جامعة الملك سعود
King Saud University

بِسْمِ اللهِ الرَّحْمَنِ الرَّحِيمِ

MED437 KING SAUD UNIVERSITY

BIO TEAM

Glycogen metabolism

Biochemistry Team 437

Color index:
Doctors slides
Notes and explanations
Extra information
Highlights

Musculoskeletal block

Objectives:

By the end of this lecture, students should be familiar with:

- 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

Location and Function of Glycogen

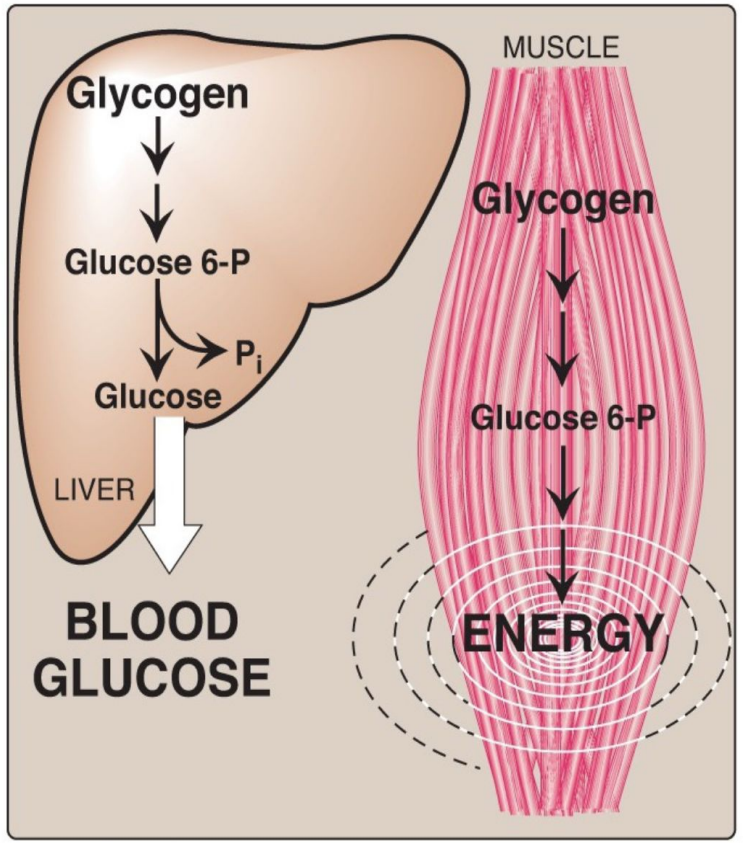
Liver

- 100 g in liver (~ 10% of well-fed liver)
- **Function:** a source for blood glucose (especially during early stages of fasting)

Skeletal Muscle

- 400 g in muscles (1-2% of resting muscles weight)
- **Function:** fuel reserve (ATP) (during muscular exercise)

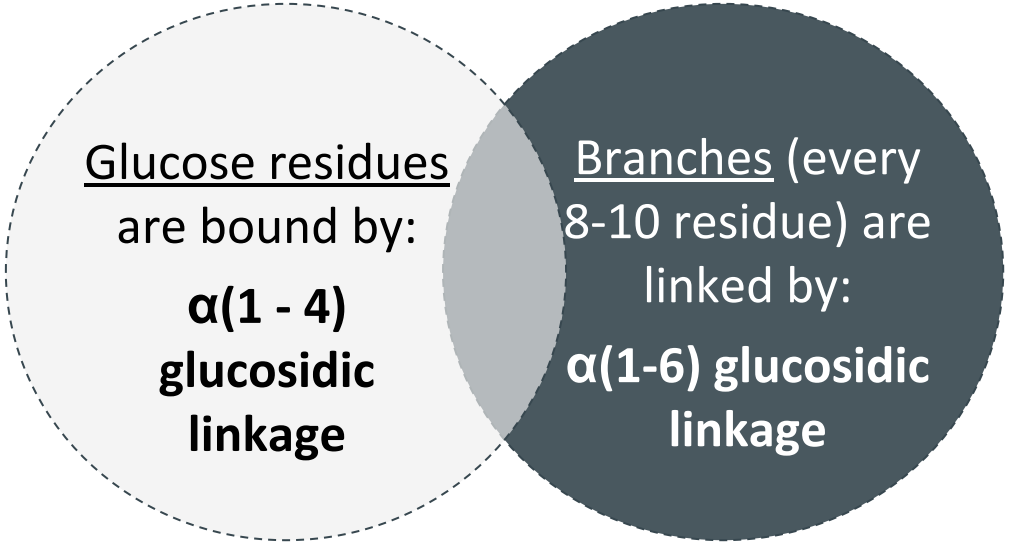
The glycogen here won't travel to the blood and instead is used to produce energy by anaerobic glycolysis

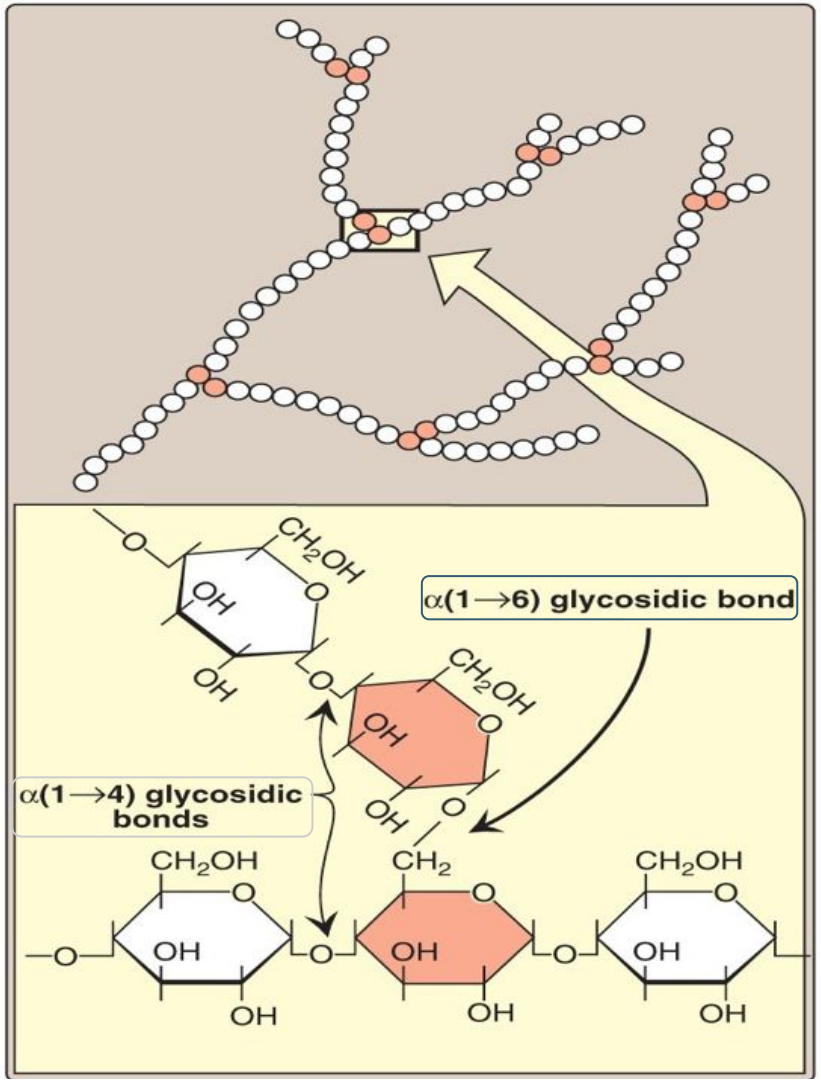


Structure of Glycogen

- Glycogen is a branched-chain homopolysaccharide made exclusively from **α- D-glucose**.
- Glycogen is present in the cytoplasm in the form of granules which contain most of the enzymes necessary for glycogen synthesis & degradation.
  - Homopolysaccharide: multiple copies of the same sugar unit.
  - Glycogen: multiple copies of glucose "polymer of glucose".

Bonds in Glycogen





Glycogenesis
(synthesis of glycogen in skeletal muscles)

Glycogenesis: Synthesis of Glycogen from Glucose

1) **Building blocks:** UDP-GLUCOSE

- Source of glucose molecules, UDP carries the glucose but it is not added to the elongated chain.

2) Initiation of synthesis (either by):

A. Elongation of pre existing glycogen fragment
B. The use of glycogen primer (glycogenin)

- Glycogen synthase can not make glycogen from nothing, it can only elongate a chain, so we add glucose to pre existing glycogen fragment, if there is no fragment we use the enzyme glycogenin, which has an autolytic activity to make a glycogen primer.

An autolytic enzyme is an enzyme acting on itself "the enzyme is its own substrate"
So glycogenin adds glucose to itself making a glycogen chain

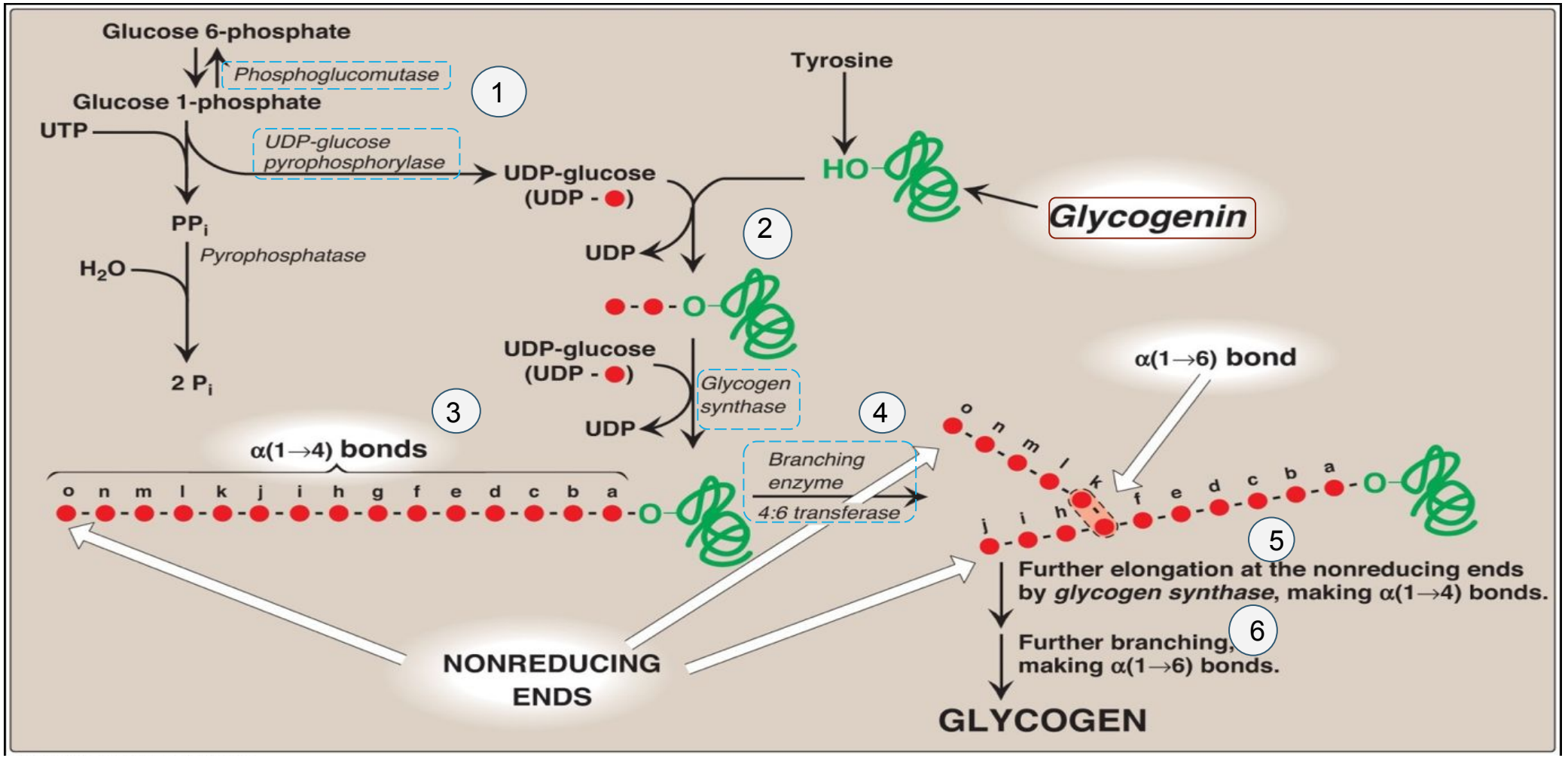
3) Elongation: Glycogen synthase (for α1-4 linkages)

- Glycogen synthase cannot initiate synthesis but only elongates pre-existing glycogen fragment or glycogen primer (glycogenin)

4) Branching:

Using Branching enzyme (for α1-6 linkages)

Synthesis of Glycogen



- Enzymes are important
- The red circles represent glucose

1) Glucose-6-phosphate $\xrightarrow{\text{phosphoglucomutase}}$ Glucose-1-phosphate

UTP + Glucose -1-phosphate $\xrightarrow{\text{UDP-glucose pyrophosphorylase}}$ UDP-Glucose

2) Glucose is added to the glycogen primer (glycogenin) and the UDP is free. The glycogenin can form bonds between two glucose molecules by removing UDP.

3) Elongation of the chain by forming (for α1-4 linkages) can be done by adding more glucose molecules and freeing UDP by the enzyme: Glycogen synthase

4) After 8-10 glucose the enzyme: Branching enzyme **4:6** transferase breaks the bond (α1-**4**) then adds it to anywhere in the chain by forming (α1-**6** linkages)

Explanation: Nonreducing end means it doesn't have an OH attached to the anomeric carbon, the more nonreducing ends the faster the glycogen synthesis and breakdown will be. So, branching makes glycogenesis faster because we'll have more reducing ends to add glucose to.

➢ More branching ⟶ more nonreducing ends ⟶ faster breaking down of glycogen and adding of glucose

Glycogenolysis
(Breakdown of glycogen in **skeletal muscles**)

Glycogenolysis: Breakdown of Glycogen to Glucose-6-phosphate

1) **Shortening of glycogen chain**: by glycogen phosphorylase (Glycogen phosphorylase contains a coenzyme: pyridoxal phosphate (PLP))

Pyridoxal Phosphate is a functional form of vitamin B6.

Cleaving of **α(1-4) bonds** of the glycogen chain producing **glucose 1-phosphate**
Glucose 1-phosphate is converted to **glucose 6-phosphate** (by mutase enzyme)

After it reaches 4 residues the enzyme will stop cleaving.

Mutase is a reversible enzyme

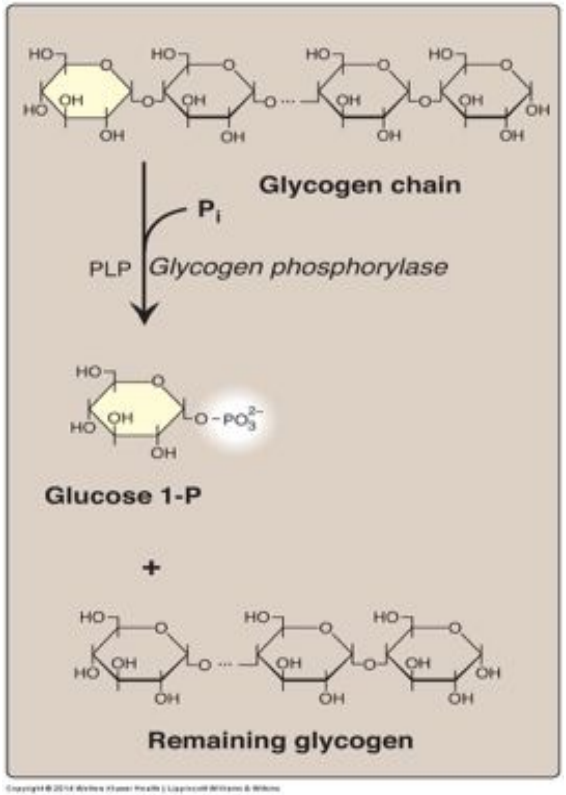
2) **Removal of branches** : by debranching enzymes
Cleaving of **α(1-6)** bonds of the glycogen chain producing **free glucose** (few quantities because the majority of the bonds are α (1,4) bonds)

3) Fate of glucose 6-phosphate (G-6-P):

- **G-6-P** is ***not*** 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)

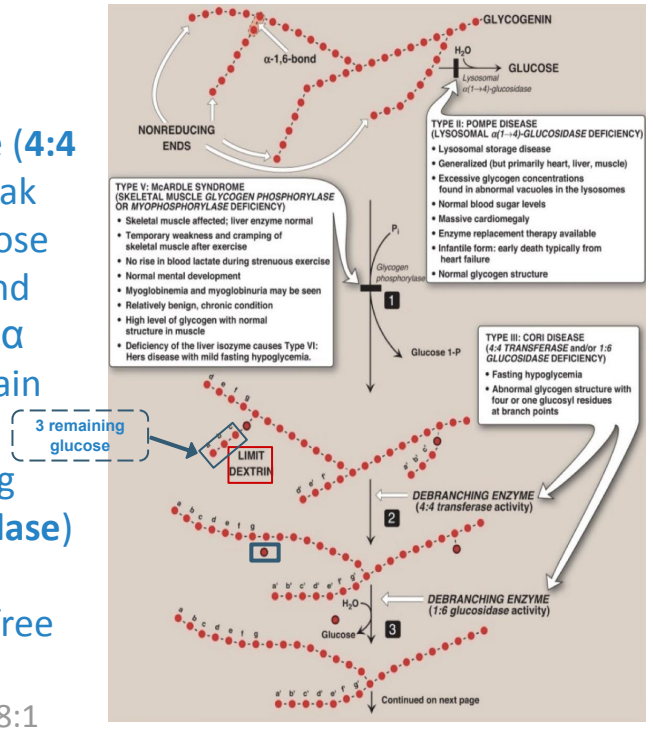
1

α(1-4) bonds of the glycogen chain will break to glucose 1-phosphate by the glycogen phosphorylase (cleaving) . this enzyme contains a coenzyme pyridoxal phosphate (PLP) which is a functional form of vitamin B6.
When glycogen phosphorylase reaches **4** residues before the branch, it will stop cleaving. These 4 residues are called **limit dextrin**



2

1. Limit dextrin stage
2. Debranching enzyme (**4:4 transferase**) will break the 3 remaining glucose with α(1-4) bonds and add it again to other α (1-4) bond on the chain
3. Another debranching enzyme (**1:6 glucosidase**) will break the α(1-6) bonds resulting in a free glucose.
4. The free glucose rate is 8:1
1 glucose for every 8 residues



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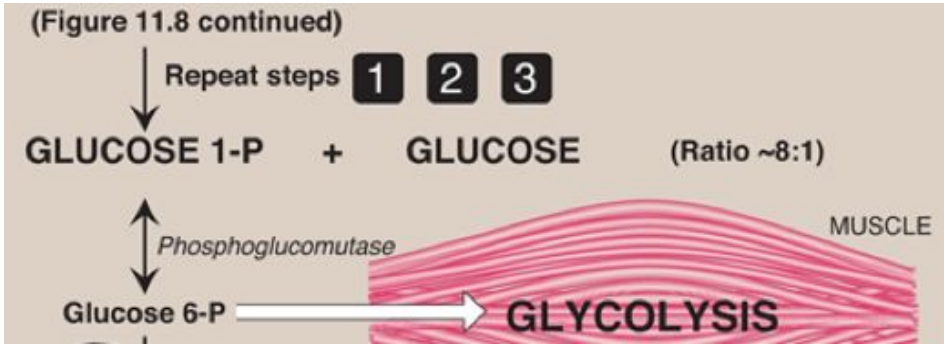
glucose 1-P will convert into glucose 6-P by the action of mutase enzyme (**phosphoglucomutase**)

during muscular exercise anaerobic glycolysis will starting from G-6-P step which will be a **source of energy for skeletal muscles**

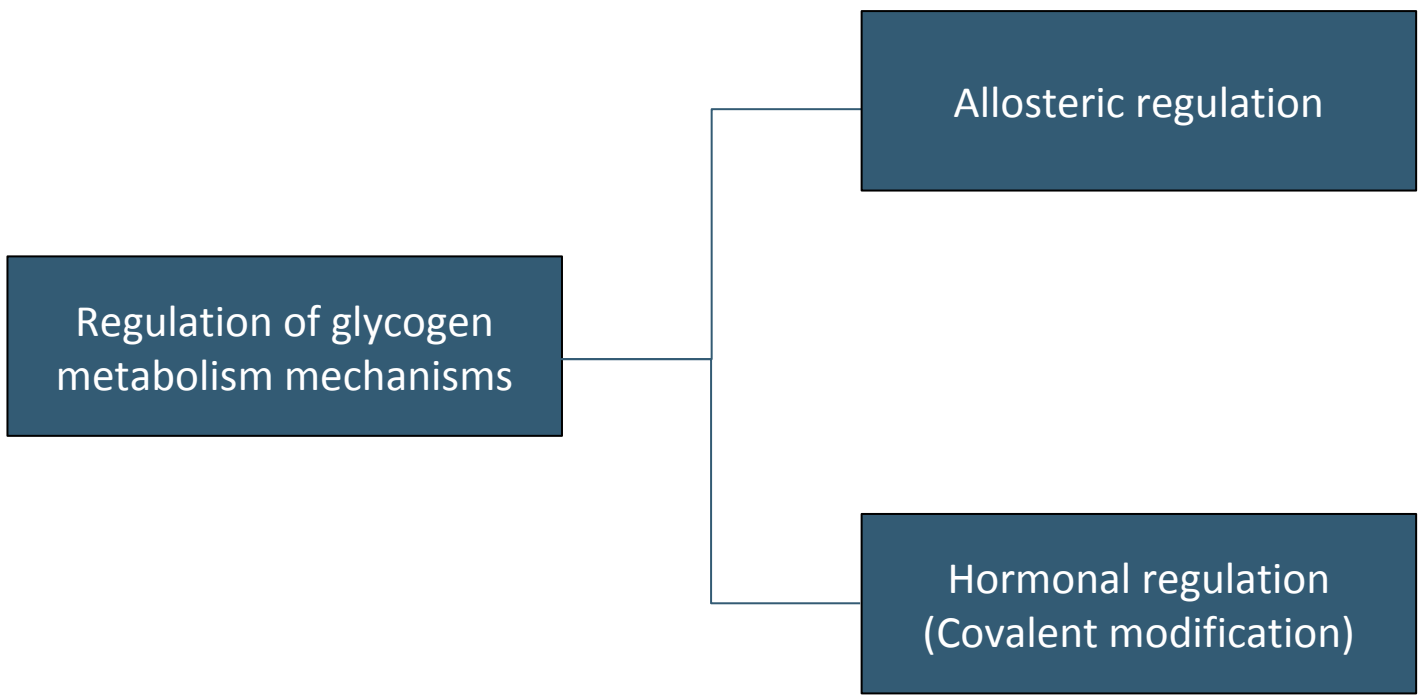


Regulation of Glycogen Metabolism

- Synthesis & degradation of glycogen are tightly regulated

In SKELETAL MUSCLES:

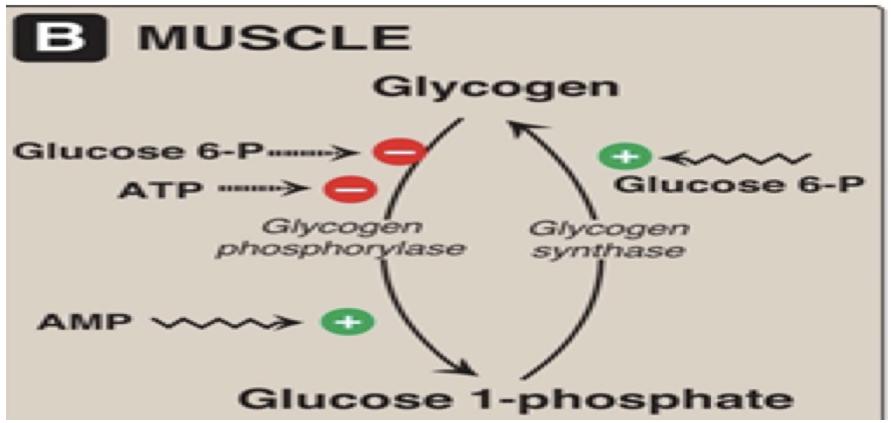
- Glycogen degradation occurs during active exercise
- Glycogen synthesis begins when the muscle is at rest



Remember:

- Allosteric regulation by affecting molecules
- Hormonal regulation (Covalent modification) by phosphorylation(adding phosphate) which can be activation or inactivation

1- Allosteric Regulation

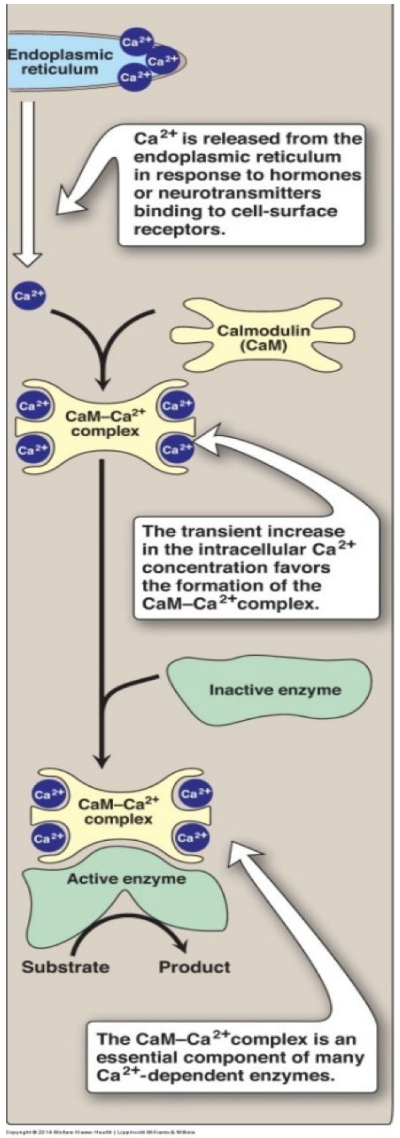


From Glycogen to Glucose 1-phosphate Glycogenolysis	From Glucose 1-phosphate to Glycogen Glycogenesis
Activation molecules: 1- AMP (when it is abundant it will activate the Glycogen phosphorylase) 2- Ca^{+2} (explained on the right) **Inhibition molecules:** 1- Glucose 6-phosphate 2- ATP (When they are abundant they will inhibit the Glycogen phosphorylase)	**Activation molecules:** Glucose 6-phosphate (When it is abundant it will activate the glycogen synthase)

Increase of calcium during muscle contraction "the calcium that is stored in the endoplasmic reticulum comes out during muscle contraction".

Formation of Ca^{+2} -calmodulin complex "because of high concentration of Ca+2 intracellularly".

Activation of Ca^{+2} -dependent enzyme, e.g. glycogen phosphorylase.



2- Hormonal Regulation

Hormonal regulation (covalent modification)

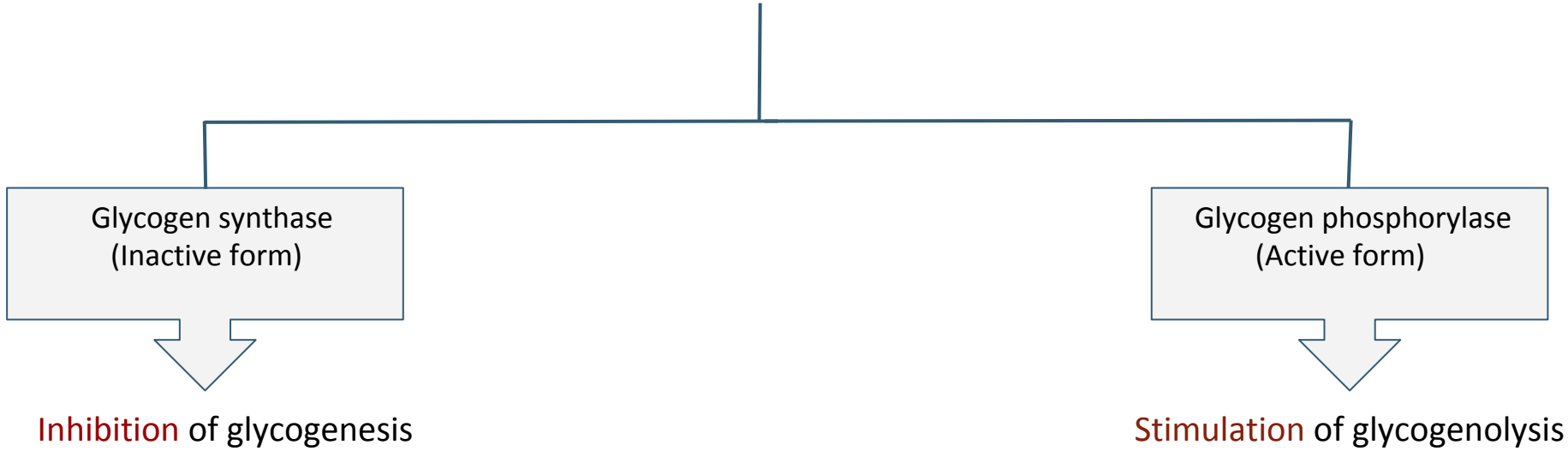
e.g: during exercise

Muscle contraction = Epinephrine release

Skeletal muscles: Epinephrine/receptor binding

Second messenger: cAMP

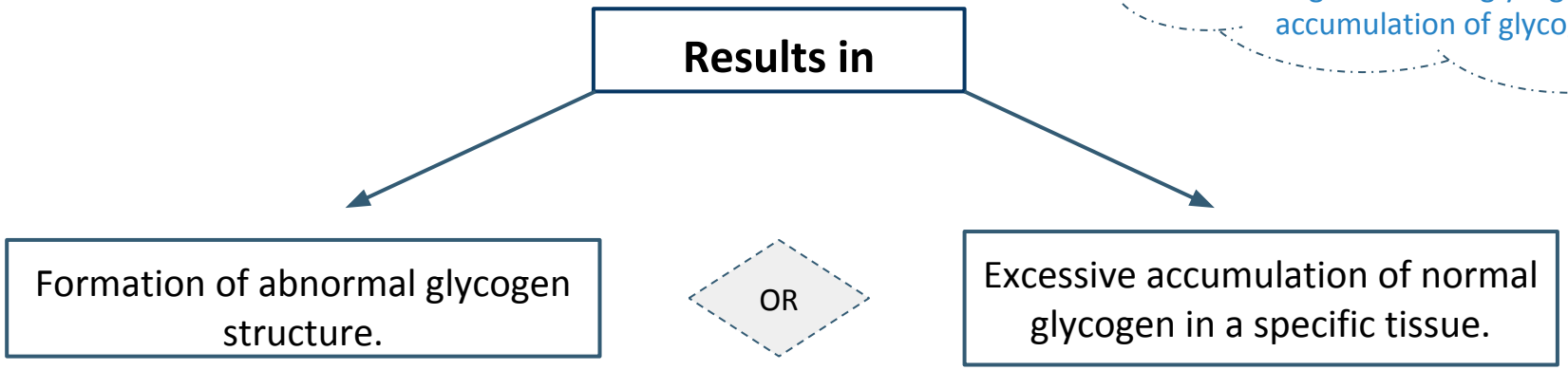
Response: Enzyme phosphorylation



Glycogen Storage Diseases (GSD)

A group of genetic diseases that result from a defect (نقص) in an enzyme required for glycogen synthesis or degradation.

GSD: Either that the glycogen produced is not correct structurally or glycogen is not degraded properly(deficiency of enzymes that are participating in the degradation of glycogen) Which causes accumulation of glycogen in the cell.



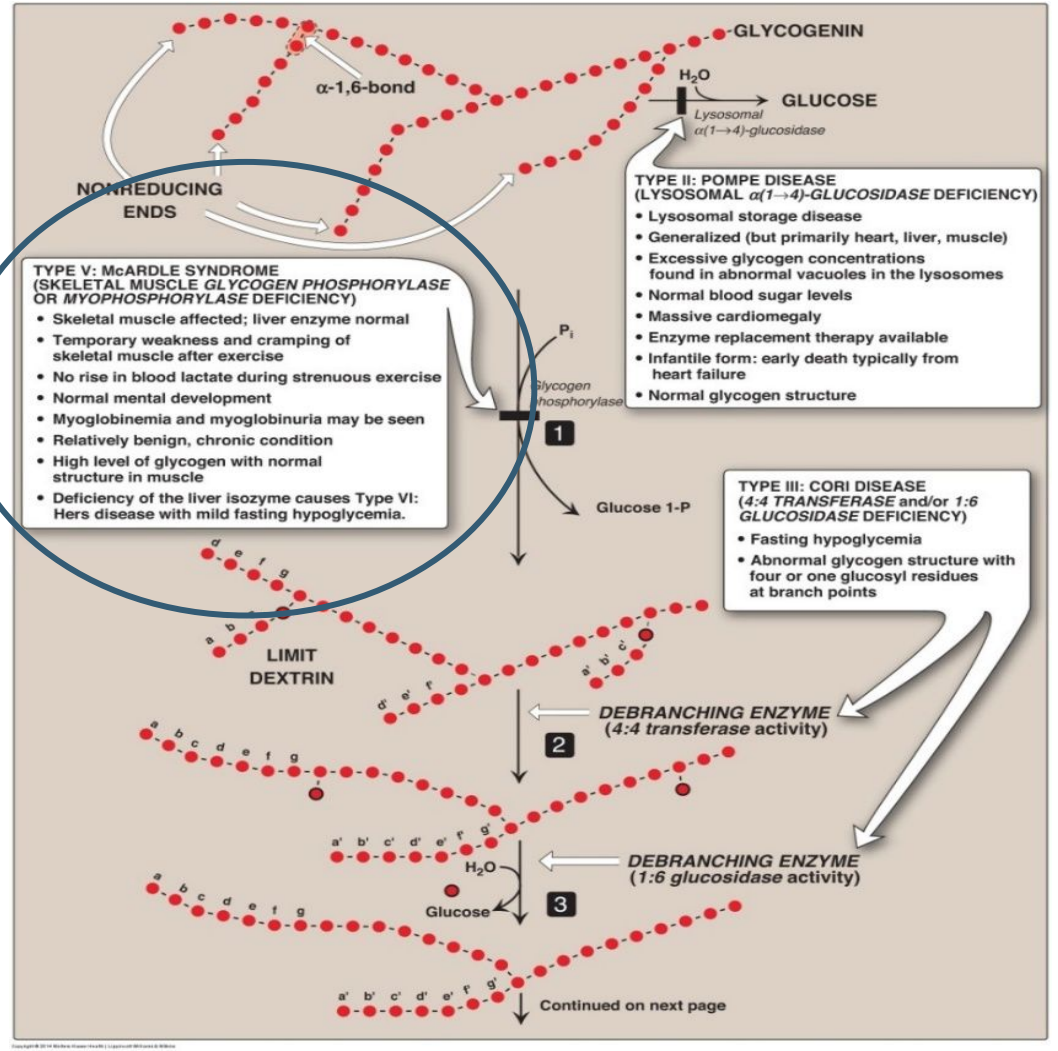
Type V: McArdle Syndrome

- Deficiency of skeletal muscle glycogen phosphorylase.

Skeletal muscle glycogen phosphorylase is an enzyme required for the degradation of glycogen, it affects skeletal muscles only. liver is not affected (wont affect blood glycogen levels because liver enzymes are fine)

- skeletal muscle affected; liver enzyme normal.
- temporary weakness or cramping of skeletal muscles after exercise.
- no rise in blood lactate during strenuous exercise.
- normal mental development.
- myoglobinemia and myoglobinuria may be seen.
- relatively benign, chronic condition.
- high level of glycogen with normal muscle structure.
- deficiency of liver isozyme causes type VI : Hers disease with mild fasting hypoglycemia.

Because skeletal muscles don't get energy from glycogen, it starts breaking down protein, increasing the myoglobin level in blood (myoglobinemia) and in urine (myoglobinuria).

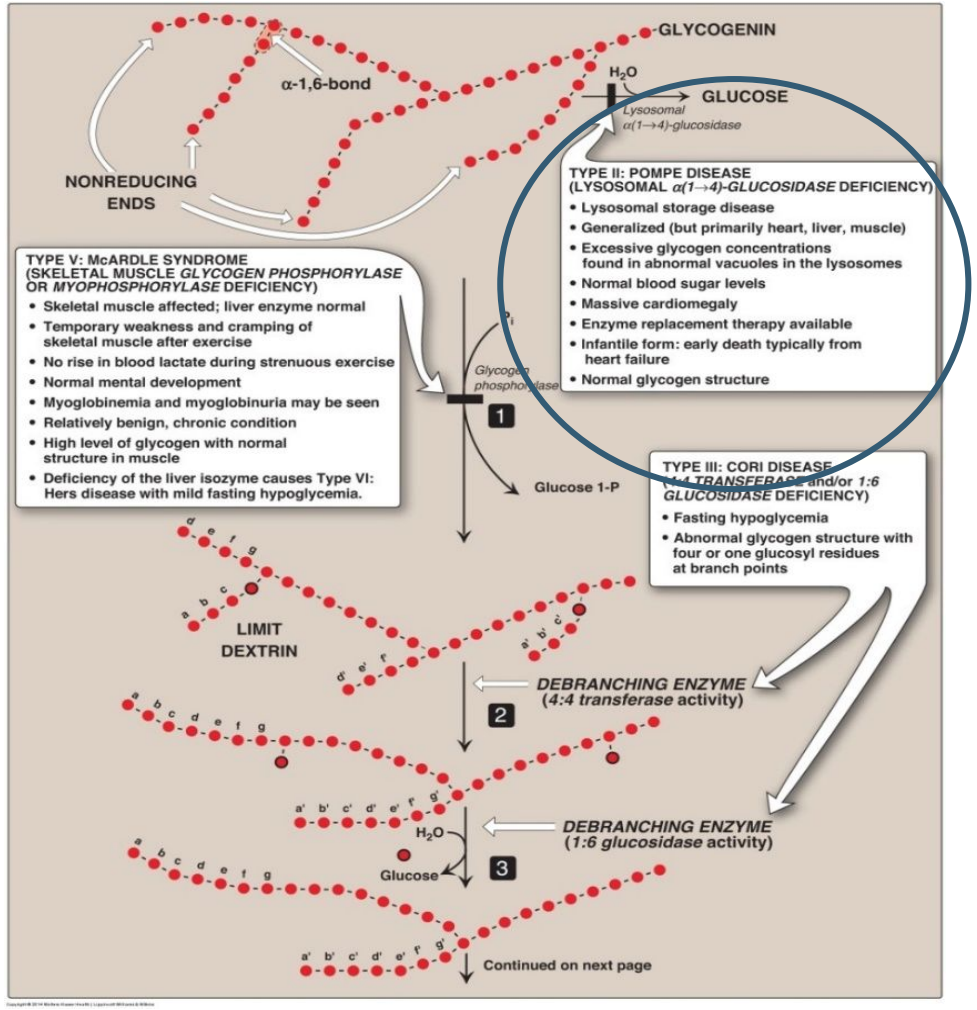


Type II: Pompe disease

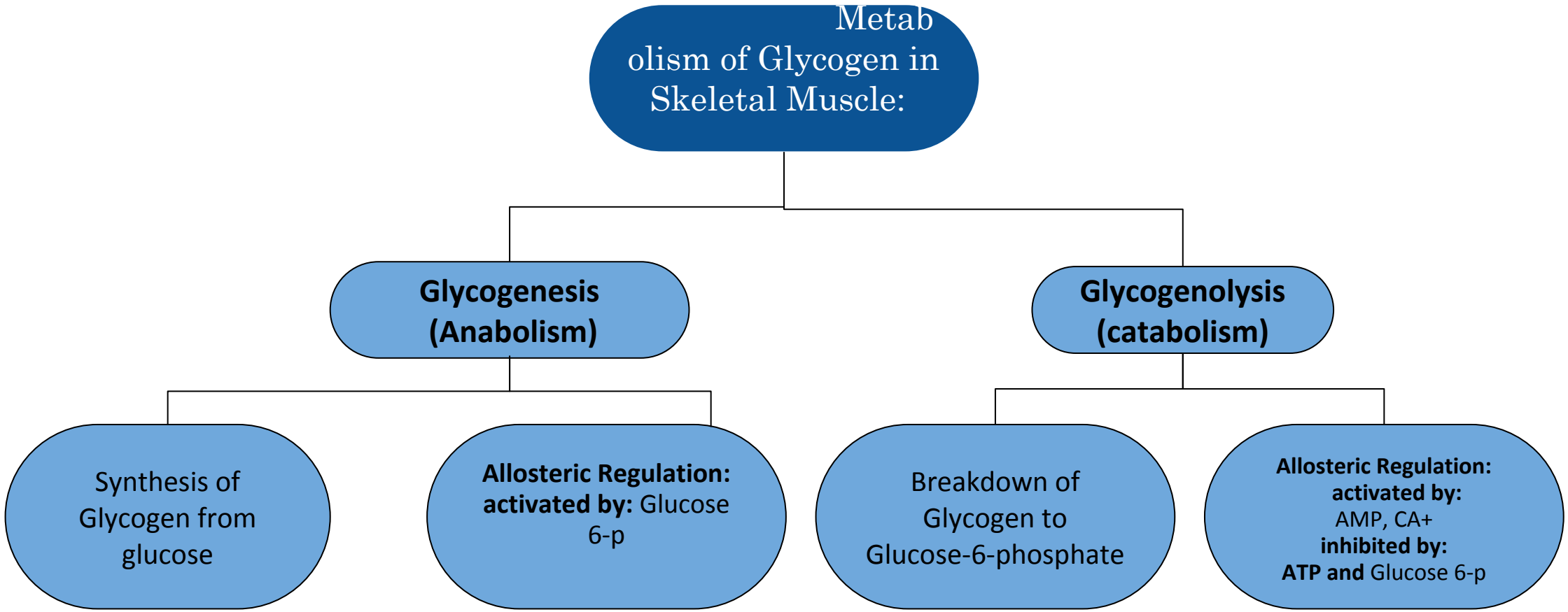
- Deficiency of lysosomal ∝(1→4) glucosidase enzyme.

Normally, 1-3% glycogen metabolism happens in lysosomes. if enzymes participating in glycogen metabolism in lysosomes are affected, it will lead to accumulation of glycogen in lysosomes.

- Lysosomal storage disease.
- Generalized (but primarily heart,liver,muscle).
- Excessive glycogen concentrations found in abnormal vacuoles in the lysosomes.
- Normal blood sugar levels.
- Massive Cardiomegaly.
- Enzyme replacement therapy available.
- infantile form: early death typically from heart failure.
- Normal glycogen structure.



Summary


Metab
olism of Glycogen in Skeletal Muscle:
Glycogenesis (Anabolism)
Glycogenolysis (catabolism)
Synthesis of Glycogen from glucose
Allosteric Regulation: activated by: Glucose 6-p
Breakdown of Glycogen to Glucose-6-phosphate
Allosteric Regulation: activated by: AMP, CA+ inhibited by: ATP and Glucose 6-p

MCQs

1) The first product formed during glycogenolysis (glycogen degradation at alpha 1,4 glycosidic bonds) is:

A. Glucose
B. glucose 1 phosphate
C. glucose 6 Phosphate
D. glucose 1,6 bisphosphate

2) Which of the following is the most important for maintenance of blood glucose?

A. liver
B. spleen
C. heart
D. bladder

3) A 35-year-old male has Muscle cramps, pain and stiffness. He also has burgundy-colored urine (myoglobinuria) and myoglobinemia. Which of the following is the most likely GSD?

A. TYPE I
B. TYPE II
C. TYPE V
D. TYPE VI

1. B
2. A
3. C

GIRLS TEAM:

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- شهد الجبرين
- لينا الرحمة
- منيرة المسعد
- ليلى الصّباغ
- العنود المنصور
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- صالح الوكيل
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