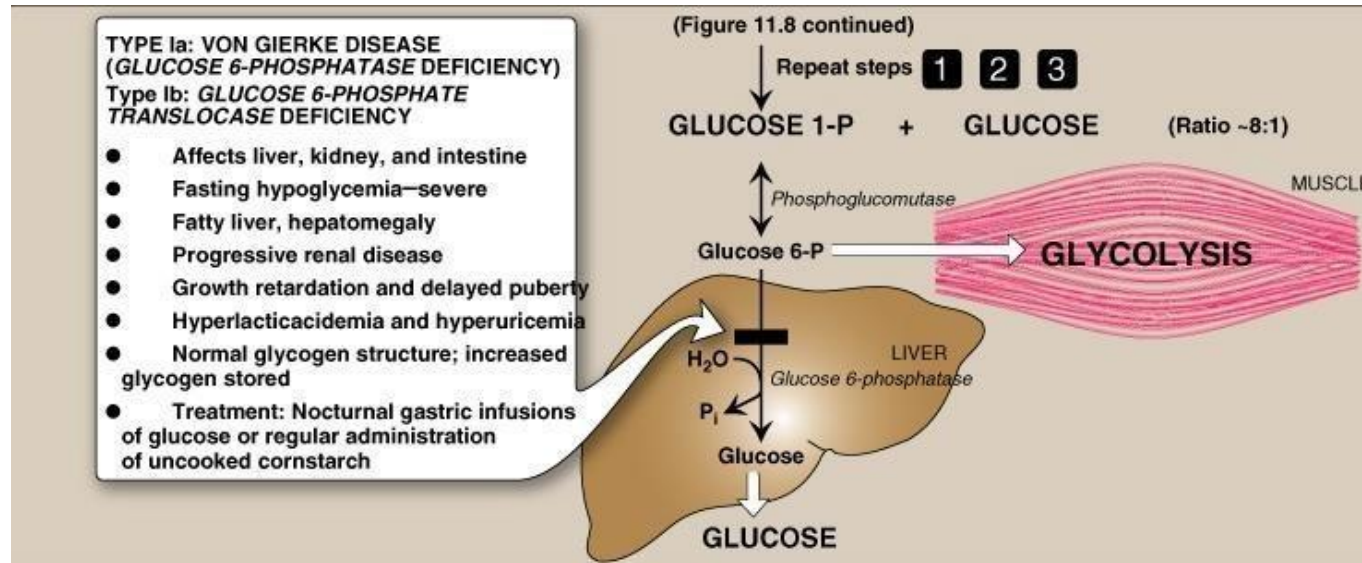


Glycogen Storage Diseases

- Genetic diseases
- Defect in an enzyme required for Abnormal glycogen structure synthesis or degradation →
- Accumulation of excessive amount of abnormal glycogen (a problem in synthesis (may look like amylose)) or normal glycogen (a problem in degradation)
- In one or more tissue
- Severity: FATAL in Infancy..... Mild disorder

Glycogen Storage Diseases

1. Glucose-6-phosphatase deficiency (von Gierke disease)



TYPE Ia: VON GIERKE DISEASE (GLUCOSE 6-PHOSPHATASE DEFICIENCY)
Type Ib: GLUCOSE 6-PHOSPHATE TRANSLOCASE DEFICIENCY

- Affects liver, kidney, and intestine
- Fasting hypoglycemia—severe
- Fatty liver, hepatomegaly
- Progressive renal disease
- Growth retardation and delayed puberty
- Hyperlactacidemia and hyperuricemia
- Normal glycogen structure; increased glycogen stored
- Treatment: Nocturnal gastric infusions of glucose or regular administration of uncooked cornstarch

Leads to accumulation of glucose 6-phosphate in the liver (less glucose in the blood) until gluconeogenesis is activated.

Muscles don't get affected as glucose-6-phosphatase isn't present there.

1. Liver, kidney and intestine.
2. Severe fasting hypoglycemia
3. Hepatomegaly fatty liver.
4. Normal glycogen structure.
5. Progressive renal disease.
6. Growth retardation.

Brain only uses glucose to get energy. If the glucose level in the blood is lower than its normal range, and the liver can't hydrolyze glucose 6-phosphate, then the brain doesn't get its energy need.

Glycogen Storage Diseases

2. Muscle glycogen phosphorylase deficiency (McArdle syndrome)

Skeletal muscle glycogen phosphorylase deficiency

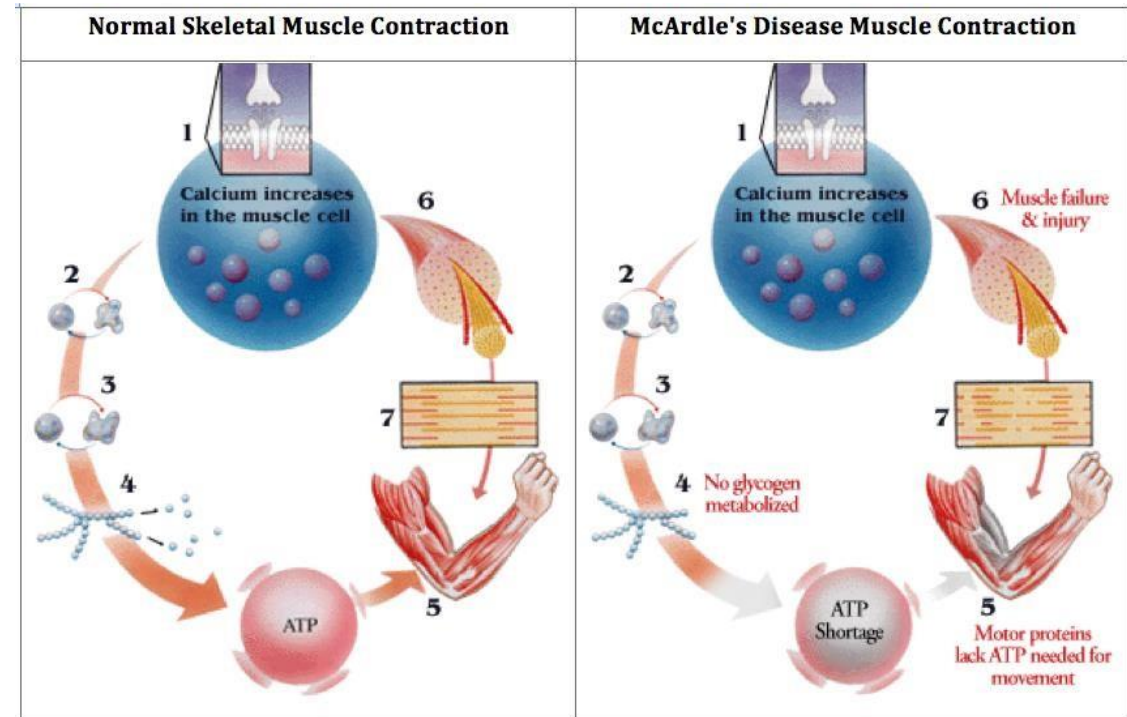
Only muscles are affected

In healthy people, the enzyme is present all over the body. However, in McArdle syndrome, the enzyme is present all over the body EXCEPT the skeletal muscle cells.

Weakness and cramping of muscle after exercise

No increase in [lactate] during exercise

Because the problem is in glycogenolysis, not glycolysis



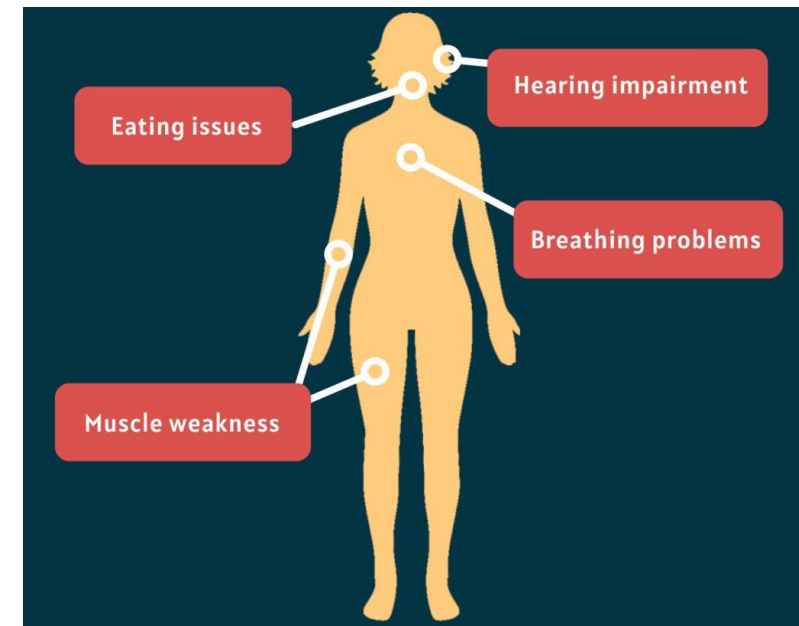
Glycogen Storage Diseases

And lysosomal storage disease

3. Lysosomes α (1-4) glucosidase -> POMPE disease

- Compromised degradation of glycogen in the lysosomes
 \approx 3% of glycogen is degraded in the lysosomes
- Affects liver, heart and muscle
- Excessive glycogen **accumulation** in abnormal vacuoles in the lysosomes
- Massive cardiomegaly
- Normal blood sugar, normal glycogen structure
No hypoglycemia
- So, disease is due to minor pathway
- Early death from heart failure

Symptoms depend on (time of onset, mutation, its location, and the severity)



Allosteric Regulation of Glycogen Metabolism

For both, synthesis & degradation

Glucose 6-P is the indicator of high glucose concentration!
When glucose is highly concentrated, it is phosphorylated to glucose 6-phosphate, and either goes to glycolysis or glycogenesis pathway.

Allosteric activator in well-fed state

Rapid response to cell's needs
Available substrate and ATP → synthesis

↓↓ Glucose and ↓ ATP → Glycogenolysis

Glucose isn't mentioned as a muscle regulator because it lacks the enzyme (glucose-6-phosphatase) that makes it.

Ending Intermediate

Indicates high energy state

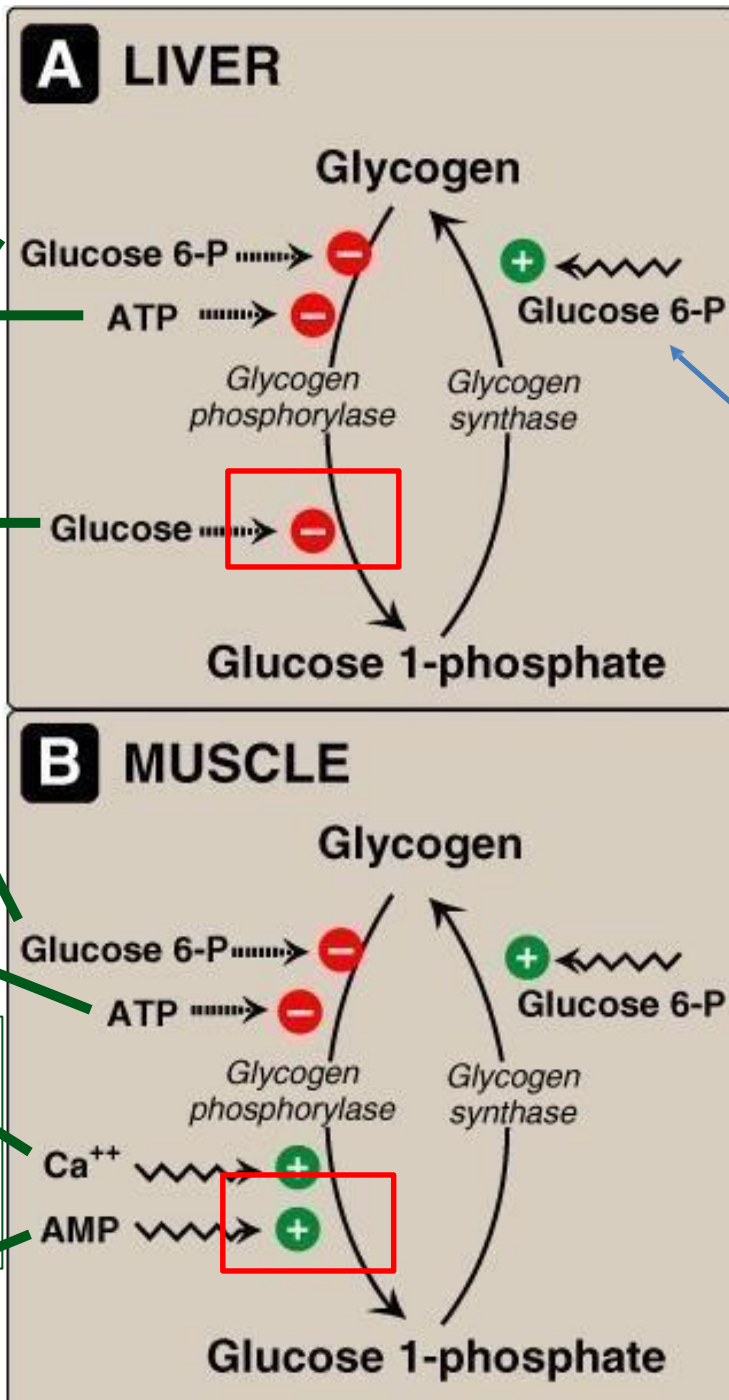
The final product

The final product in muscle cells

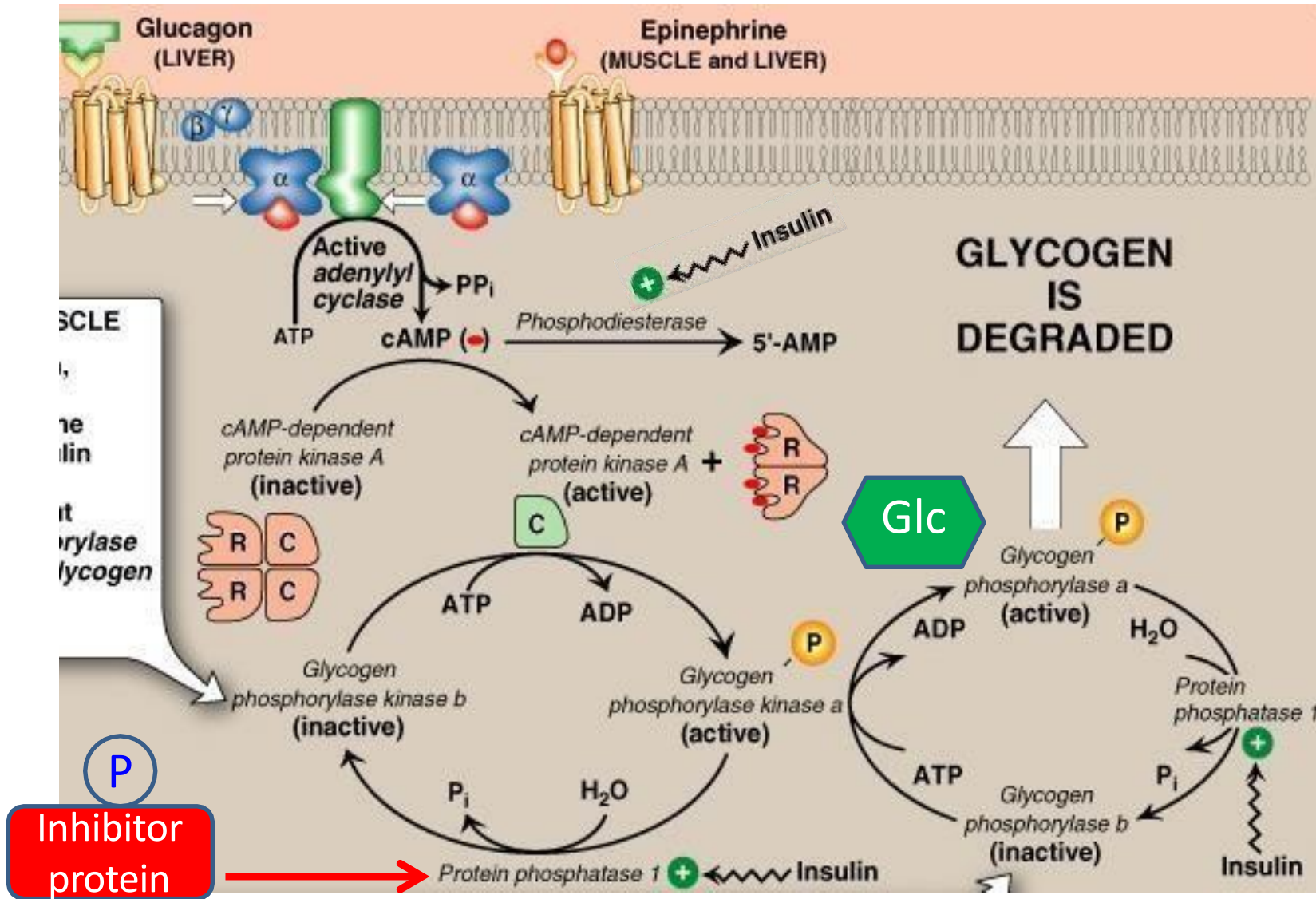
Indicates high energy state

Indicates the need of energy due to contraction

Indicates low energy state



Hormonal Regulation of Glycogen Metabolism



Explanation of the figure

1. Glucagon (liver) and Epinephrine (muscle and liver): These hormones activate adenylyl cyclase by binding to GPCR, making cAMP. Increased cAMP activates **protein kinase A (PKA) & releases the catalytic subunit.**

2. Glycogen phosphorylase kinase activation: The catalytic subunit phosphorylates and activates **glycogen phosphorylase kinase** (a regulatory enzyme), which then activates **glycogen phosphorylase**, which starts glycogen degradation.

3. Insulin: Insulin doesn't bind to GPCR, so none of the above occurs. It activates **protein phosphatase 1 (PP1)**, which dephosphorylates (inactivates) both glycogen phosphorylase and glycogen phosphorylase kinase, stopping glycogen breakdown. It also reduces cAMP levels, by activating phosphodiesterase, which changes cAMP to 5'-AMP, turning off PKA.

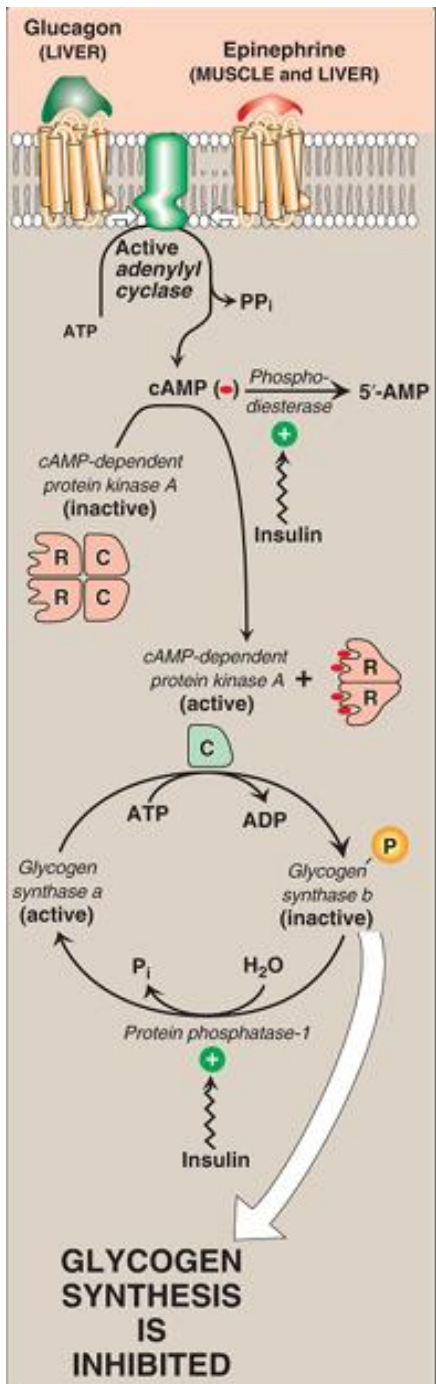
Shortly, **glucagon and epinephrine promote glycogen breakdown, while insulin promotes glycogen storage.**

Regulation of Glycogen Synthesis

Phosphorylation at different sites

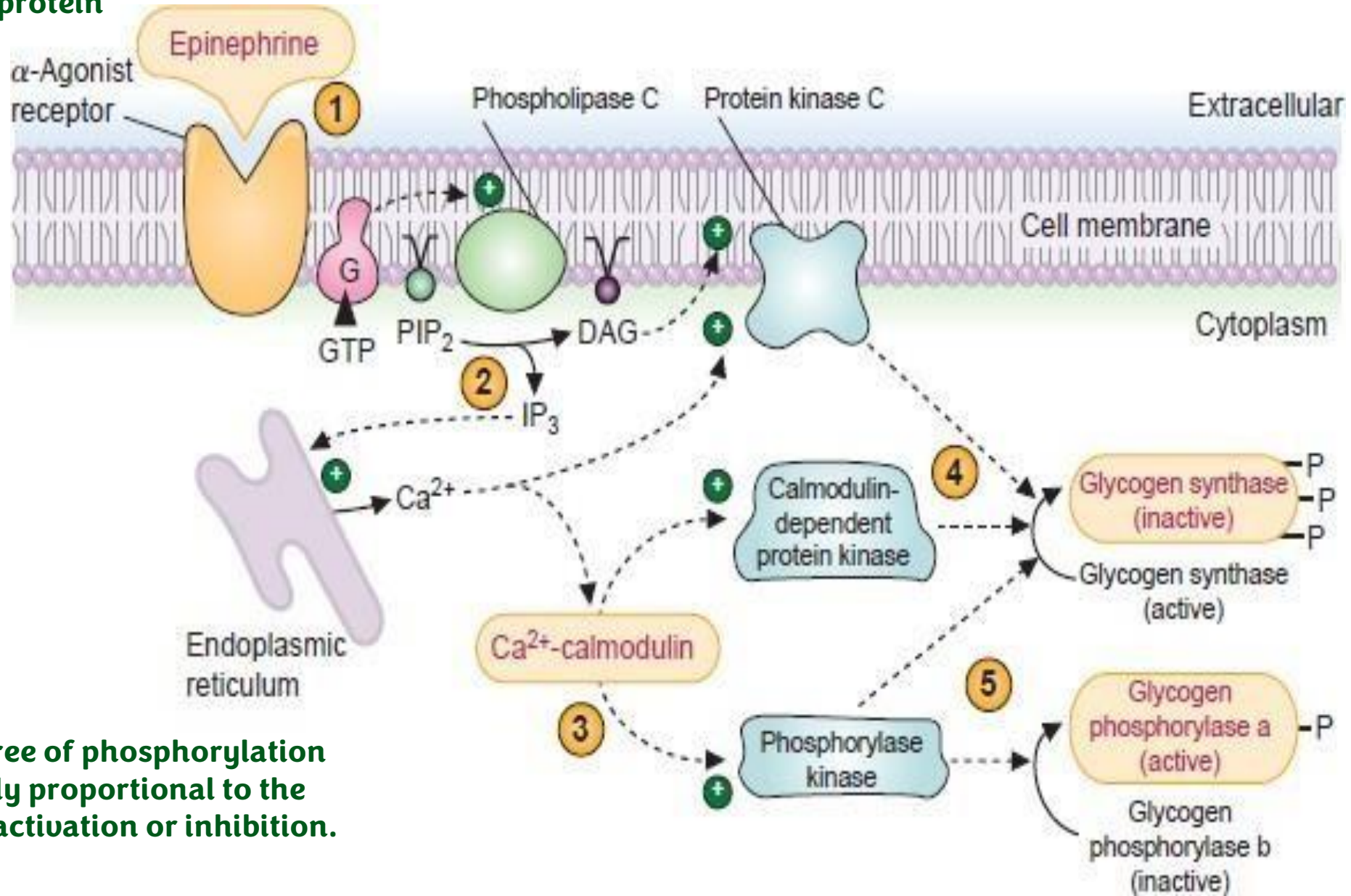
Inhibition is proportional to the degree of phosphorylation

Glucagon and epinephrine inactivate glycogen synthase. While insulin activates it to promote glycogen storage.



Hormonal Regulation of Glycogen Metabolism

Notice: another pathway of G-protein



The degree of phosphorylation is directly proportional to the level of activation or inhibition.

Explanation of the figure

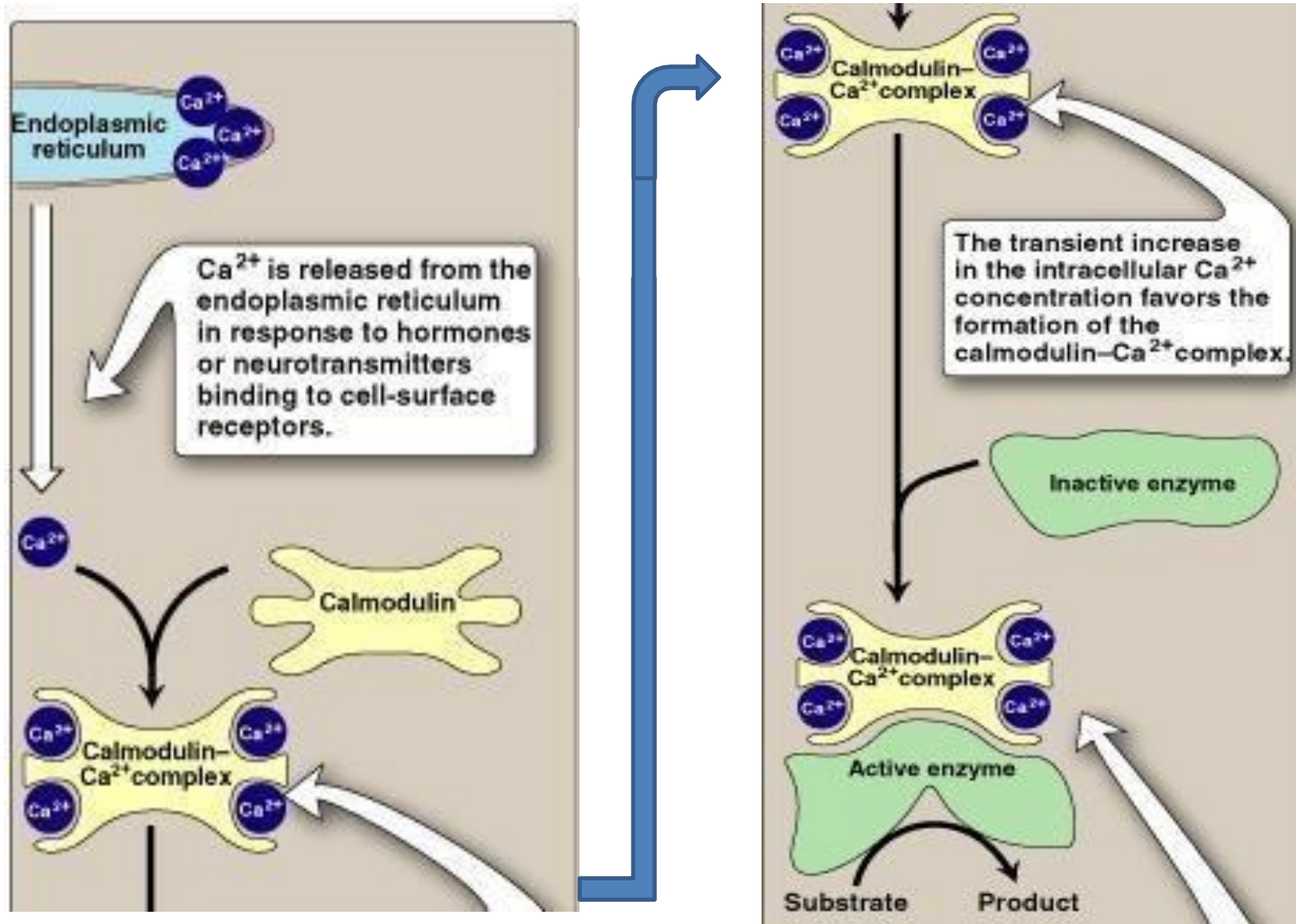
1. Epinephrine Binding: Epinephrine binds to an α -agonist receptor, activating a G-protein.
2. Signal Cascade Activation: The G-protein activates phospholipase C (degradative enzyme of phospholipids), which converts PIP₂ (3 phosphates) by removing all polar structures into IP₃ (the polar one) and DAG which stays in the membrane (both are second messengers).
3. Calcium Release: IP₃ exits the membrane and stimulates the release of Ca²⁺ from the endoplasmic reticulum to the cytosol by binding to IP₃ gated channels on the ER.
4. Inactivation of Glycogen Synthase: Ca²⁺ either activates protein kinase c, which phosphorylates and inactivates glycogen synthase, stopping glycogen synthesis, or Ca²⁺ binds to a protein called calmodulin making it active. Ca²⁺-calmodulin activates calmodulin-dependent protein kinase, which phosphorylates and inactivates glycogen synthase, stopping glycogen synthesis.
5. Activation of Glycogen Phosphorylase: Ca²⁺-calmodulin also activates phosphorylase kinase, which phosphorylates glycogen phosphorylase, activating it to degrade glycogen.

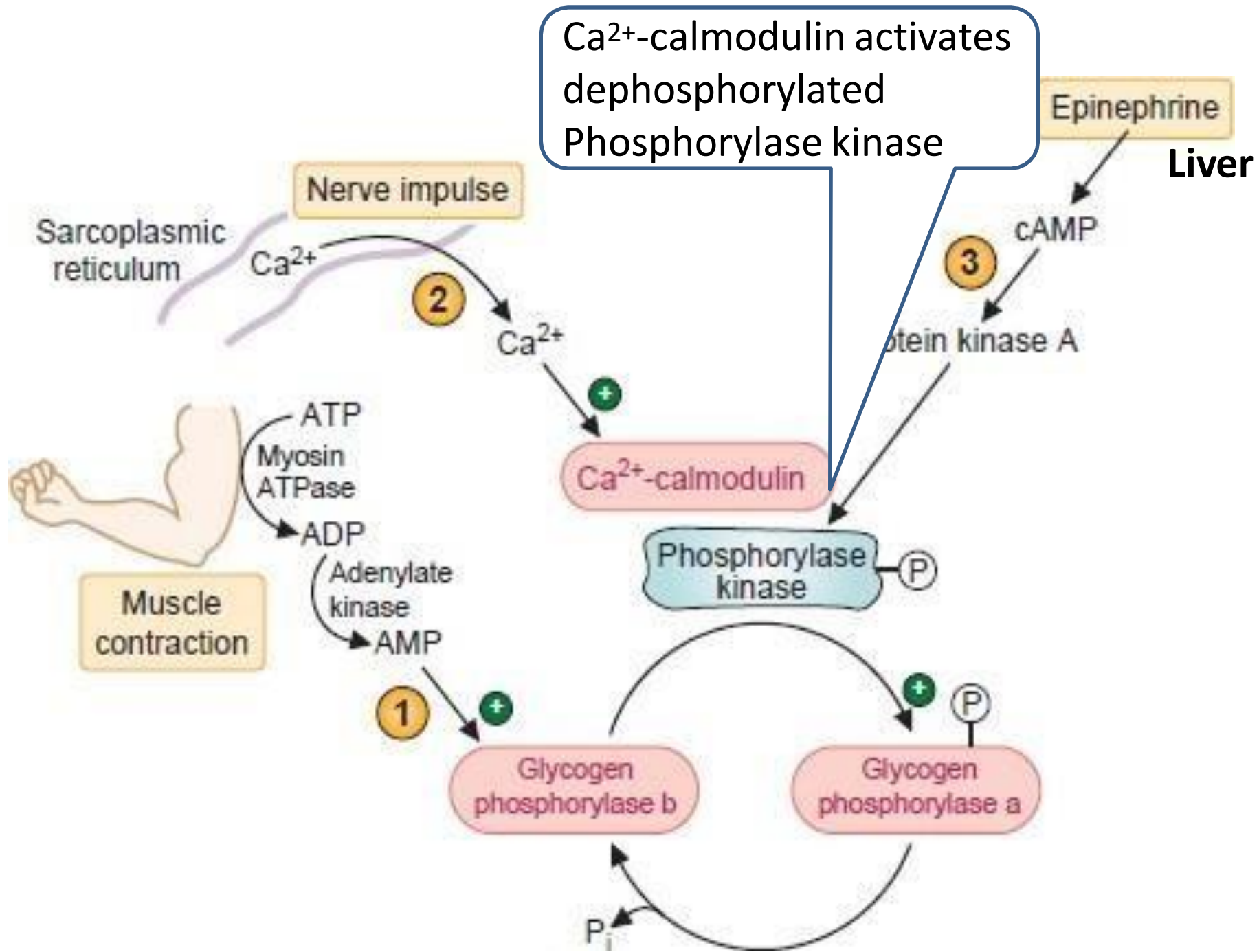
In summary, epinephrine also stops glycogen synthesis and promotes glycogen breakdown by using calcium as a messenger to regulate key enzymes.

(Recheck slide 33 for better understanding of the enzymes activated)

Ca²⁺ -Calmodulin Complex Function

Ca²⁺-calmodulin isn't a kinase (It doesn't phosphorylate)





Explanation of the figure

1. Muscle contraction: ATP is used by myosin ATPase, converting ATP to ADP. Adenylate kinase then converts ADP to AMP which is an allosteric regulator of muscle glycogen phosphorylase and activates it as mentioned earlier.
2. Nerve impulse: This triggers the release of Ca^{2+} from the sarcoplasmic reticulum(ER). Ca^{2+} binds to calmodulin, forming the Ca^{2+} -calmodulin complex, which activates dephosphorylated phosphorylase kinase, that activates glycogen phosphorylase.
3. Liver response: Epinephrine activates adenylyl cyclase, which increases cAMP levels. cAMP then activates protein kinase A, which phosphorylates phosphorylase kinase, promoting glycogen breakdown.

For any feedback, scan the code or click on



Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	Slide 5, first box on the left	The carbonate is converted to OH	The carbonyl is reduced
	Slide 8, bottom right	Lactic acidosis is the most common congenital cause of this metabolic imbalance	Lactic acidosis is the most common congenital consequence of this metabolic imbalance
	Slide 41, point 2	that activates glycogen phosphorylase kinase	that activates glycogen phosphorylase.
	Slide 41, point 3	Epinephrine activates adenylate cyclase	Epinephrine activates adenylyl cyclase

Additional Resources:

رسالة من الفريق العلمي:

Reference Used:

(numbered in order as cited in the text)

1. Lippincott's Illustrated Reviews:
Biochemistry 8th edition (137-148)

هو الطب المبارك من قديم
رجاه الناس إحسانًا فجادا
وفكّ طلاسّم اللغز المعادي
وطاب له على المرض الطرادا
فيا هذا الطبيب إليك شعري
على التمييز نصبًا والمنادى
لقد شُرِّفت عن غيرٍ كثيرًا
كما رمضان شُرِّف عن جمادى

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