جامعة الملك سعود
King Saud University

Biochemistry team 436

Glycogen Metabolism

- Color Index:

- Important.
- Extra Information.
- **Doctors slides.**

436 Biochemistry team

Objectives:

By the end of the lecture. Students should be familiar with :

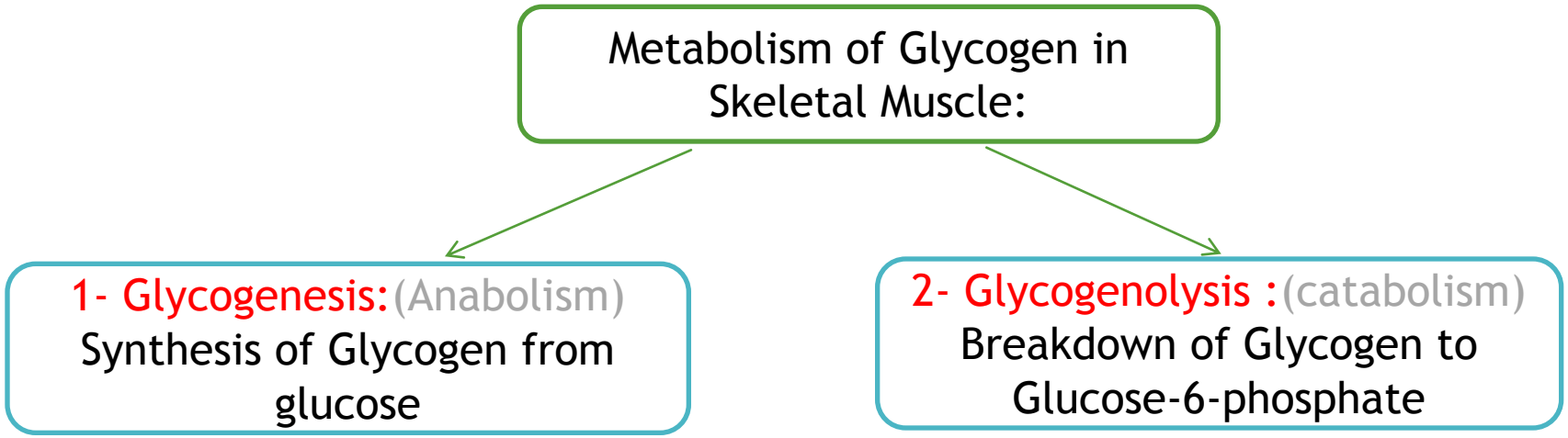
- The need to store carbohydrates in muscle
- The reason for carbohydrates to be stored as glycogen
- An overview of glycogen synthesis (Glycogenesis)
- An overview of glycogen breakdown (Glycogenolysis)
- Key elements in regulation of both Glycogenesis and Glycogenolysis (this objective is important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

Glycogen Metabolism

Remember metabolism is a mixed up between catabolism and anabolism

- **Glycogen:** is a branched – chain homopolysaccharide of glucose that serves as a form of energy storage made from α -D-Glucose

- Glycogen could be found in all types of cells, but in very small amounts (traces of glycogen), the main stores of glycogen are found in skeletal muscle and liver.



Structure of Glycogen

Bonds in Glycogen

The primary glycosidic bond is
α (1→4) Glycosidic linkage
Between glucose residues
(linear)

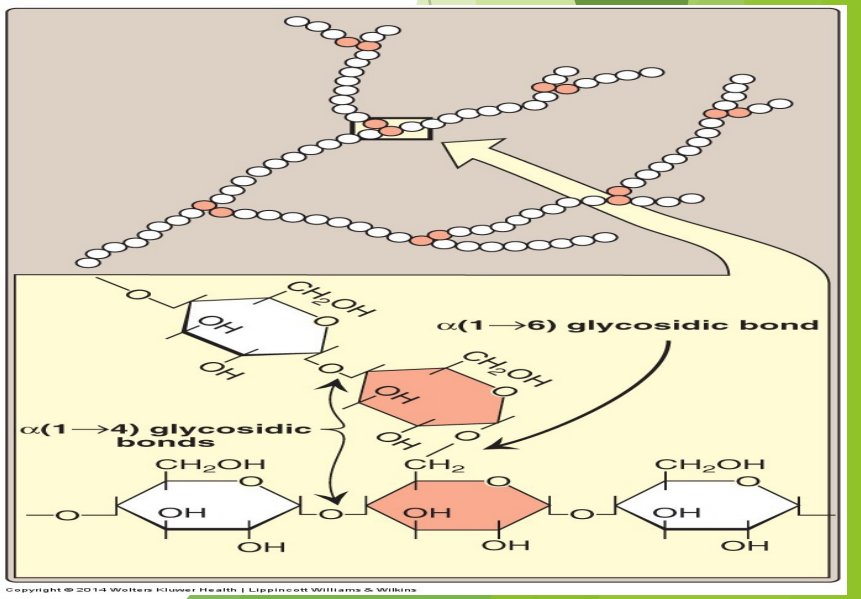
After 8 to 10 residues there is a branch containing α (1→6) Glycosidic linkage

N.B.
*All glucose residues in human are alpha.

- These polymers of glucose (Glycogen) exist in cytoplasmic granules حبيبات which contain most of the enzymes necessary for glycogen synthesis and degradation .

Residue is a partial of UDP-Glucose

*كل وحدة من الروابط عندها انزيم مميز يكونها ويفكها



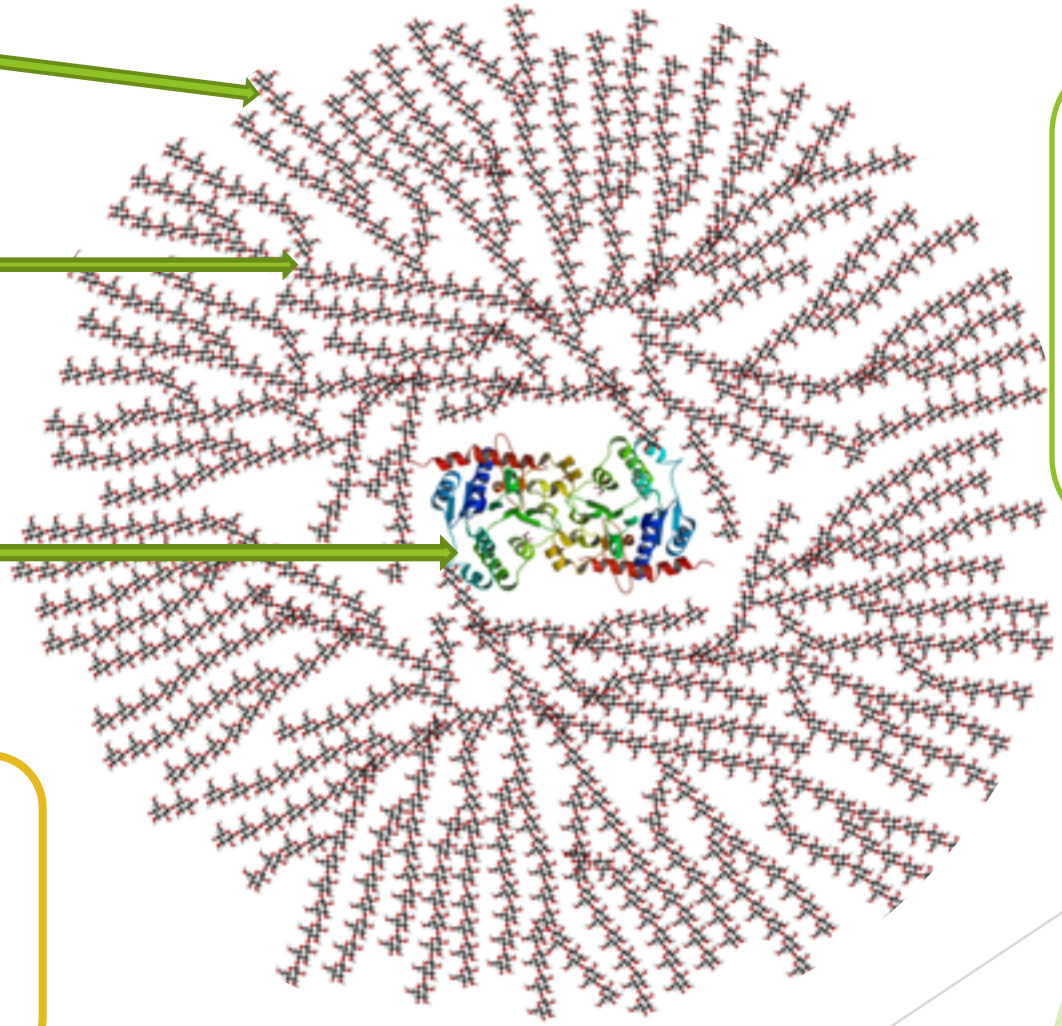
Glycogen Structure

α (1-4) Glycosidic linkage
Between the glucose residues

α (1-6) Glycosidic linkage
In Branches

The colorful molecule in the middle is a protein called :
Glycogen Primer (Glycogenin)

The hole structure represent a Glycogen Granule which is present in the Cytoplasm

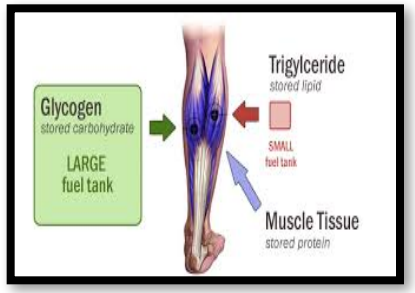


Why is glycogen a branched-chain ?

To contain high number of homopolysaccharides within a small space.

*the aim of glycogenolysis in muscle cells is to generate energy, so it's better to start from glucose 6-P rather than glucose to avoid losing 1 ATP.

Location and function of glycogen :



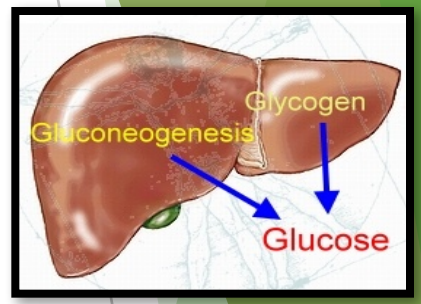
Skeletal muscle

Glycogen → Glucose 6-P → Energy

400 g of glycogen
make up 1-2% of the weight of resting muscle

Fuel reserve (ATP)
(during muscular exercise)

liver



Glycogen → Glucose 6-P → Glucose

100 g of glycogen
make up ~10% of the weight of a well-fed (healthy) adult liver

A source for blood glucose
(especially during early stages of fasting 10-17 hours)

GLYCOGENESIS

(Synthesis of Glycogen in Skeletal Muscles)

1- building blocks : Synthesis (UDP-glucose)* (source of all residues that are added to the growing glycogen molecule.)

2- Initiation of synthesis

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

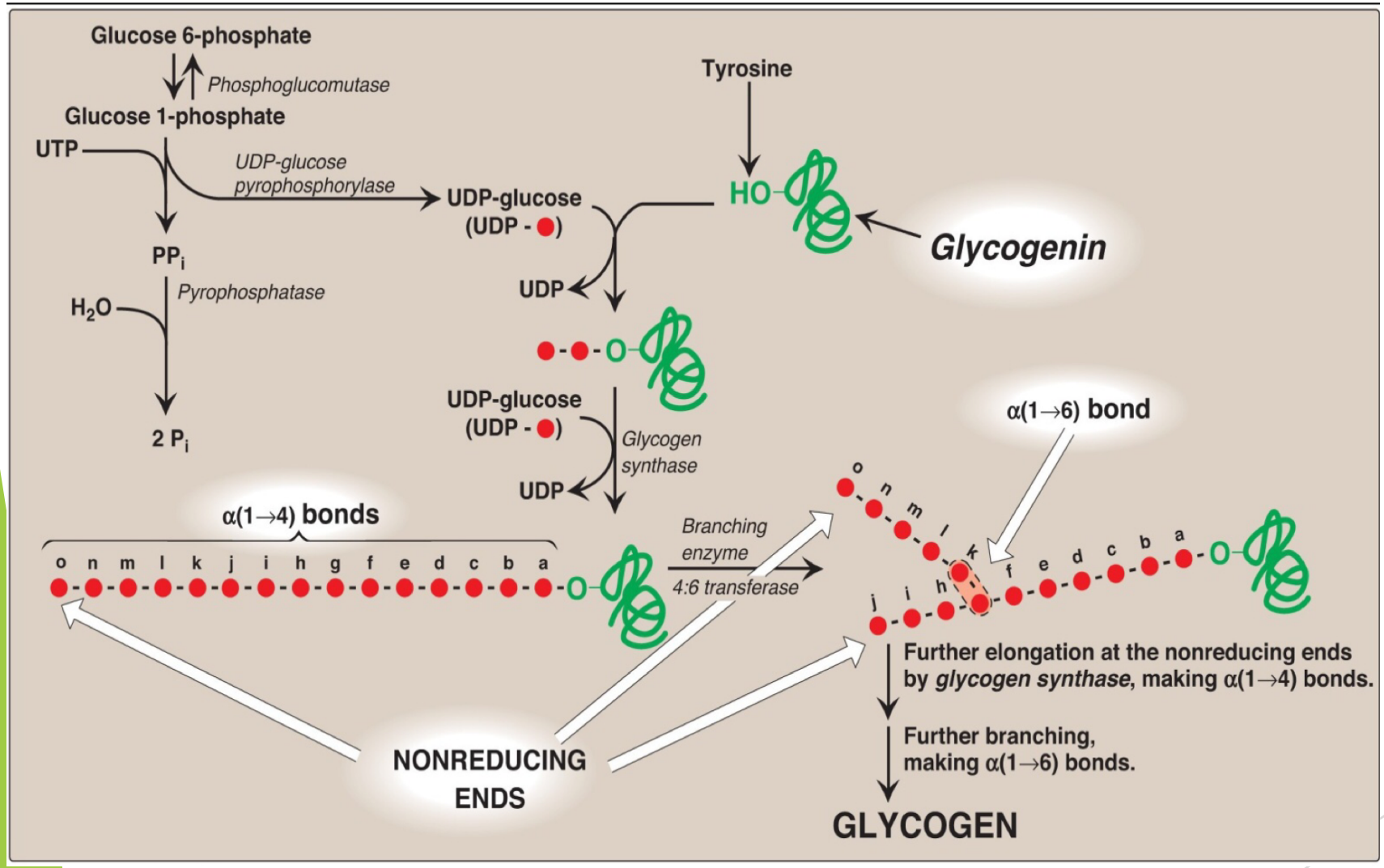
4- Branching:
Using **branching enzyme** (makes α 1-6 linkages) .

2- Initiation of synthesis :
The enzyme **glycogen synthase** (which makes α 1→4 linkages) cannot 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.

EXPLINATION:
Glucose synthase cannot start making glycogen from nothing, all it does is (1)elongation of pre existing glycogen fragments,
OR via using (2)glycogen primer (glycogenin), it acts like glycogen (UDP chains) to start the elongation.

*uridine diphosphate glucose is the building block of glycogen

Synthesis of Glycogen



1- Glucose 6-P + phosphogluco-mutase (Isomeration) → **Glucose 1-P**

2- Glucose 1-P + UTP (energy) + UDP-glucose pyrophosphorylase (enzyme) → **UDP-glucose unit.**

3- Start of elongation by binding of UDP glucose complex to glycogenin (primer) by glycogen synthase (enzyme)

*UDP: a nucleotide and it is an important factor in glycogenesis.

*Before glucose can be stored as glycogen in the liver and muscles, the enzyme UDP pyrophsphorylase forms a UDP glucose complex

Glycogenolysis

(Breakdown of glycogen in skeletal muscles)

1- Shortening of glycogen chain: by glycogen phosphorylase:

Glycogen phosphorylase contains a coenzyme: pyridoxal phosphate (PLP).

(Note: Pyridoxal Phosphate is a functional form of vitamin B6.)

They cleave (break) α(1→4) bonds of the glycogen chain → Producing glucose 1-P.

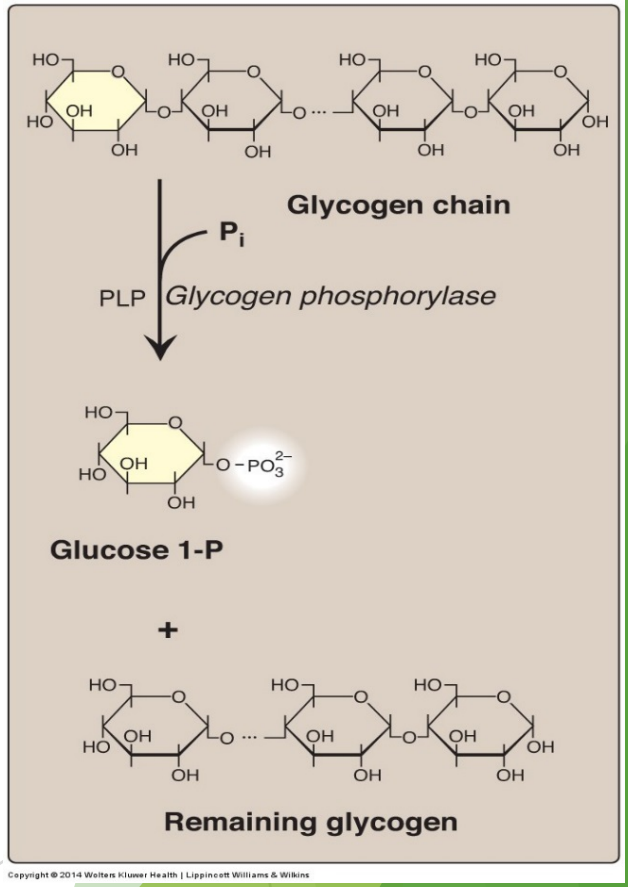
Note: After it reaches 4 residues the enzyme will stop cleaving

2- Removal of branches: by debranching enzymes

Cleaving of α(1→6) bonds at the branches of glycogen which releases free glucose directly

(in few quantities because the majority of the bonds are α (1,4) bonds)

3- Conversion of glucose 1-P to glucose 6-P: Glucose 1-P is converted to glucose 6-P by phosphogluco-mutase .



Glycogenolysis

Fate of Glucose 6-Phosphate (G-6-P)

In the liver glucose 6-P is converted to free glucose.

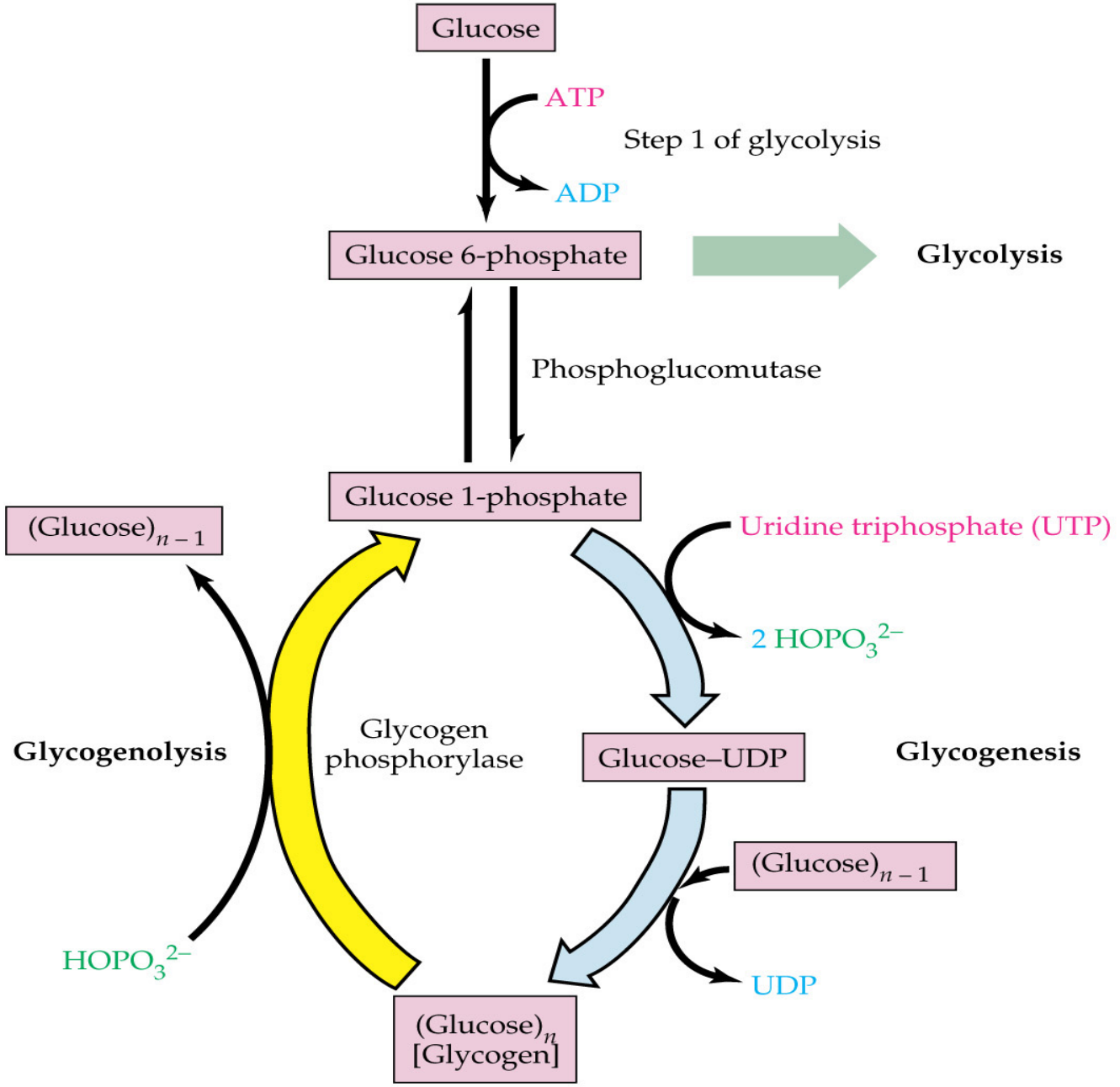
In the skeletal muscle: glucose 6-P CAN NOT be converted to free glucose and sent into the blood, because it doesn't have the enzyme for it. It is used as a source of energy for skeletal muscles during muscular exercise (by anaerobic glycolysis starting from G-6-P step). And produces 2 ATP because it's in the muscle (anaerobic).

The majority is in the muscle because it's bigger and more abundant in the body

Note : the ratio of glucose 1-phosphate to free glucose is ~8:1, meaning every 8 molecules of G-1-P, one molecule of free glucose will be produced

Summery

Glycogenolysis



Glycogenesis

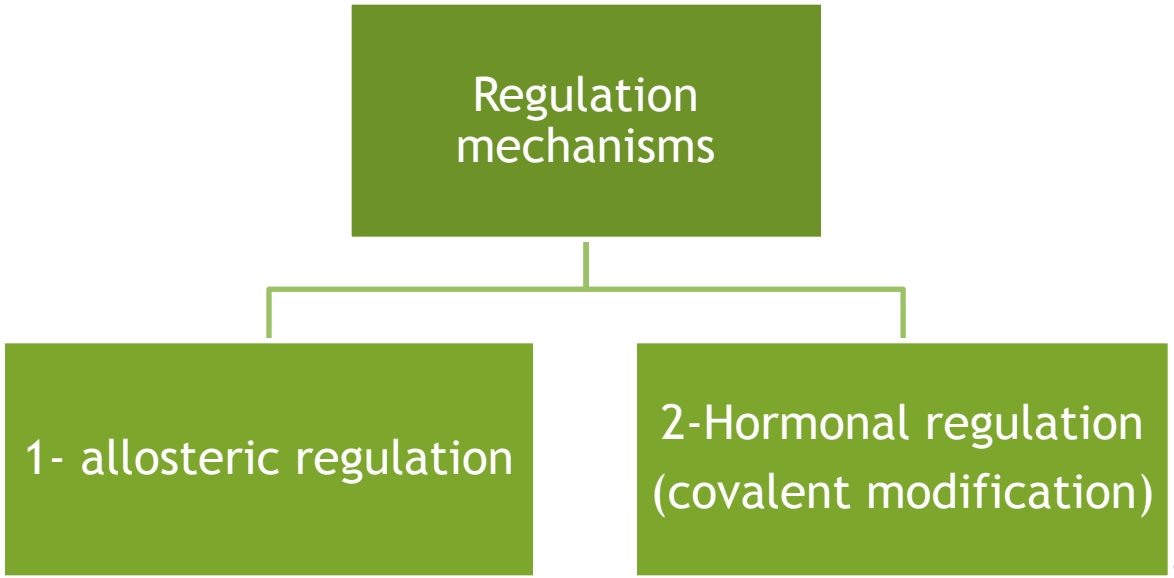
Regulation of Glycogen Metabolism

- 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:
Covalent modification: is regulating enzyme activity by adding molecule on it. The most common way is Phosphorylation and dephosphorylation.

Regulation of glycogen metabolism
(Allosteric regulation)

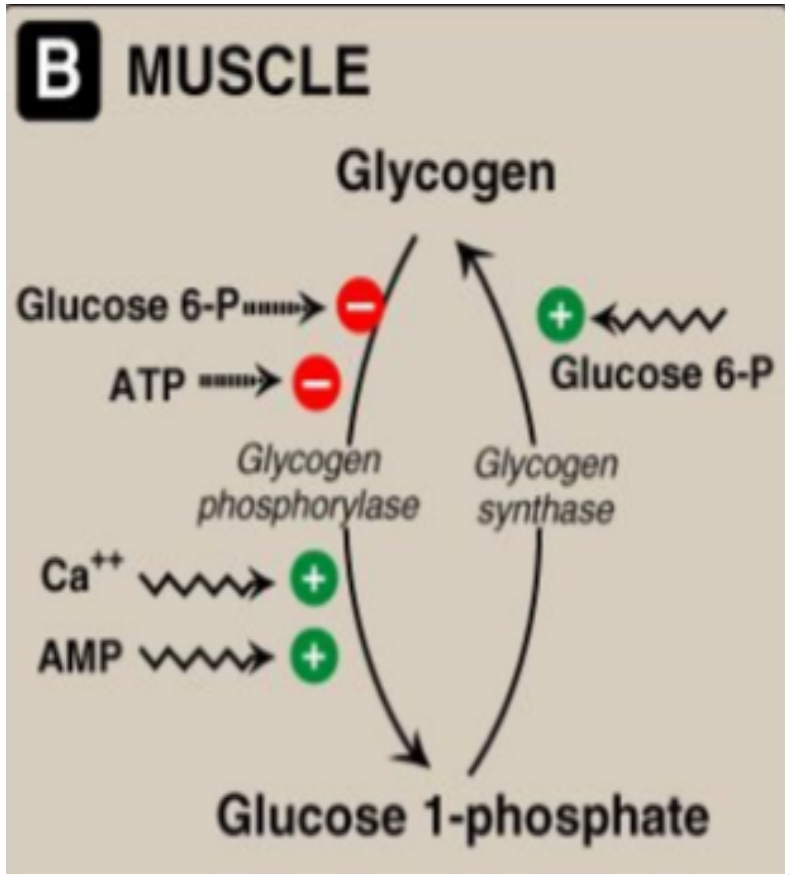
Glycogen phosphorylase

-Inhibited by:(Inhibit glycogen break down)

- glucose 6-p (High energy signal in the cell).
- ATP (ATP is abundant, no need for more energy).

-Activated by:(activate glycogen break down)

- Ca++ (we will explain it in the next slide).
- AMP (low energy signal).



Glycogen synthase

Activated by: (activate glycogen synthesis)

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

Regulation of Glycogen Metabolism

(Allosteric regulation)

Ca Releasing

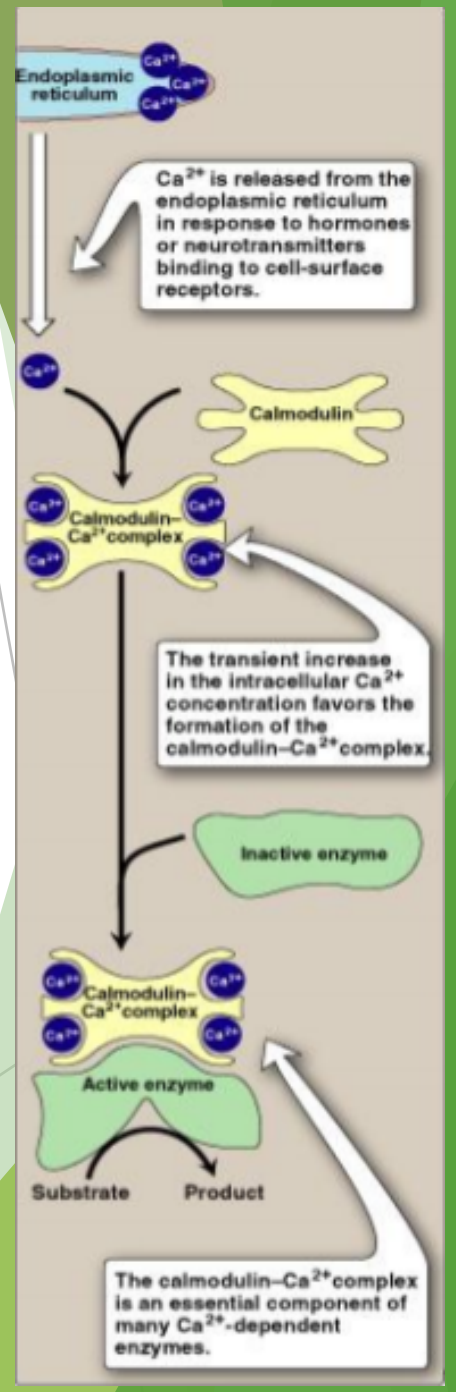
- Ca^{+2} is released from endoplasmic reticulum in response to hormone/neurotransmitter binding to cell-surface receptors which will lead in our case to increase Ca^{+2} conc. during muscle contraction.

Formation Ca^{+2} calmodulin complex

- High conc of Ca^{+2} in the Intracellular will lead to formation of calmodulin-Ca^{+2} complex (4 molecules of Ca^{+2} bind to calmodulin)

Enzyme activation

- calmodulin-Ca^{+2} complex will activates Ca^{+2}-dependent enzyme e.g. glycogen phosphorylase



Regulation of Glycogen Metabolism

قال دكتور الاولاد انه مهم

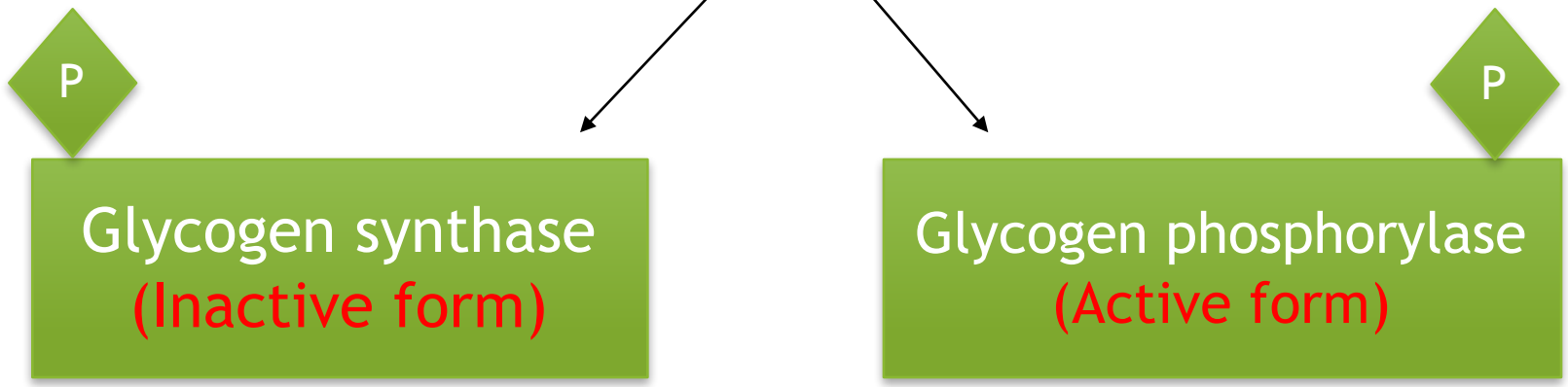
Hormonal Regulation(Covalent Modification)

Muscle Contraction

Skeletal Muscle: Epinephrine/receptor binding

Second Messenger: cAMP

Response: Enzyme phosphorylation



Inhibition of glycogenesis Stimulation of glycogenolysis

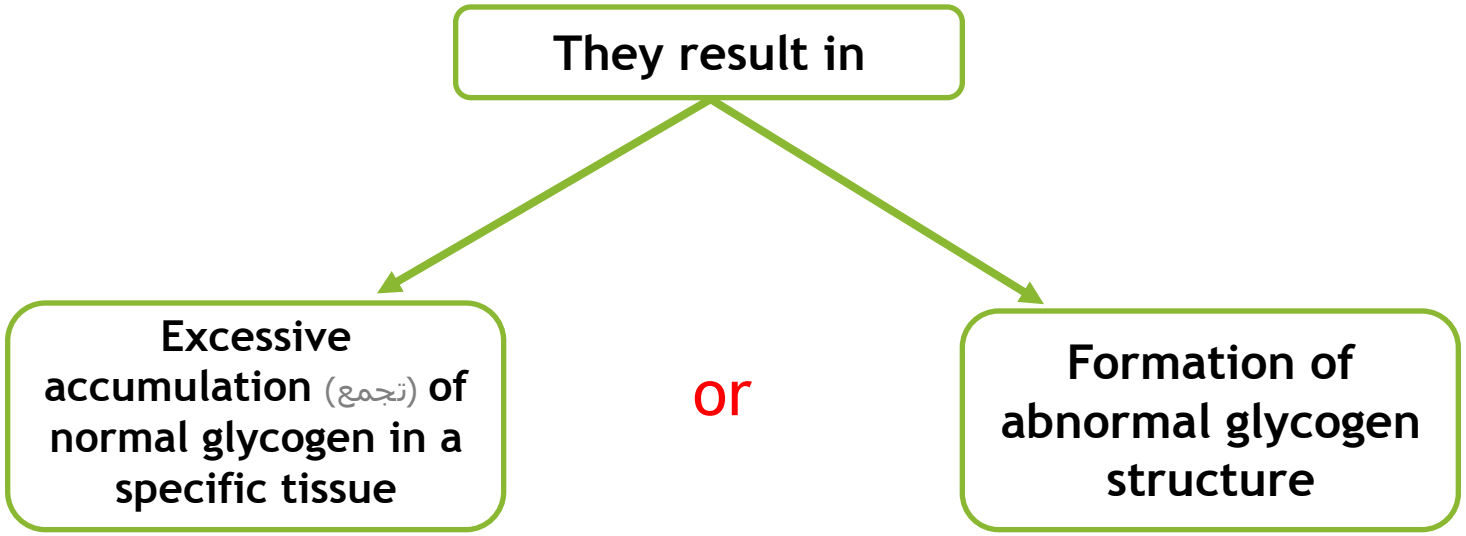
Epinephrine stimulates glycogenolysis (Skeletal muscle)

Glucagon stimulates Glycogenolysis (Liver)

Both use second messenger: cAMP

Glycogen Storage Diseases (GSD)

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



Glycogen Storage Diseases (GSD)

GSD Type V (McArdle Syndrome)

- Deficiency of skeletal muscle glycogen phosphorylase

Common in saudi arabia

GSD Type II (POMPE DISEASE)

- Deficiency of Lysosomal α(1-4) glucosidase.

Brief about McArdle Syndrome

body is not able to break down glycogen, due to Myophosphorylase defect.

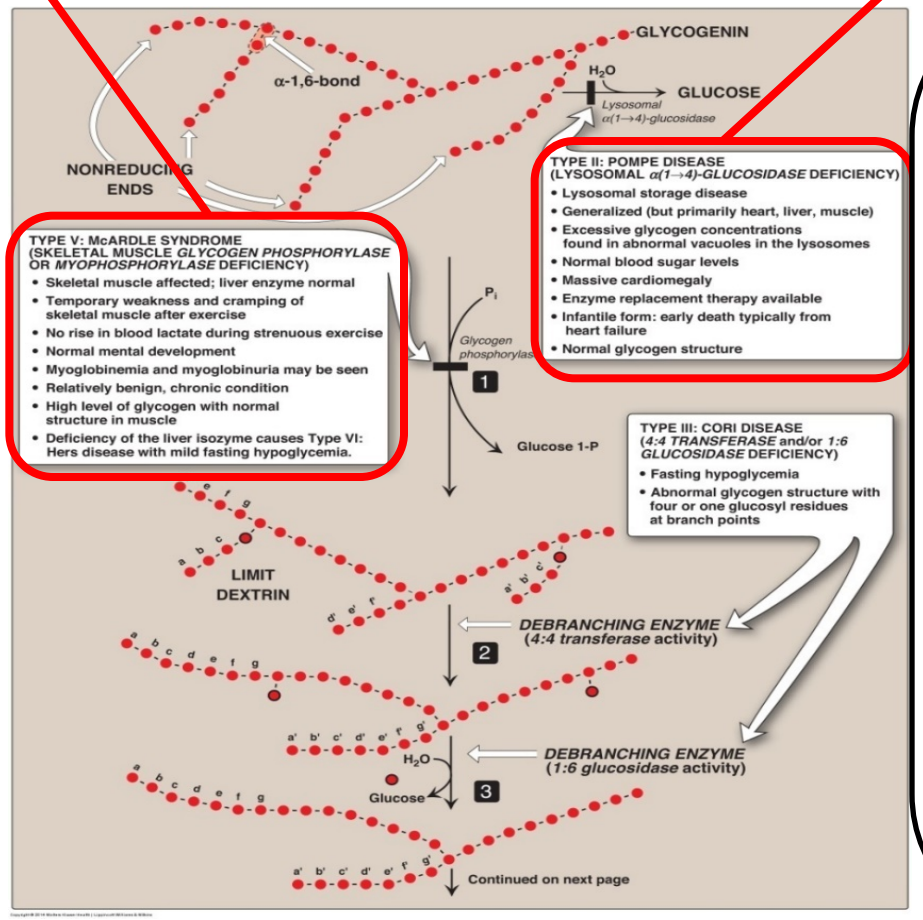
Symptoms:

Usually start during early childhood, but diagnosis may not occur until a person is over 20 or 30 years old.

- Muscle cramps, pain, stiffness & weakness
- Fatigue
- Burgundy-colored urine
- Exercise intolerance, poor stamina

Prognosis:

People with McArdle disease can live a normal life by managing their diet and physical activity



Brief about Pompe Disease

Absence or deficiency of the lysosomal enzyme ∝-glucosidase. Which is required to breakdown the complex carbohydrate glycogen and convert it into the simple sugar glucose.

Symptoms:

- Progressive proximal muscle weakness (trunk and lower limbs)
- Gait abnormalities.
- Muscle pain.
- Difficulty climbing stairs.
- Frequent falls.
- Scapular winging.
- Difficulty chewing or jaw muscle fatigue.

Prognosis:

These babies die before the age of one year

**They may ask about these diseases as cases, so knowing the etiology & symptoms is imortant

Girls team members:

1- نوره الشبيب.
2- ريم السرجاني.
3- نورة السهلي.
4- ربا برناوي
5- هيفاء الوعيل

Boys team members:

1- محمد المهوس.
2- فهد الزهراني.
3- عبدالعزيز الصومالي.
4- خالد القحطاني.
5- طلال الطخيم.
6- محمد حبيب.
7- حمد الحسون.
8- محمد المطلق

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Reference :

Lippincott's Illustrated Reviews Biochemistry: Unit II, Chapter 11, Pages 125 - 136.