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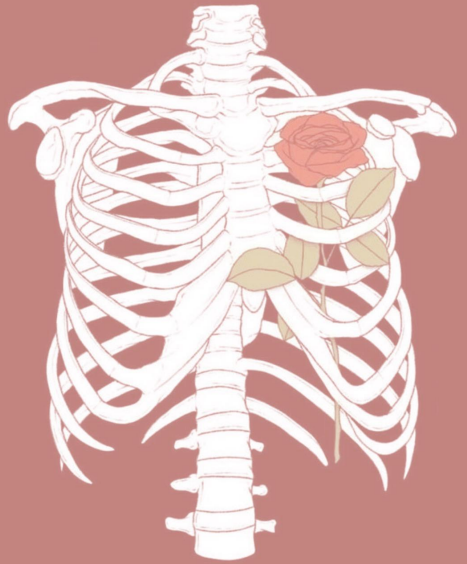
# Glycogen Metabolism



Color index :

Main text

IMPORTANT

Extra Info

Drs Notes

Muskuloskeletal Block - Biochemistry Team

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MED439

# Objectives:

- The need to store carbohydrates in muscle
- The reason for carbohydrates to be stored as glycogen
- An overview of glycogen synthesis (Glycogenesis)
- An overview of glycogen breakdown (Glycogenolysis)
- Key elements in regulation of both Glycogenesis and Glycogenolysis

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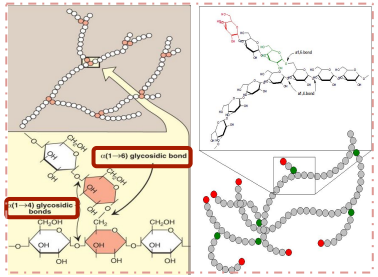
# Location and Function of Glycogen

| Location | Liver | Skeletal Muscle |
|---|---|---|
| Weight of Glycogen | 100 g | 400 g |
| Percentage of the total organ weight | Makes up 10% of well-fed liver (healthy adult liver) | Makes up 1-2% of resting muscles weight |
| Function | 1. **Major**: Source for blood glucose (especially during early stages of fasting 10-18 hours).<br>- (The glycogen in the liver maintains the blood glucose from 10 - 18 hours)<br>2. **Minor**: Fuel reserve for hepatic cell | - Fuel reserve (ATP) "during muscular exercise"<br>- In the muscles we don't want to make glucose, we want to make energy. |
| Pathway |  Glycogen → Glucose -6-P → Glucose ($P_i$) |  Glycogen → Glucose-6-P → Energy; Starting reactant in glycolysis |

# Structure of Glycogen

- **Glycogen**: is a branched-chain homopolysaccharide made exclusively from a- D-glucose.
- Glycogen is present in the **cytoplasm** in the form of granules (Contains all enzymes needed for glycogen) which contain most of the enzymes necessary for glycogen **synthesis** and **degradation.**




## Bonds in the Glycogen

- After 8-10 residues there is a branch containing a (1-6) glycosidic linkage.
- a (1 - 4) glycosidic linkage between Glucose residues

- **Residue**: means that the glucose molecule is a monomer in a polymeric branch (like starch or glycogen).
- The advantage of branching In Glycogen molecule:
  1. Stability
  2. Fast or Quick synthesis and degradation
  3. Increase the solubility of glycogen in water "inside the cytoplasm of the cell".
- The ratio of a 1-6 glycosidic linkage to 1-4 glycosidic linkage 1/10

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# Synthesis of Glycogen (Glycogenesis)

**1** Glucose 6-phosphate (6C) ⇌ (Phosphoglucomutase) Glucose 1-phosphate (6C)

- **Isomerization** of Glucose 6-phosphate to Glucose 1-phosphate with the help of **Phosphoglucomutase.**

**2** Glucose 1-phosphate (6C) → (UDP - Glucose Pyrophosphorylase) UDP - Glucose (6C)

- UTP In.
- $PP_i$ Out.

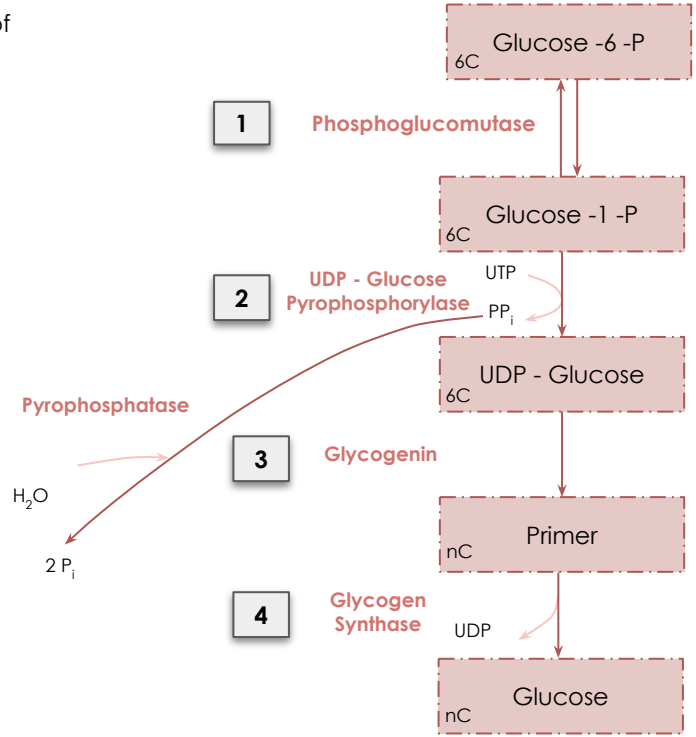
1. **Building blocks:** Synthesis (UDP- glucose. Uridine triphosphate (UTP) "a high-energy molecule" reacts with Glucose 1-phosphate to produce UDP-Glucose by the help of **UDP - Glucose Pyrophosphorylase.**

**3+4** UDP - Glucose (6C) → (Glycogenin) Primer (nC) → (Glycogen Synthase) Glucose (nC)

- UDP Out. ***R4***

2. **Initiation of synthesis:** The enzyme **glycogen synthase** (which makes a 1→4 linkages) can't initiate chain synthesis using free glucose. So, it elongates an already existing chain of glucose and therefore requires a primer.
- A fragment of glycogen can serve as a primer. In the absence of a glycogen fragment,a protein called glycogenin acts as a primer.
- **Production** of a chain of 4 glucose molecules connected by a (1, 4) bonds by the help of **Glycogenin**. This short chain acts as a primer for **Glycogen synthase** to continue elongation.
- Glycogenin has tyrosine. it's a protein and can add group of glucoses to itself until it becomes a ready fragment for glycogenesis.

3. **Elongation:** Using the enzyme **glycogen synthase** (which makes a 1→4 linkages)

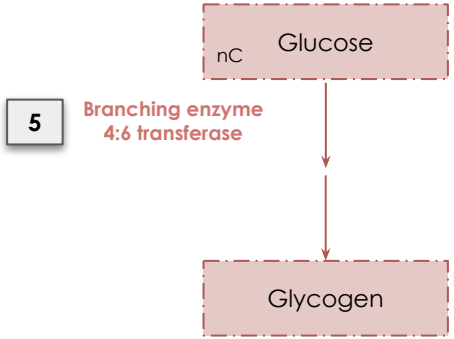


# Synthesis of Glycogen (Glycogenesis), Contd...

**5** Glucose(nC) —(Branching enzyme 4:6 transferase)→ Glycogen

4. **Branching:** Using branching enzyme (makes a 1→6 linkages).

- **Branching enzyme (4:6 transferase)** go to the end of the chains and cuts off "breaking the (a 1→4 linkage)" of 4-6 glucose residues in minimum. The branching enzymes transfer the 4-6 residues to a different site and making a (a 1→6 linkage) on the main chain.
- Further elongation at the nonreducing ends by glycogen synthase making (a 1→4 linkage) bonds.
- Further branching making (a 1→6 linkage) and that makes glycogen.



★ extra explanation

# Summary of the Glycogenesis in order for you to gain a better understanding In tables

| Reaction 1 | |
|---|---|
| Reactant | Glucose 6-phosphate |
| Product | Glucose 1- phosphate |
| Enzyme | **Phosphoglucomutase** |
| Action | Isomerization from G6P to G1P |
| Consume | - |

| Reaction 2 | |
|---|---|
| Reactant | Glucose 1- phosphate |
| Product | UDP-glucose complex |
| Enzyme | **UDP-glucose pyrophosphorylase** |
| Action | Formation of UDP glucose complex |
| Consume | UTP |

| Reaction 3 | |
|---|---|
| Reactant | UDP-glucose complex |
| Product | Primer |
| Enzyme | **Glycogenin** |
| Action | Elongation of an already existing chain of glucose and therefore requires a primer. |
| Consume | - |

| Reaction 4 | |
|---|---|
| Reactant | Glycogen + UDP-glucose complex |
| Product | Glucose - Glucose ... |
| Enzyme | **Glycogen synthase** |
| Action | Continue elongation. |
| Consume | - |

| Reaction 5 | |
|---|---|
| Reactant | Glucose - Glucose ... |
| Product | Glycogen |
| Enzyme | **Branching enzyme 4:6 transferase** |
| Action | 1-breaking the (a 1→4 linkage) of 4-6 residues minimum.<br>2-transfer the 4-6 residues to a different site and making a (a 1→6 linkage). |

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# Glycogenolysis

★ The reactants , products and enzymes are very important

**1** Glycogen chain —(Glycogen Phosphorylase + Debranching Enzyme)→ Glucose 1-phosphate (6C)

- The first step in the breakdown of glycogen is catalyzed by two enzymes which act independently.
- CoEnzyme: Pyridoxal Phosphate (PLP).

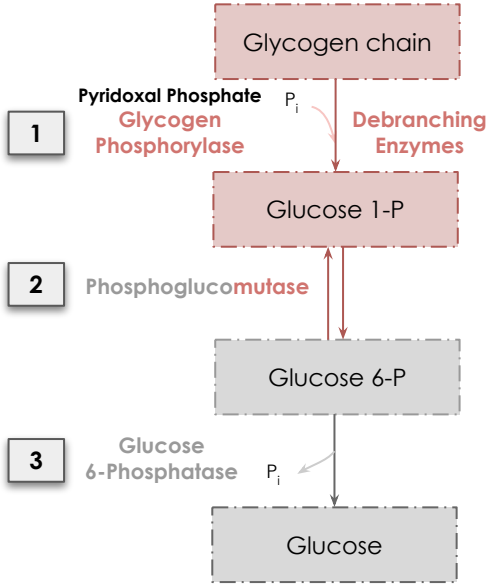
1. **Shortening of Glycogen chain**: The first enzyme, namely **glycogen phosphorylase** that is important in cleaving of a (1-4) bonds of the glycogen chain producing glucose 1-phosphate.The enzyme glycogen phosphorylase cannot cleave a 1-6 linkage so this is carried out by another enzyme called the debranching enzyme.
2. **Removal of Branches:** The second enzyme, **Debranching enzymes (4:4 transferase and a 1-6 glucosidase) 4:4 transferase** takes 3 glucose and bind them to another branch then **1-6 glucosidase** comes and it is important in cleaving of a (1-6) bonds of the glycogen chain producing free glucose "In few quantities because the majority of the bonds are a (1→4) bonds".

**2** Glucose 1-phosphate (6C) ⇌(Phosphoglucomutase) Glucose 6-phosphate (6C)

- **Isomerization** from Glucose 1-phosphate to Glucose 6-phosphate with the help of **Phosphoglucomutase**

**3** Glucose 6-phosphate (6C) —(Glucose 6-Phosphatase)→ Glucose (6C)

- $P_i$ Out.
- **Dephosphorylation** of Glucose 6-phosphate to Glucose with the help of **Glucose 6-Phosphatase** that takes place ONLY in liver and kidney.(Glucose 6-phosphate will enter the glycolysis to produce energy)
- Other than the liver and kidney, it won't be converted to free glucose.It is used as a source of energy for skeletal muscles during muscular exercise (by anaerobic glycolysis starting from G 6-P step).



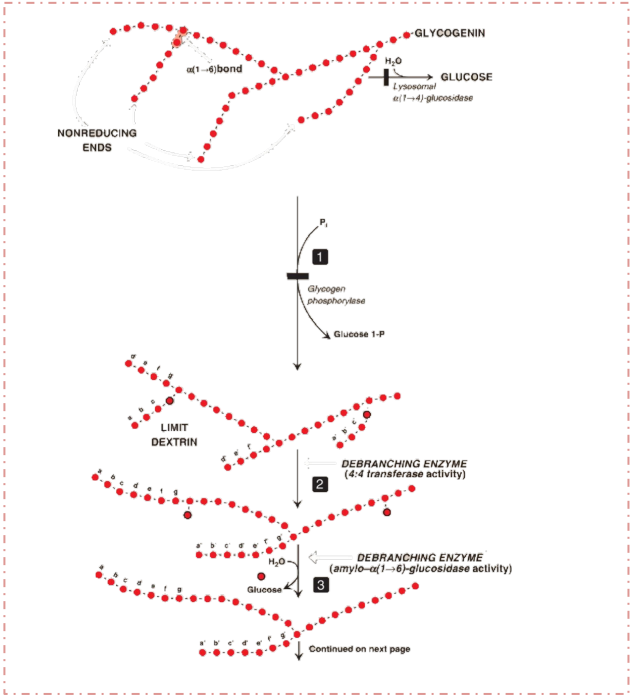
# Glycogenolysis

★ extra explanation

- **Limit Dextrin**: in this point the glycogen phosphorylase can`t continue shorting the chine (it remains).
- **Debranching Enzymes:**

1. **4:4 transferase:** take three glucose molecules by breaking a(1→4) bonds from one end and bind it to the other end.
2. **1:6 glucosidase:** it's the same enzyme above except that it unbinds the a(1→6) bonds.

- Every 8 molecules of G-1-P, one molecule of free glucose will be produced



★ extra explanation

## Summary of the Glycogenolysis in order for you to gain a better understanding In tables

| Reaction 1 | |
|---|---|
| Reactant | Glycogen chain |
| Product | Glucose 1-Phosphate |
| Enzyme | **Glycogen phosphorylase** |
| Action | Shortening of Glycogen chain and removal of Branches |
| Coenzyme | PLP (pyridoxal phosphate) |

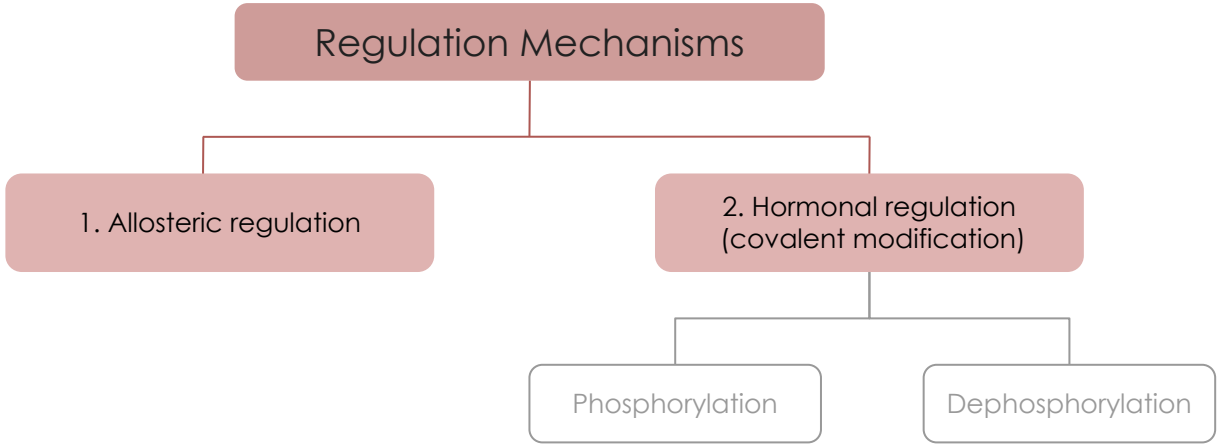
| Reaction 1, Contd.. | |
|---|---|
| Reactant | Glycogen chain |
| Product | Glucose 1-Phosphate + Free glucose |
| Enzyme | **Debranching enzymes** |
| Action | Take three glucose and bind them to another branch and then unbind the 1:6 linkage |

| Reaction 2 | |
|---|---|
| Reactant | Glucose 1-Phosphate |
| Product | Glucose 6-Phosphate |
| Enzyme | **Phosphoglucomutase** |
| Action | Isomerization from G1P to G6P |
| Consume | - |

# Regulation of Glycogen Metabolism

- Synthesis and degradation of glycogen are tightly regulated.
- In Skeletal muscles:

1. Glycogen degradation occurs during active exercise.
2. Glycogen synthesis begins when the muscle is at rest.



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# Regulation of Glycogen Metabolism

## "1- Allosteric regulation"

★ The enzymes are very important

1. Glycogen phosphorylase:

- **Inhibited by:**

a. Glucose 6-Phosphate (High energy signal in the cell and it's the end product of the pathway)

b. ATP (ATP is abundant, no need for more energy)

- **Activated by:**

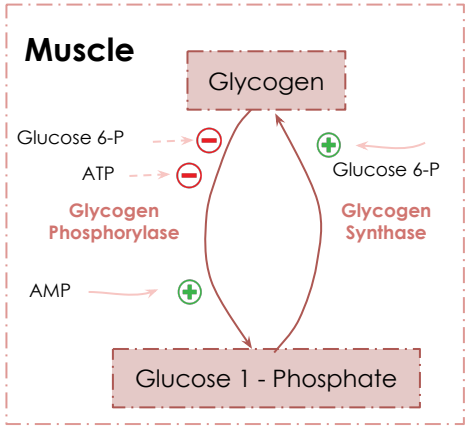
a. AMP (low energy signal).

b. $Ca^{++}$

2. Glycogen synthase:

- **Activated by:**

a. Glucose 6-Phosphate (High energy signal in the cell)



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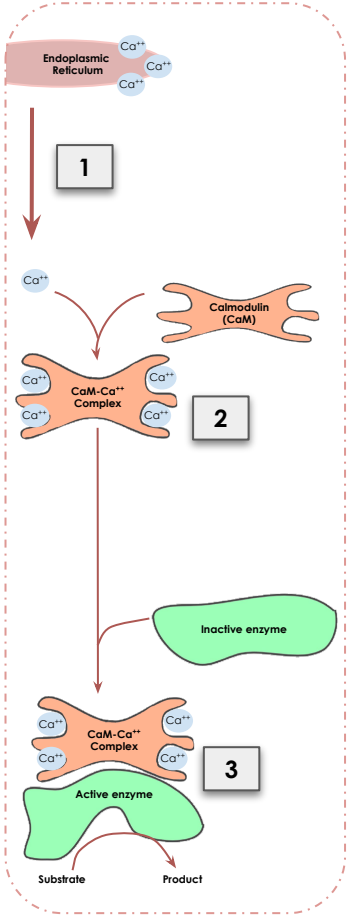
# Regulation of Glycogen Metabolism

## "1- Allosteric regulation, Contd..."

1. $Ca^{++}$ is released from the endoplasmic reticulum in response to hormones or neurotransmitters binding to cell-surface receptors.
2. The transient increase in the intracellular $Ca^{++}$ concentration favors the formation of the CaM-$Ca^{++}$ complex.
3. The CaM-$Ca^{++}$ complex is an essential component of many $Ca^{++}$ dependent enzymes.

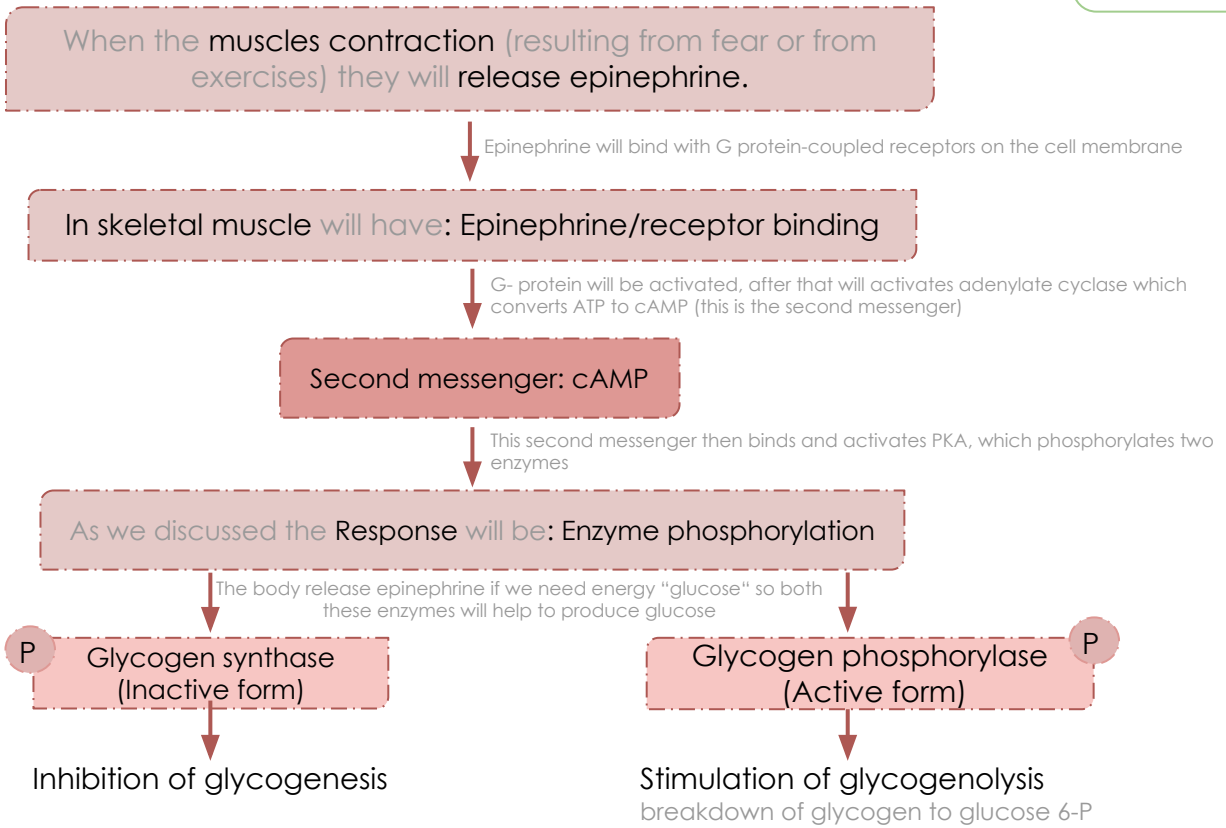
Exercising → Muscle contraction → Increase Calcium "Recall the mechanism of muscle contraction from physiology: the calcium comes out from sarcoplasmic reticulum during muscle contraction" → Formation of $Ca^{++}$ - Calmodulin Complex "Because of high concentrations of Ca++ intracellularly" → Activation of $Ca^{++}$ dependent enzyme e.g. Glycogen phosphorylase "Glycogenolysis"→ Glycogen degradation



# Regulation of Glycogen Metabolism
## "2- Hormonal regulation"

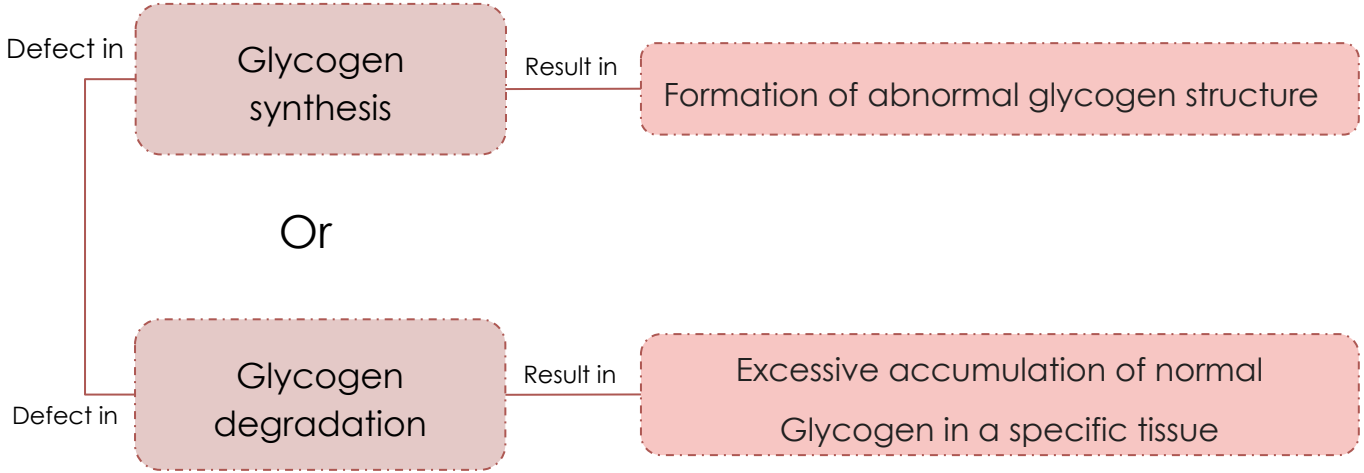
PKA : protein kinase A (cAMP- dependent protein kinase) Remember ?

- Covalent Modifications by epinephrine (Adrenaline).



# Glycogen Storage Diseases (GSDs)

- A group of genetic diseases that result from a defect in an enzyme required for :



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# Glycogen Storage Diseases (GSDs)

| GSD Type II (Pompe diseases) | GSD Type III (Cori disease) | GSD Type V (McArdle Syndrome) |
|---|---|---|
| • In liver, heart and skeletal muscle<br>• Deficiency of lysosomal a (1-4) glucosidase.<br>- Lysosomal storage disease<br>- Generalized (but primarily heart, liver and muscle).<br>- Excessive glycogen concentrations found in abnormal vacuoles in the lysosomes.<br>- Normal blood sugar level<br>- Massive cardiomegaly<br>- Enzyme replacement therapy available<br>- Infantile form: early death typically from heart failure.<br>- Normal glycogen structure. | • 4;4 Transferase and/or 1;6 glucosidase deficiency.<br>- Fasting hypoglycemia<br>- Abnormal glycogen structure with four or one glucosyl residues at branch points. | - In skeletal muscle.<br>- Skeletal muscle glycogen phosphorylase or myophosphorylase deficiency.<br>- Skeletal muscles affected: liver enzyme normal.<br>- Temporary weakness and cramping of skeletal muscle after exercise.<br>- No rise in blood lactate during strenuous exercise.<br>- Normal mental development.<br>- Myoglobinemia (increased myoglobin in blood) and myoglobinuria (increased myoglobin in urine) may be seen.<br>- High level of glycogen with Normal structure in muscle.<br>- Deficiency of the liver isoenzyme causes Type VI : Hers disease with mild fasting hypoglycemia. |

# Glycogen Storage Diseases (GSDs), Contd...

| GSD Type II (Pompe diseases) | GSD Type V (McArdle Syndrome) |
|---|---|
| • **General info:** Absence or deficiency of the lysosomal enzyme a-glucosidase which is required to breakdown the complex carbohydrate glycogen and convert it into the simple sugar glucose.<br>• **Symptoms:**<br>- Progressive proximal muscle weakness (trunk and lower limbs).<br>- Gait abnormalities.<br>- Muscle pain.<br>- Difficulty climbing stairs.<br>- Frequent falls.<br>- Scapular winging.<br>- Difficulty chewing or jaw muscle fatigue.<br>• **Prognosis:**<br>- These babies die before the age of one year. | • **General info:** body is not able to break down glycogen, due to Myophosphorylase defect.<br>• **Symptoms:**<br>- Usually start during early childhood, but diagnosis may not occur until a person is over 20 or 30 years old.<br>- Muscle cramps, pain, stiffness and weakness.<br>- Fatigue.<br>- Burgundy-colored urine.<br>- Exercise intolerance and poor stamina<br>• Prognosis:<br>- People with McArdle disease can live a normal life by managing their diet and physical activity. |

You should know the name of the disease, deficiency in which enzyme, general info about each disease and focus on the symptoms because the questions may coe as a case

# Quiz

| | | | |
|---|---|---|---|
| Q1 : Which one of the following site has the highest mass of glycogen? | | | |
| A ) Liver | B ) Skeletal muscle | C ) Lungs | D ) Kidney |
| Q2 : Which enzyme is responsible for elongation? | | | |
| A ) Glycogen synthase | B ) 4:6 transferase | C ) Glycogenin | D ) Phosphoglucomutase |
| Q3 : Which enzyme will take glucose molecules by breaking a(1→4) bonds from one end and bind it to the other end? | | | |
| A ) 4:4 transferase | B ) 1:6 glucosidase | C ) 1:4 transferase | D ) 1:6 transferase |
| Q4 : Which one of the following has role in stimulations of glycogenolysis? | | | |
| A ) AMP | B ) Ca calmodulin complex | C ) Epinephrine | D ) All of them |
| Q5 : Glycogen phosphorylase can be activated by: | | | |
| A ) UDP | B ) ATP | C ) ADP | D ) AMP |
| Q6 : Deficiency of glycogen phosphorylase enzyme will cause? | | | |
| A ) GSD type I | B ) GSD type II | C ) GSD type III | D) GSD type V |

## SAQs :

Q1: Parents brought their infant to the clinic because the infant had difficulty in breathing , after examination the doctor found an enlarged heart with non specific condition defects , what type of GSD does the infant have?

Q2: Enumerate two substrates that inhibit glycogen phosphorylase?

★ **MCQs Answer key:**

1) B 2) A 3) A 4) D 5) D 6) D

★ **SAQs Answer key:**

1) GSD type II POMPE disease
2) ATP and G-6-P

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- Alia Zawawi
- Noura Alshathri
- Reem Alamri
- Renad Alhomaidi
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- Bdoor Almobarak

## Boys team:

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- Nawaf Algarni
- Abdullaziz Alrabiah
- Abdullah Almazro
- Mishal Alhamed
- Omar Alsuliman
- Abdullah Alanzan
- Abdullaziz Alomar
- Ahmed Alkhayyat
- Hamad Almousa

"You can't have a better tomorrow if you're still thinking about yesterday"

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