Biochemistry Team 435

جامعة الملك سعود
King Saud University 1957

GLYCOGEN METABOLISM

Color index:
- Important
- Extra explanation

"DO NOT DWELL IN THE PAST, DO NOT DREAM OF THE FUTURE, CONCENTRATE THE MIND ON THE PRESENT MOMENT."

435 Biochemistry Team

OBJECTIVES:

- Storage of carbohydrates in liver & muscle
- Carbohydrates storage as glycogen
- Overview of glycogen synthesis (Glycogenesis)
- Overview of glycogen breakdown (Glycogenolysis)
- Key elements in regulation of both Glycogenesis and Glycogenolysis

LOCATION & FUNCTIONS OF GLYCOGEN

Location of Glycogen

Skeletal muscle	Liver
400 g	**100 g**
1-2% of resting muscles weight	10% of well-fed liver)
fuel reserve (ATP) (during muscular exercise)	a source for blood sugar especially during early stages of fasting

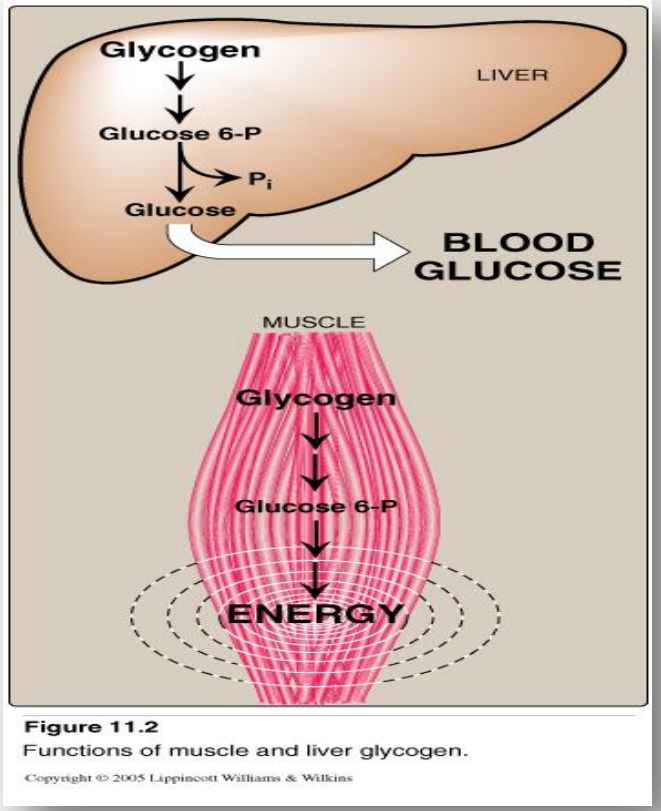


Figure 11.2
Functions of muscle and liver glycogen.

Notes:

- In the body, muscle mass is greater than liver mass. Consequently, most of the body glycogen is found in muscle.

ـ كتلة العضلات في الجسم أكبر من كتلة الكبد ، لهذا السبب الـ١% أو الـ٢% من وزن العضلات عادلت ٤٠٠ جرام ، بينما ال١٠% من الكبد عادلت ١٠٠ جرام.

Note :

- Glycogen in **muscles** cannot get converted to glucose, instead it gets converted to glucose 6-p due to absence of glucose-6 phosphatase,
- in **liver** glycogen is converted to glucose due to presence of that enzyme

STRUCTURE OF GLYCOGEN

- **what is glycogen?**

It is a highly branched-chain homopolysaccharide made exclusively from α- D-glucose

Bonds in the glycogen

- α(1-4)glucosidic linkage — Between Glucose residues
- α(1-6) glucosidic linkage — Between Branches (every 8-10 residue)

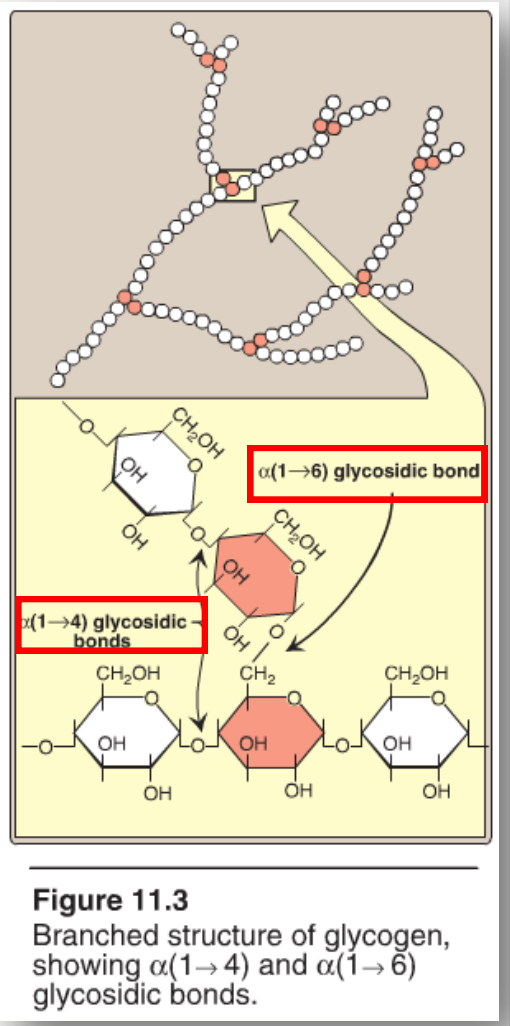


Figure 11.3
Branched structure of glycogen, showing α(1→4) and α(1→6) glycosidic bonds.

- **Glycogen is present (exist) in:**

- the cytoplasm in the form of granules which contain most of the enzymes necessary for glycogen synthesis & degradation

Metabolism of Glycogen in Skeletal Muscle

Glycogenesis

Synthesis of Glycogen from Glucose

- Glucose → Glycogen

Glycogenolysis

-Breakdown of Glycogen to Glucose-6-phosphate.

- Glycogen → Glucose-6-phosphate

GLYCOGENESIS

(SYNTHESIS OF GLYCOGEN IN SKELETAL MUSCLES)

1- Activation of Building blocks: formation of **UDP-GLUCOSE**

2- Initiation of synthesis:

A- Elongation of pre-existing glycogen fragment

OR

B- The use of glycogen primer (glycogenin)

3- ELONGATION: by using the enzyme **Glycogen synthase** (for α1-4 linkages)

4- BRANCHING: by using the enzyme **Branching enzyme** (for α1-6 linkages)

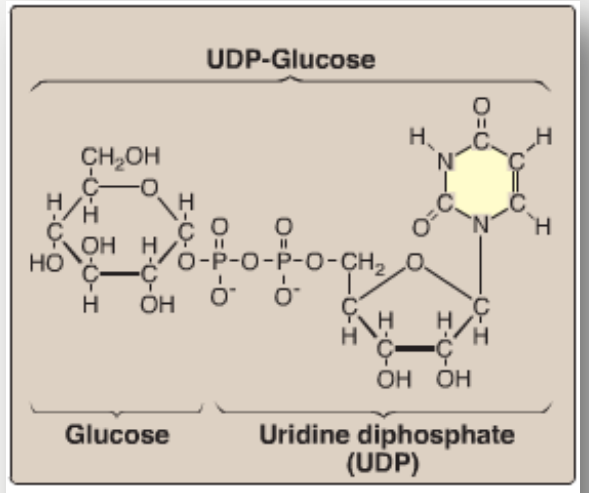
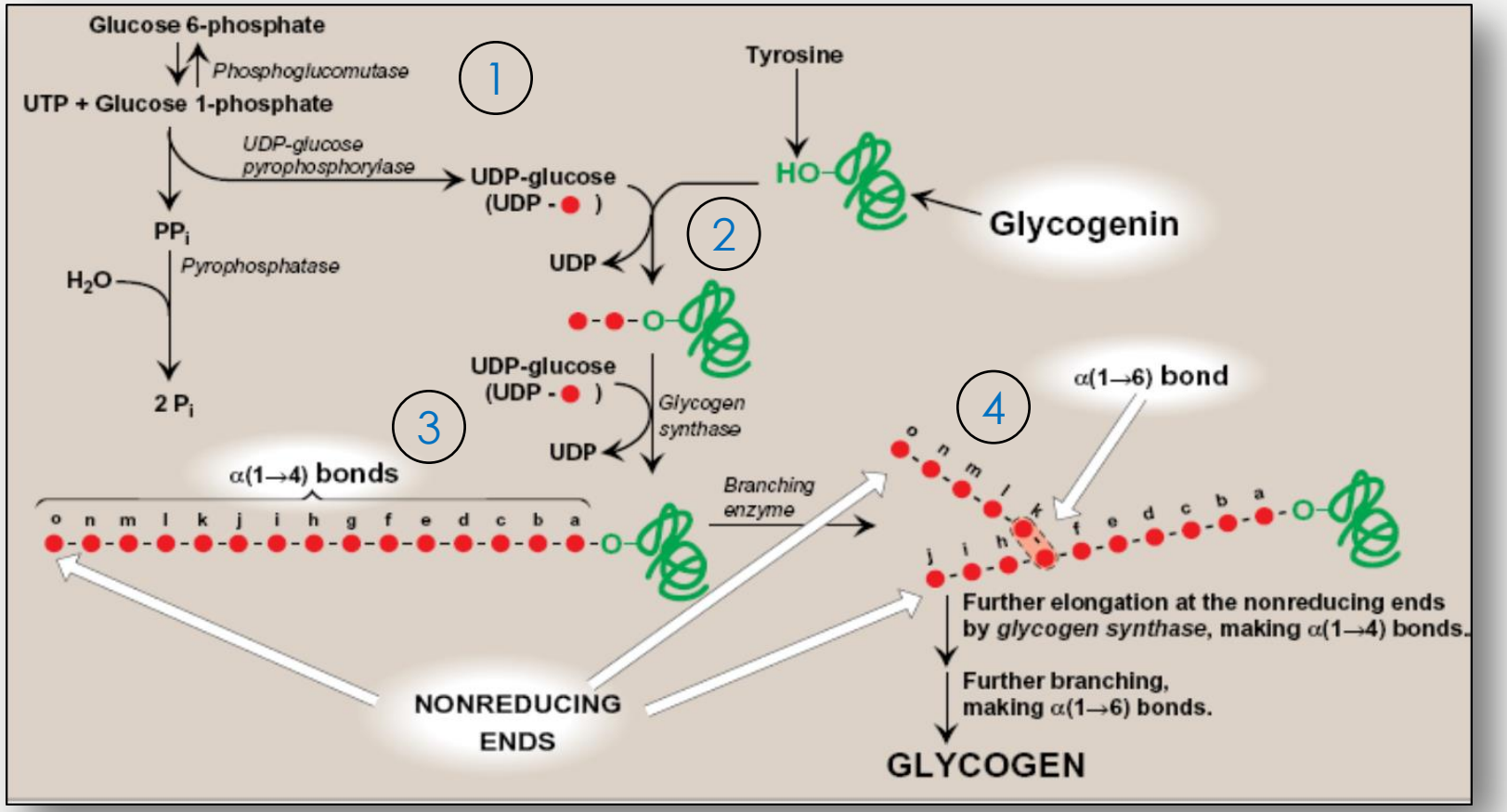


Figure 11.4
The structure of UDP-glucose, a nucleotide sugar.

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

SYNTHESIS OF GLYCOGEN

(SYNTHESIS OF GLYCOGEN IN SKELETAL MUSCLES)



SYNTHESIS OF GLYCOGEN

(SYNTHESIS OF GLYCOGEN IN SKELETAL MUSCLES)

1. **Glucose 6-phosphate** is converted to **glucose 1-phosphate** by **Enzyme : phosphoglucomutase** after that, **glucose 1-phosphate** is added to **UTP** (uridine tri-phosphate) to form **UDP-glucose** by **Enzyme : UDP-glucose pyrophosphorylase**

2. The glycogen primer is protein called **Glycogenin** which has the ability to initiate the synthetic process of glycogen, it can form the bonds between 2 glucose molecules by removing UDP molecules.

3. Then **Enzyme : glycogen synthase** can elongate the chain by forming (α1-4 linkages).

4. After 8-10 units of glucose, **Enzyme : Branching enzyme** breaks the bond (α1-4) then adds this segment to anywhere in the chain by forming (α1-6 linkage).

SYNTHESIS OF GLYCOGEN

(SYNTHESIS OF GLYCOGEN IN SKELETAL MUSCLES)

• الشرائح 8,9,10,11 هي شرائح إضافية لتعميق فهم Glycogenesis

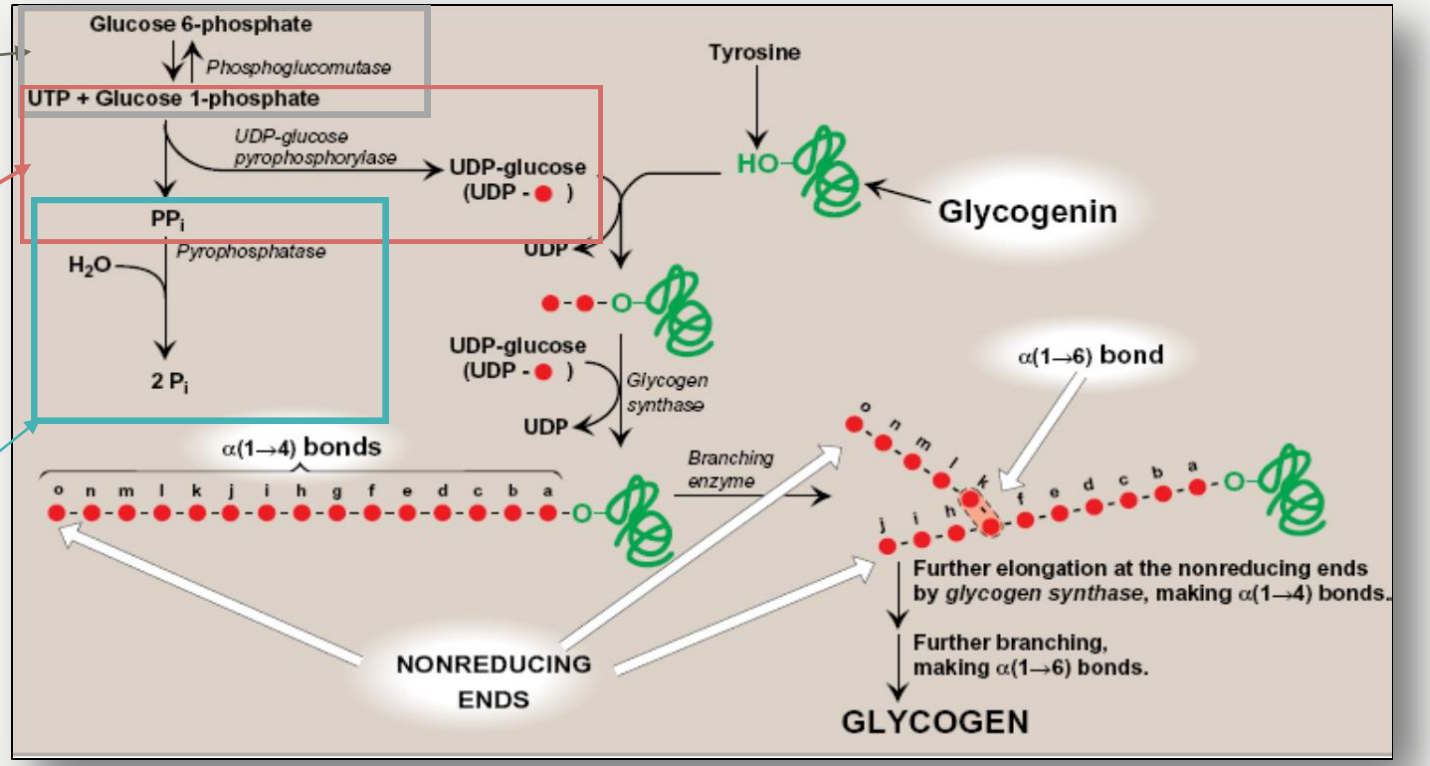
1- Activation of Building blocks (formation of UDP-Glucose):

- **Aim of this step:** formation of The source of all the glucose molecules that are added to the growing glycogen chain is: uridine diphosphate-glucose (UDP-glucose).

1) A **glucose 6-phosphate** molecule is converted to **glucose 1-phosphate** by phosphoglucomutase enzyme.

2) - A **glucose 1-phosphate** and a **UTP** will form **UDP-glucose** in a reaction catalyzed by UDP-glucose pyrophosphorylase enzyme.
- The products of this reaction are: UDP-glucose and pyrophosphate (PP_i)

3) - The high-energy bond in **PP_i** is hydrolyzed (broken) by pyrophophatase enzyme.
- The products of this reaction are: inorganic phosphate P_i and energy.
- The energy is used in glycogenesis.



SYNTHESIS OF GLYCOGEN

(SYNTHESIS OF GLYCOGEN IN SKELETAL MUSCLES)

2- Initiation of synthesis :

Glycogen synthase:

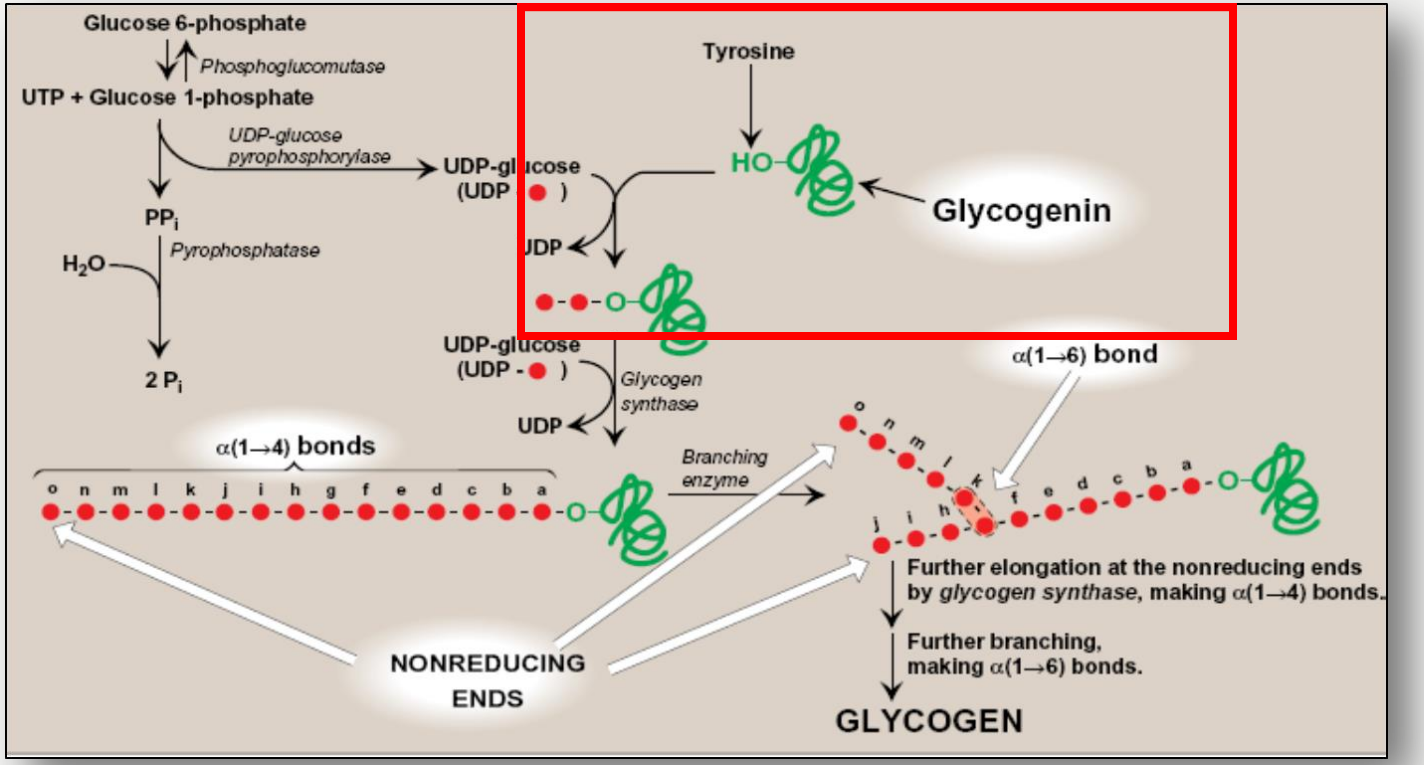
- it is responsible for making the a1-4 linkages in glycogen.
- This enzyme **cannot** initiate synthesis.
- It can only elongate a pre-existing molecule (primer).

- **This pre-existing molecule can be:** a glycogen fragment or a glycogen primer (glycogenin).
- In the absence of a glycogen fragment Glycogenin can serve as an acceptor of glucose residues from UDP-Glucose .

-**Glycogenin :**

- Is a protein that can be the acceptor of glucose residues from UDP-glucose.
- it catalyzes this reaction and the transfer of the next few molecules of glucose from UDP-glucose to produce a short chain.

The short chain will serve as a primer that can be used by the glycogen synthase enzyme



SYNTHESIS OF GLYCOGEN

(SYNTHESIS OF GLYCOGEN IN SKELETAL MUSCLES)

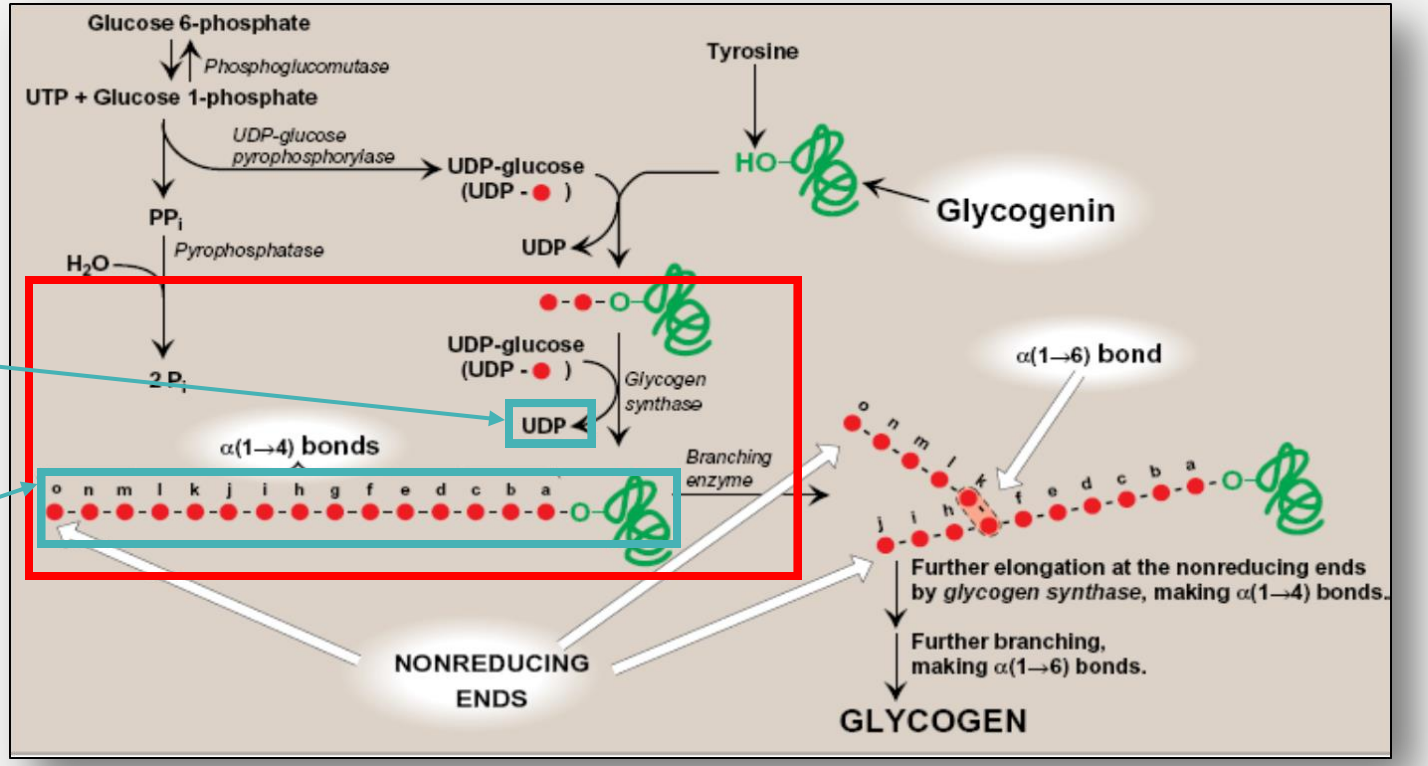
3- Elongation by Glycogen synthase:

- **Glycogen synthase:**

- it is the responsible enzyme for making the **α1-4 linkages in glycogen**.
- This involves the transfer of glucose from **UDP-glucose** to the **nonreducing end** of the growing chain forming a new glycosidic bond .

- **The products of this reaction are:**

1. a UDP (which can be converted back to UTP by nucleoside diphosphate kinase).
2. a glycogen molecule with an extra glucose residue.



SYNTHESIS OF GLYCOGEN

(SYNTHESIS OF GLYCOGEN IN SKELETAL MUSCLES)

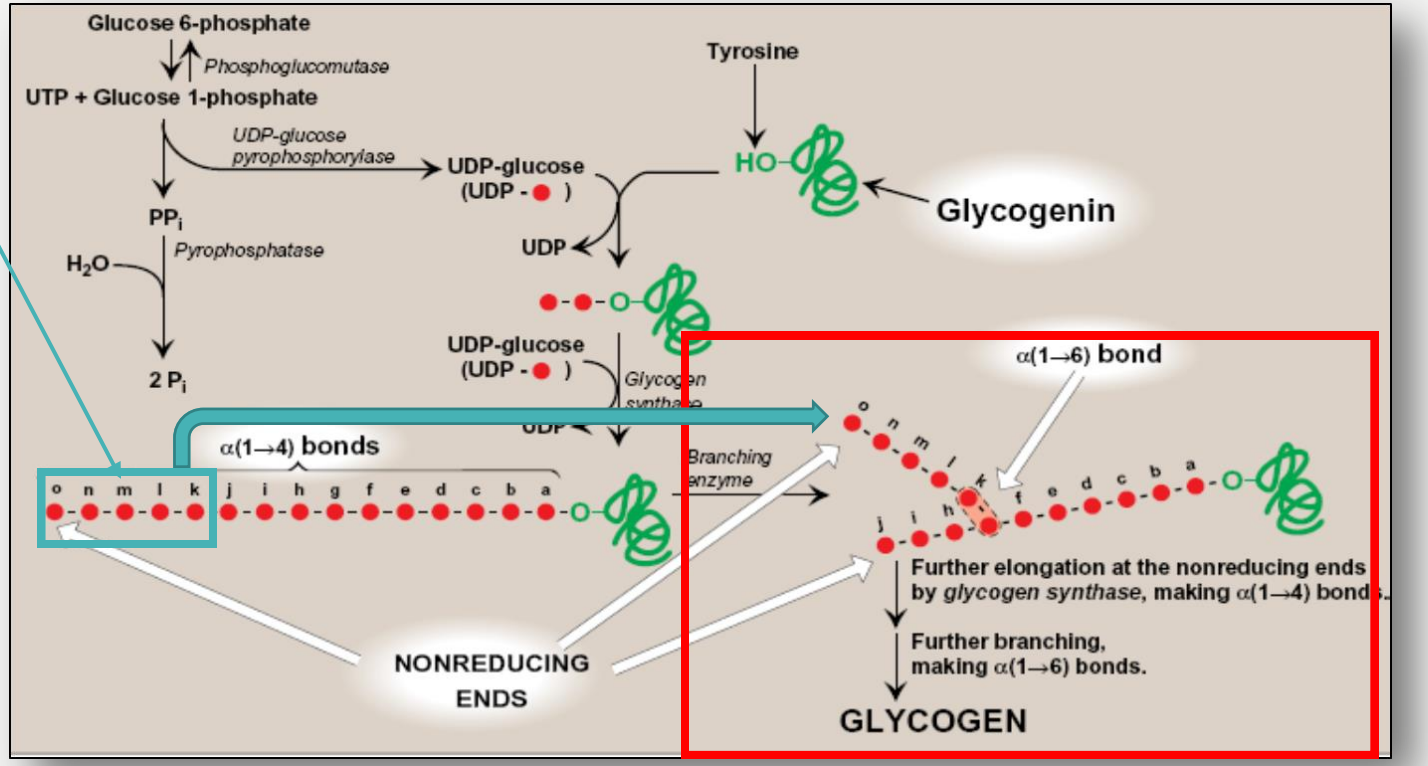
4- Branching :

- **Glycogen synthase** will continue working till sufficient number of glucose residues has been added (after an average of 8 to 10 glucose remember?), Then a branch has to be introduced.

The branching enzyme will transfer a chain of 6-8 glucose residues from the nonreducing end of the straight chain by **breaking** an α 1-4 linkage, to another residue on the chain, and will attach it by an a 1-6 linkage.

-This results in : a molecule with 2 nonreducing ends and a branch.

- The resulting **new nonreducing end** and **the old nonreducing end** from which the glucose residues were removed can now be further elongated by glycogen synthase.
- This process of elongation and branching continues.



* يأتي البرانشنق إنزايم ويقطع من السلسلة الرئيسية وذلك بتكسير الرابطة α 1-4 linkage ومن ثم يضيف الجزء المقطوع لاحد الرزيديوز وذلك بتكوين رابطة α 1-6 linkage .
* وبذلك سيكون لدينا ٢ نون ريدوسنق اندز ، وستسمر عمليتي التفرع و الاستطاله.

GLYCOGENOLYSIS

(BREAKDOWN OF GLYCOGEN IN SKELETAL MUSCLES)

1- Shortening of glycogen chain

- **Enzyme**
glycogen phosphorylase

it requires **Coenzyme:**
pyridoxal phosphate.

- It sequentially cleaves **α (1-4) bonds** from the nonreducing ends of the glycogen chain producing glucose 1-phosphate.

- Glycogen phosphorylase will continue its action of phosphorylation until 4 glucose units remain on each chain of the glycogen molecule which will be called: limit dextrin.

- The glycogen phosphorylase cannot degrade the limit dextrin any further.

2- Removal of branches

- **Enzyme:**
Debranching enzyme
has 2 enzymatic activities:

1) **α (1-4)→ α (1-4) transferase:**
It removes the outer 3 of the 4 glucose residues attached at a branch.

2) Hydrolytic cleavage of the α(1-6) bond:
at the branch point producing free glucose

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

- Glucose 1-Phosphate is converted to Glucose 6-Phosphate by **Enzyme** :
phosphoglucomutase.

- **In the skeletal muscles:** 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).

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

REGULATION OF GLYCOGEN METABOLISM

IN SKELETAL MUSCLES:

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

1- Allosteric regulation

Glycogen phosphorylase:

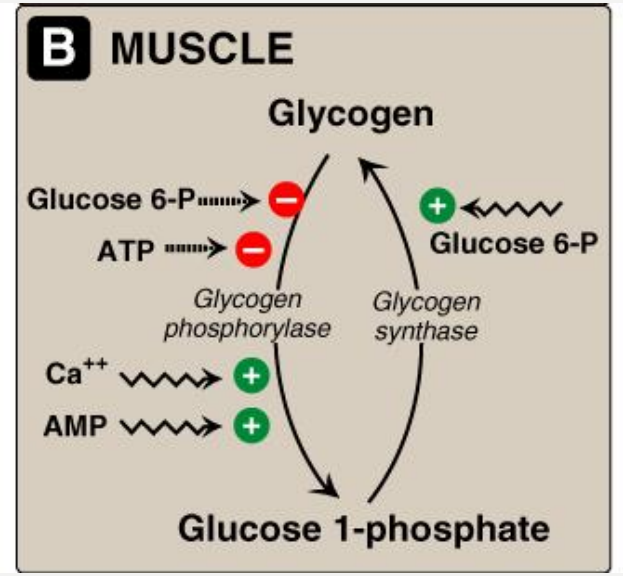
- Inhibited by:

1- glucose 6-P (High energy signal in the cell)

2- ATP. (يوجد طاقه اذا لانحتاج ان نكسر الجلايكوجين)

- Activated by:

1) Ca^{2+} (we will explain it in the next slide).
2) AMP (low energy signal). اشارة على قلة الطاقة وإحتياج الخلية للطاقة.



Glycogen Synthase:

- Activated by:

1- glucose 6-P (when it is present in elevated concentrations in the well-fed state).

REGULATION OF GLYCOGEN METABOLISM

(ALLOSTERIC ACTIVATION OF GLYCOGEN PHOSPHORYLASE BY CALCIUM)

Ca^{2+} releasing

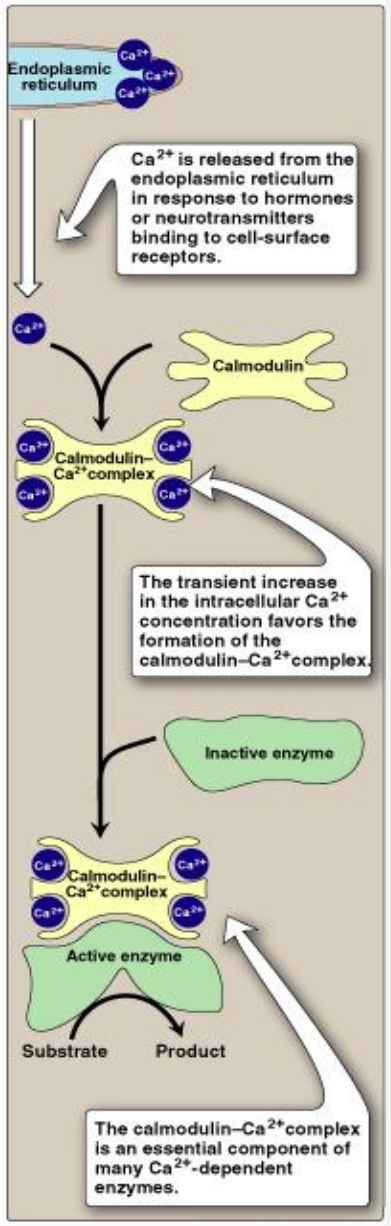
- The Endoplasmic reticulum release Ca^{2+} (increase of calcium during muscle contraction)

Formation Ca^{2+} calmodulin complex

- When 4 molecules of Ca^{2+} bind to protein called calmodulin they all form calmodulin-Ca^{2+} complex

Enzyme activation

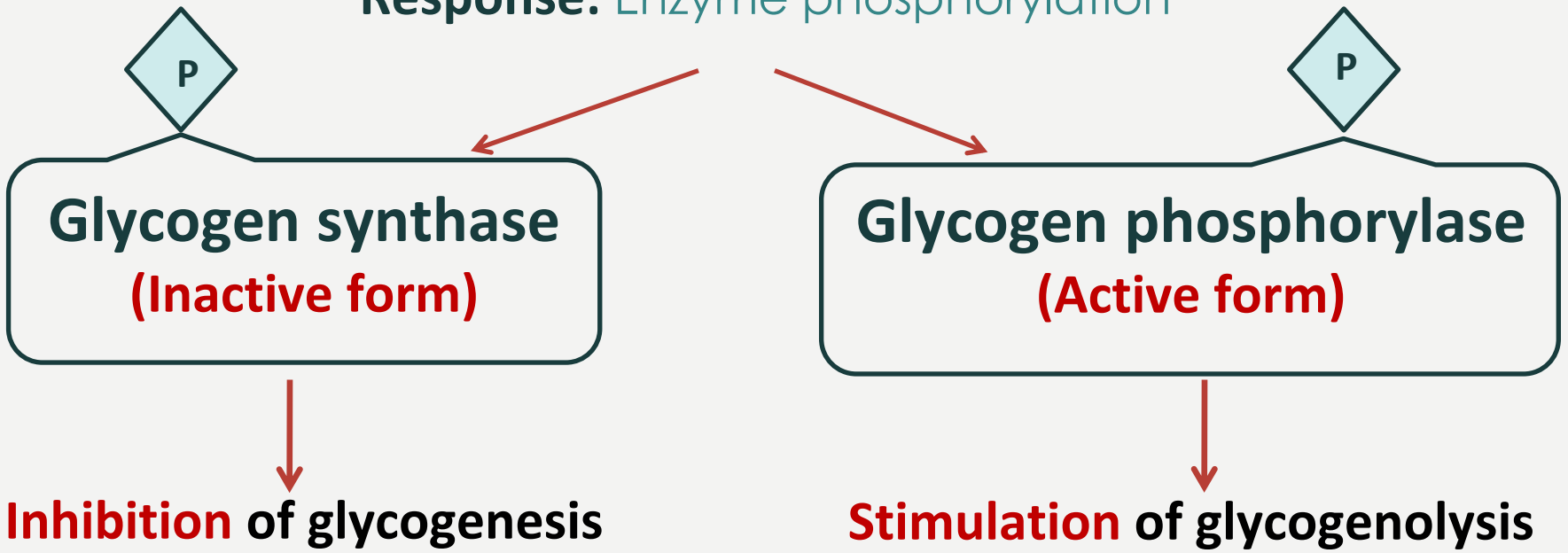
- calmodulin-Ca^{2+} complex activates Ca^{2+} -DEPENDENT enzyme
  E.G.: glycogen phosphorylase



REGULATION OF GLYCOGEN METABOLISM:

2. Hormonal Regulation (covalent modification) By Epinephrine

Muscle contraction
Epinephrine release
Skeletal muscle: Epinephrine/receptor binding
Second messenger: cAMP
Response: Enzyme phosphorylation



GLYCOGEN STORAGE DISEASES (GSD)

- **WHAT are they ?**

A group of genetic diseases that result from a defect

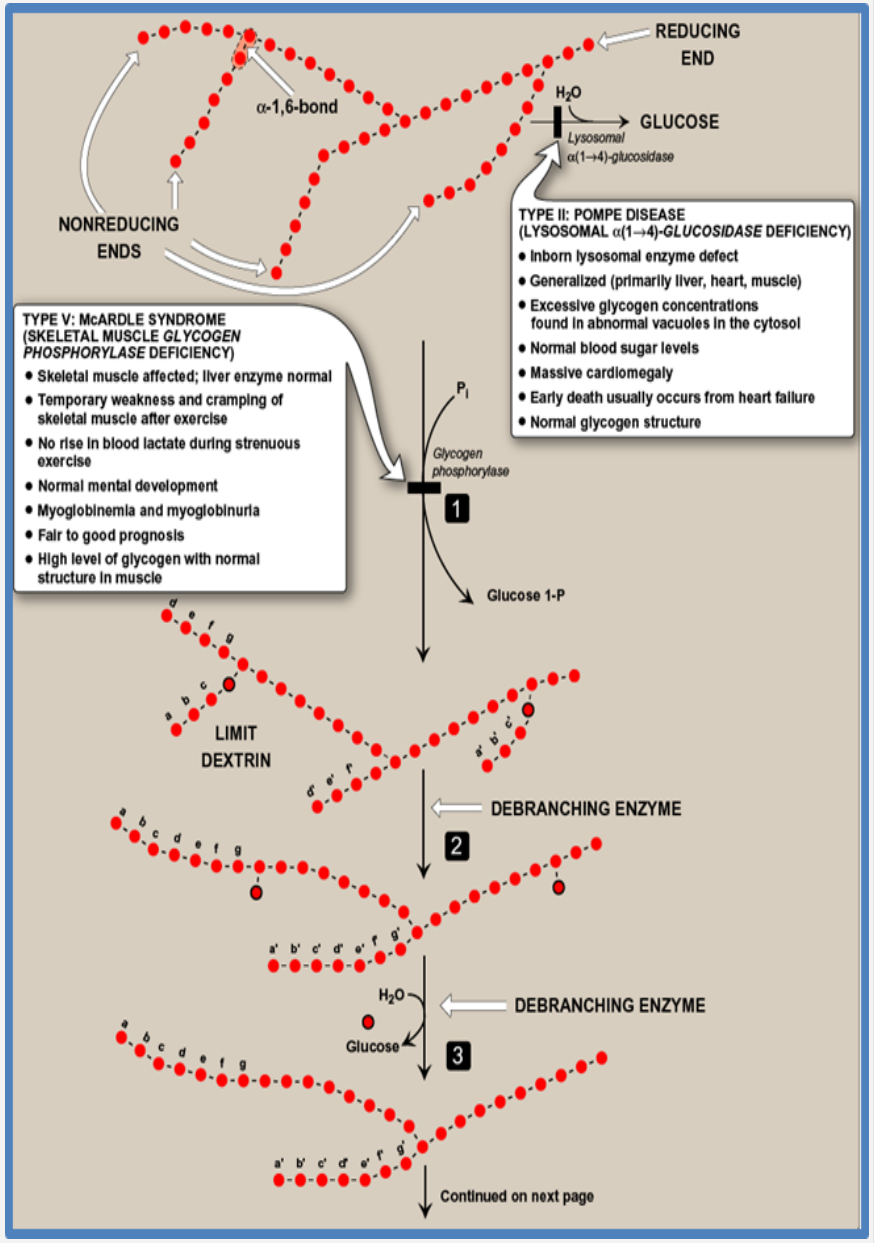
in an enzyme required for glycogen synthesis or degradation.

- **They result in:**

- Formation of abnormal glycogen structure

OR

- Excessive accumulation of normal glycogen in a specific tissue



GLYCOGEN STORAGE DISEASE

McARDLE SYNDROME

- **Type v**
- **What is it?** skeletal muscles glycogen phosphorylase deficiency.
- It is a relatively benign, chronic condition
- Normal mental development.
- **Affected** skeletal muscles enzymes (The liver enzyme is normal).
- **Symptoms :**

- weakness & cramping of muscles during exercise
- Myoglobinemia (increased myoglobin in blood) & myoglobinuria (increased myoglobin in urine)

- **Prognosis :** fair to good
- Skeletal muscles show high Normal glycogen structure

POMPE DISEASE LYSOSOMAL a(1→4) GLUCOSIDASE DEFICIENCY

- **Type II**
- **What is it?** 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
- **PROGNOSIS :** BAD, early death typically from heart failure
- Skeletal muscles show Normal glycogen structure.

*مهم جدا التركيز على الأمراض وأسبابها والآلية التي تتبعها ، فقد تأتي بالساك على صورة حالة أو سيناريو وتطلب أمثلة على **DEFICIENCY**، بالإضافة إلى كم سؤال من المحاضرة .

MCQ's

A-Synthesis of glycogen from glucose:

1- glycogenesis
2- glycogenolysis
3- Glycogenesis
4- gluconeogenesis

B- Break down of glycogen to Glucose-6-phosphate:

1- glycogenesis
2- glycogenolysis
3- Glycogenesis
4- gluconeogenesis

C- the job of "glycogen phosphorylase" :

1-branching enzymes
2-debranching enzymes
3-elongation of glycogen chain
4- shortening of glycogen chain

MCQs

D- glycogen synthase " inactive form " :

1- inhibition of glycogenolysis
2- stimulation of glycogenesis
3- inhibition of glycogenesis
4-stimulation of glycogenolysis

E- glycogen phosphorylase " Active form " :

1- inhibition of glycogenolysis
2- stimulation of glycogenesis
3- inhibition of glycogenesis
4-stimulation of glycogenolysis

F- how many molecules of free glucose will be produced for to 24 molecules of G-6-P Mostly:

1-TWO
2-THREE
3-FOUR
4-ONE

G- True or false:

1- glycogen is a branched-chain homopolysacharide made from several types of glucose.
2- branches of glycogen are linked by α(1-4) glucosidic linkage .
3- In allosteric regulation the second messenger is cAMP.
4- glycogen elongation is initiated by glycogen synthase.

SAQs

1) Mohammed is working out in the Gym.

A. what kind of reaction is occurring at the time of exercise regarding “glycogen metabolism”?
B. How can we regulate that?
C. Give two examples of the Deficiencies that might occur to him.

2) Tariq is14 year old male, experiencing muscle cramps after windsprints and calisthenics in high school gym class and while taking the history Tariq told the doctor that exercise "hurts“ him.

A. Name the disease and What is the enzyme activity that is deficient here?
B. What biochemical reaction does the deficient enzyme catalyze?
C. Explain why this patient complains that it "hurts" when he exercises?

Answers

MSQs :

A- 1
B- 2
C- 4
D-3
E- 4
F-2
G:
1- F
2- F
3- F
4- T

Helpful videos

https://www.youtube.com/watch?v=Eovh2X4sLLA ⟵ فيديو ممتاز
https://www.youtube.com/watch?v=3Ceq-5iYBuc

SAQs Answers

1)

a- Glycogen degradation. لأنه قاعد يتمرن فبالتالي يحتاج إلى طاقة عن طريق تكسير الجلايكوجين

b– 1- allosteric regulation.

- Inhibited by:
  1- glucose 6-P
  2- ATP.

Activated by:

1) Calcium (we will explain it in the next slide).
2) AMP

2- hormonal regulation. (By norepinephrine)

C- Glycogen storage disease (GSD)
E.g. Mc Ardle Syndrome and POMPE DISEASE(LYSOSOMAL α(1→4)-GLUCOSIDASE DEFICIENCY.

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2)

A- McArdle's disease is due to a deficiency in glycogen phosphorylase

B- glycogen phosphorylase is responsible for breaking down glycogen into glucose 1-P, which then is converted to glucose 6-P for further metabolism.

C- Low or negligible levels of glycogen phosphorylase activity will result in a general inability to break down glycogen quickly; it will be hard for the body's muscles to draw on glycogen as a quick source of energy, and other sources of glucose must be utilized instead. Thus, sudden demands for energy can cause painful cramps and weakness, due to a buildup of lactic acid.

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- نوره الرميح.
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- بدور جليدان.
- جواهر الحربي.
- علا النهير.
- أفنان المالكي.
- نوف التويجري.
- لولوه الصغير.
- خوله العريني.
- دلال الحزيمي.
- وضحى العتيبي.
- رزان السبتي.
- دانيا الهنداوي.
- رهف بن عباد.
- غاده القصيمي.
- أسماء العمار.
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