glycogen metabolism lecture 3

Third year-biochemistry subject – laboratory science departments -Alzahraa university

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SUMMARY OF THE PREVIOUS LECTURE

- pyruvate is oxidatively decarboxylated to acetyl CoA by pyruvate dehydrogenase (PDH) enzyme complex
- Pyruvate $\xrightarrow{\text{PDH}}$ acetyl CoA
- **PDH reqire 5 co enzyme which are**

1. Thiamine pyrophosphate (TPP) VITAMIN B1 (usually deficient in alcoholic people)
2. FAD (ribofalvin vit B2)
3. NAD+ (niacin vit B3)
4. Lipoic acid
5. Co-enzyme A (CoA)

acetyl CoA enter kreps cycle to be completely oxidized to co2 +water yielding 2 ATP

6 NADH ,2 FADH2 that enter electron transport chain to produce ATP through oxidative phosphorylation.

In gluconeogenesis the same steps are exactly the same as glycolysis only the process is in reverse except for the irreversible steps which are

- (1) conversion of pyruvate to PEP via oxaloacetate, catalyzed by pyruvate carboxylase and **Phosphoenol pyruvate carboxy kinase** ;
- (2) dephosphorylation of fructose 1,6- bisphosphate by fructose 1,6- bisphosphatase
- (3) dephosphorylation of glucose 6- phosphate by glucose 6- phosphatase.

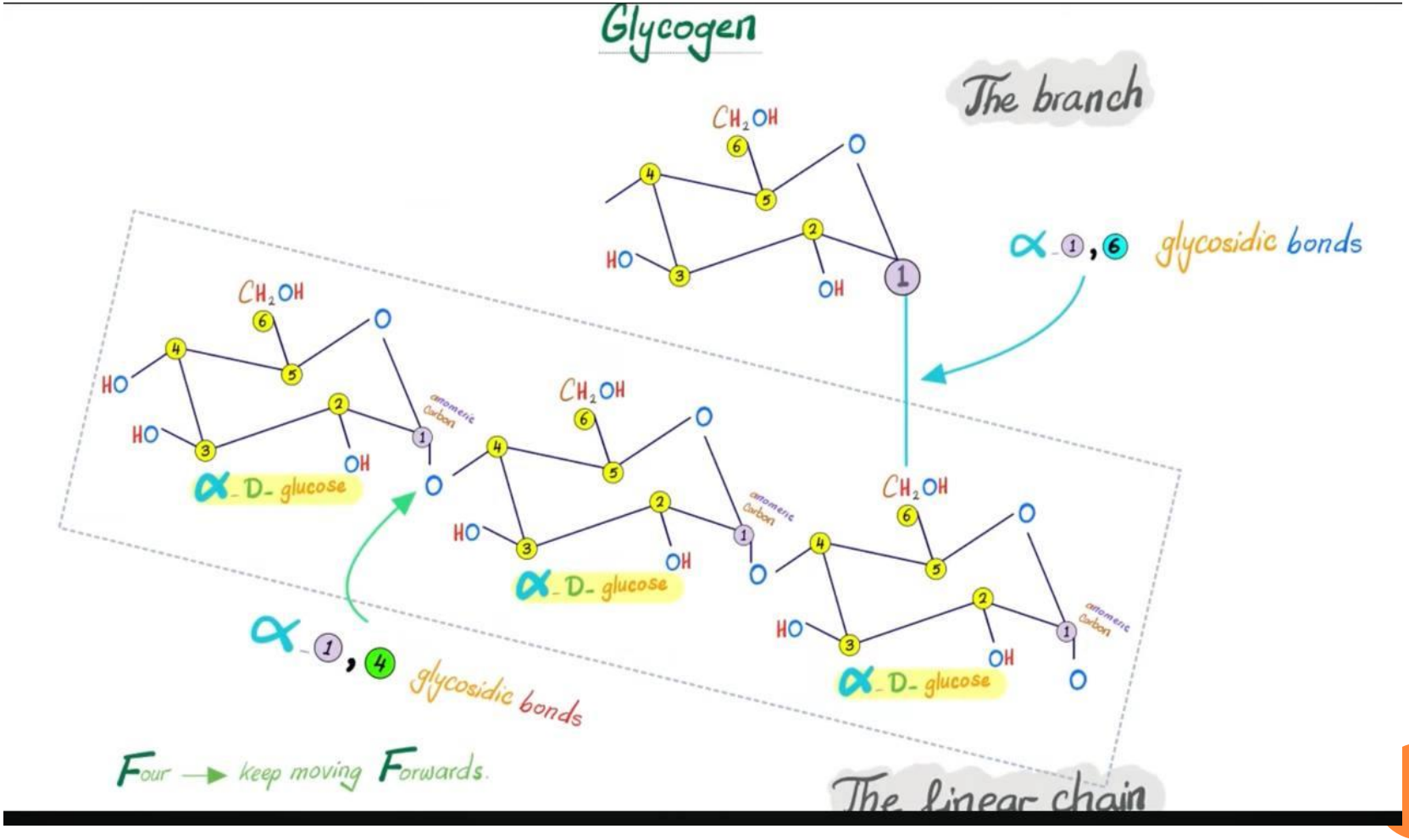
Learning objectives

1. **Understand the structure of glycogen & where it stored**
2. **Outline the steps involved in glycogen synthesis starting from glucose to glycogen**
3. **Explain the process of glycogen breakdown**
4. **Discuss the hormonal regulation of glycogen metabolism**
5. **Identify common glycogen storage diseases**

Introduction

- Glycogen is a highly branched polymer of glucose (homopolysaccharides) that allows rapid mobilization of glucose units when energy is needed.
- **Structure of Glycogen**:
- Core: A glycogenin protein serves as the base for the glycogen particle.
- Chains:
  - **α-1,4 glycosidic bonds** form the linear backbone.
  - **α-1,6 glycosidic bonds** form branches.
- **This branching increases solubility and provides multiple sites for enzymatic action.**

Glycogen structure

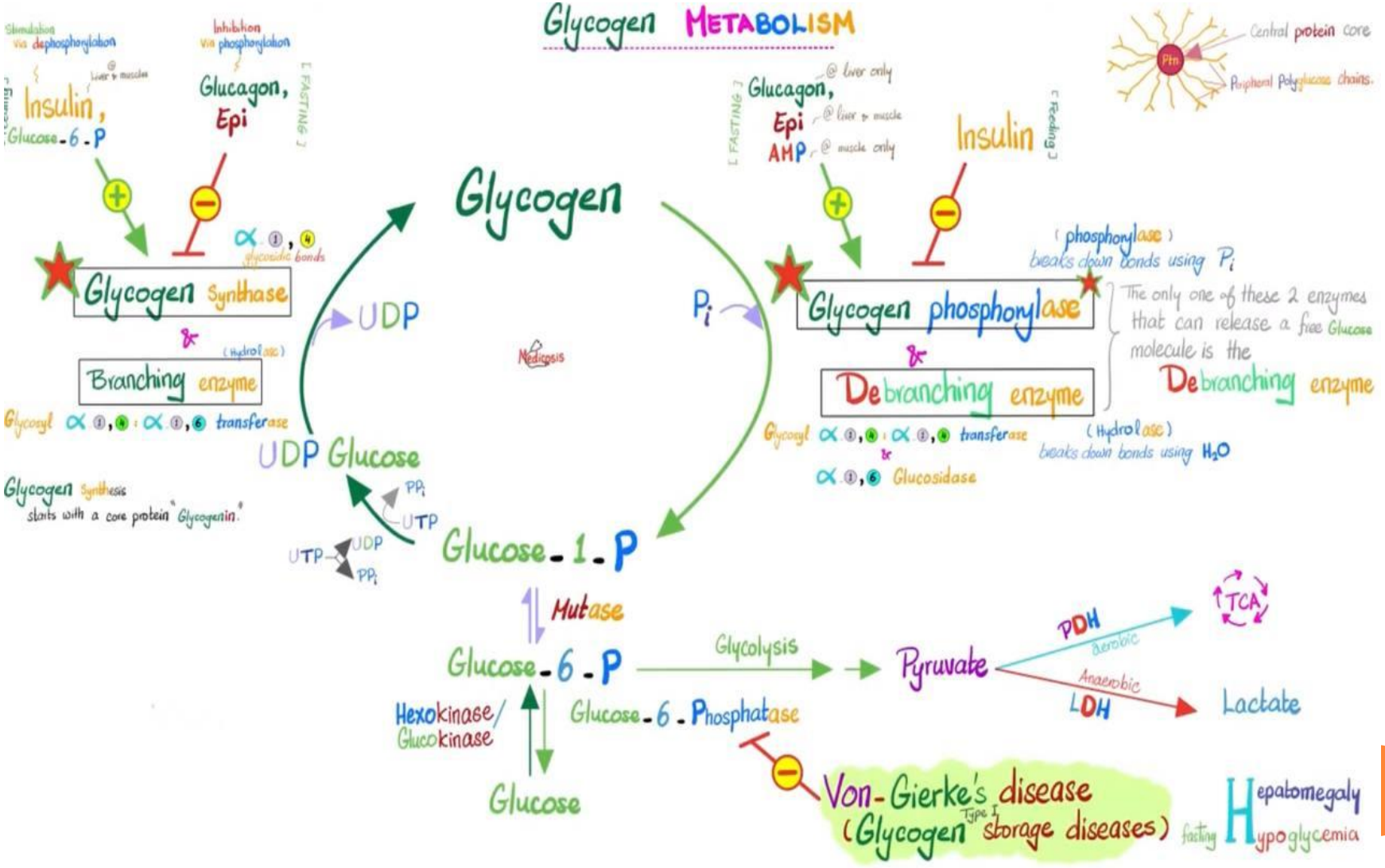


Introduction

- **Glycogen** is the storage form of glucose in animals and humans.
- It is mainly stored in the **liver** and **skeletal muscles**.

  - **Liver** :- Contains the highest concentration of glycogen (~5-8% of liver weight
  - serves to maintain blood glucose levels during fasting.
  - **Muscle :** Stores a large amount of glycogen (~1-2% of muscle weight)
  - provides glucose for energy during muscle contraction.

Overview about glycogen metabolism



Glycogen anabolism vs catabolism

Steps of glycogen synthesis

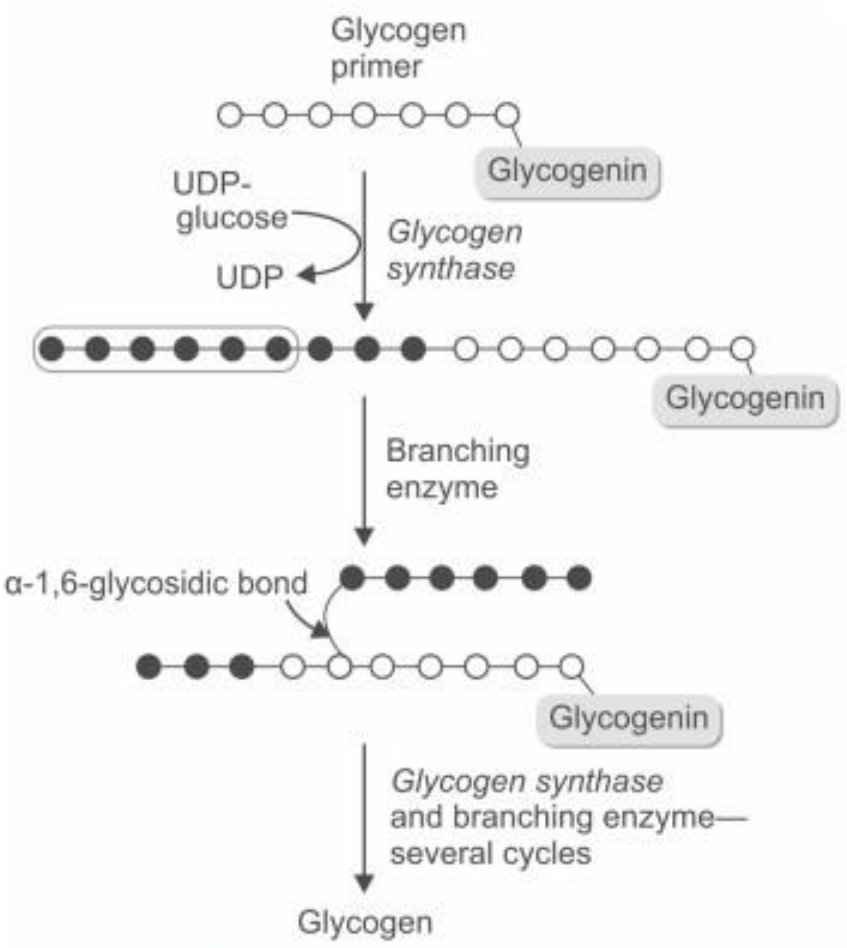
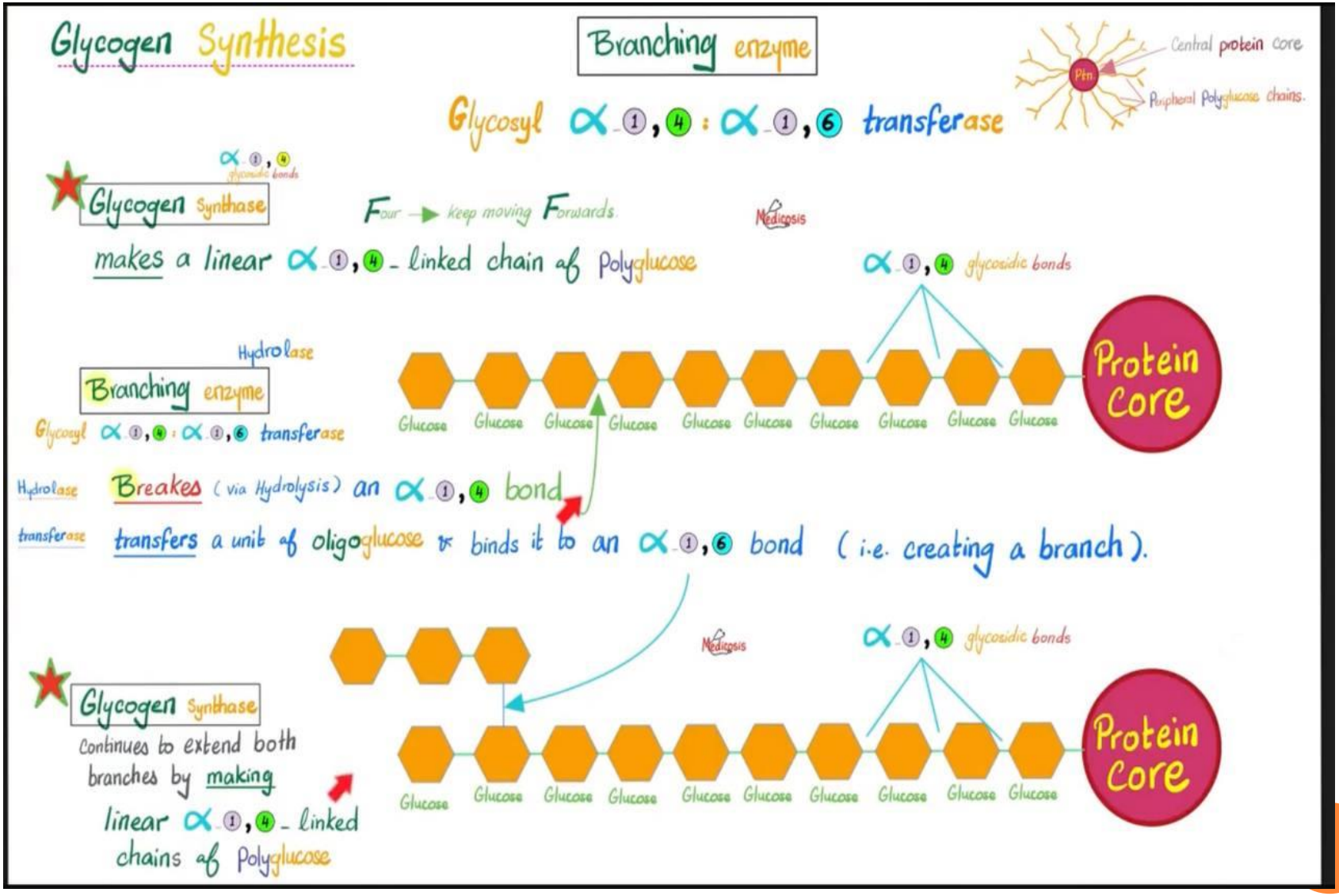


Fig. 4.12: Glycogen synthesis

Glycogenesis (Synthesis of Glycogen)



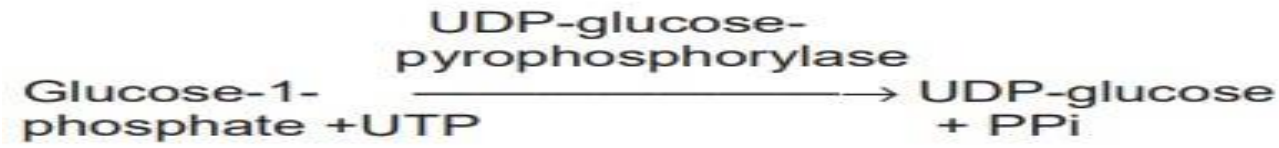
Glycogenesis (Synthesis of Glycogen)

- **Steps of Glycogenesis**
- **1- Glucose Uptake**:
  - Mediated by **GLUT transporters**:
    - **GLUT2** in the liver allows bidirectional glucose transport.
    - **GLUT4** in muscle is insulin-dependent and facilitates glucose uptake during high insulin states.
- **2- Hexokinase/Glucokinase**:
  - Phosphorylates glucose to **glucose-6-phosphate (G6P)**.

Steps of Glycogenesis

- **3- Phosphoglucomutase**:
  - Catalyzes the reversible conversion of G6P ↔ G1P.

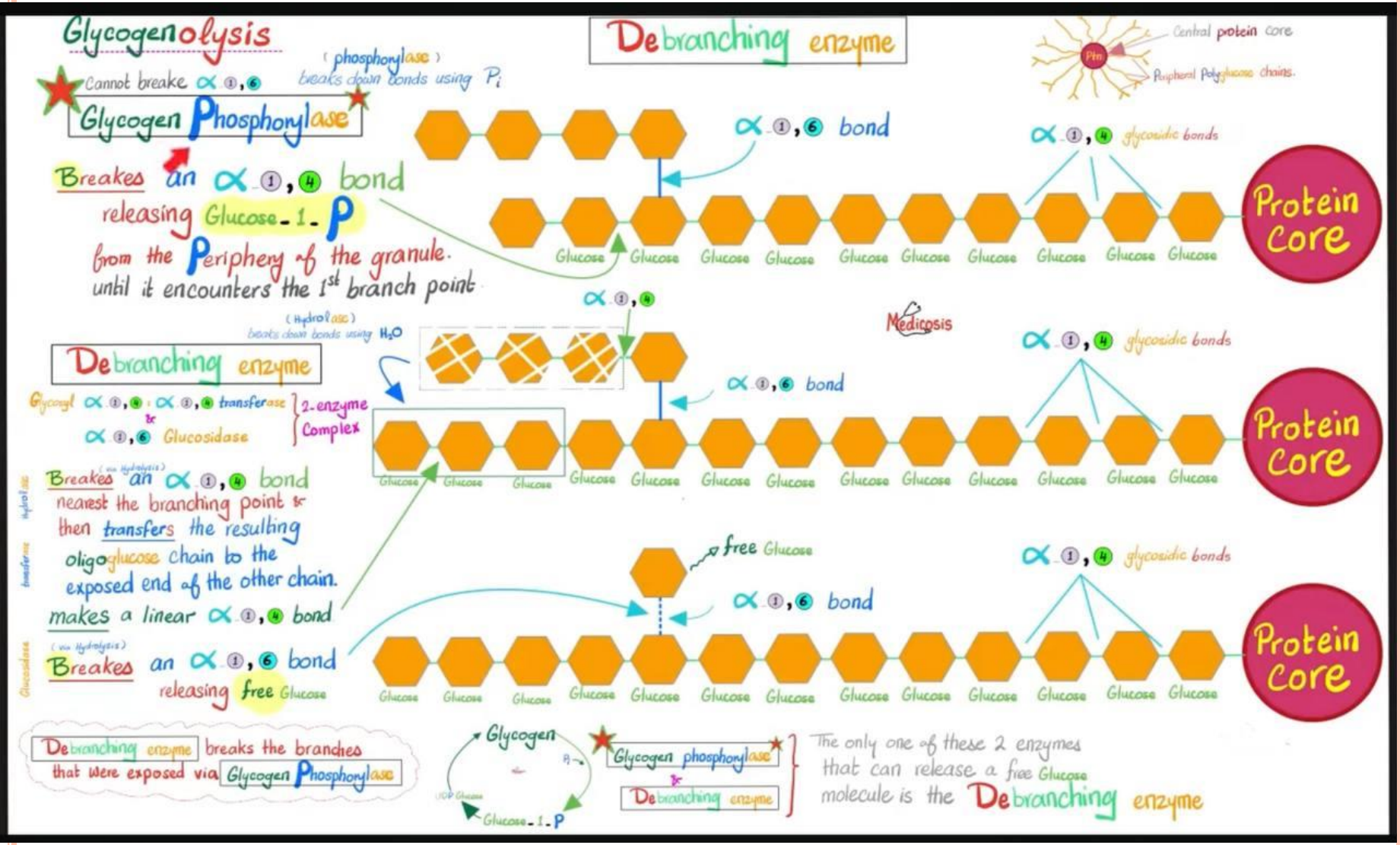
- **4- UDP-Glucose Pyrophosphorylase**:
  - **Activates G1P by attaching it to UTP, forming UDP-glucose.**



  - Releases **pyrophosphate (PPi)**, which is rapidly hydrolyzed by **pyrophosphatase,** driving the reaction forward.

- **Glycogenin**:
  - is made up of a protein-carbohydrate complex
  - Acts as a primer by auto-glycosylating its tyrosine residue with UDP-glucose.
- **Glycogen Synthase:**
  - Adds glucose residues from UDP-glucose to the growing glycogen chain via α-1,4 linkages.
  - Requires prior chains for activity
  - . **The glycogen synthase can add glucose units only in alpha-1,4 linkage**
  - **Branching Enzyme**:
  - Breaks (via hydrolysis) an α 1,4 glycosidic bond (creating a an oligosaccharide) then Transfers & bind it to an α 1,6 bond (creating a branch)
  - **Ensures compact glycogen structure and enhances solubility.**
- Then glycogen **Synthase continue to extend branches by making a** α 1,4 linked chain .

Glycogenolysis (Breakdown of Glycogen)



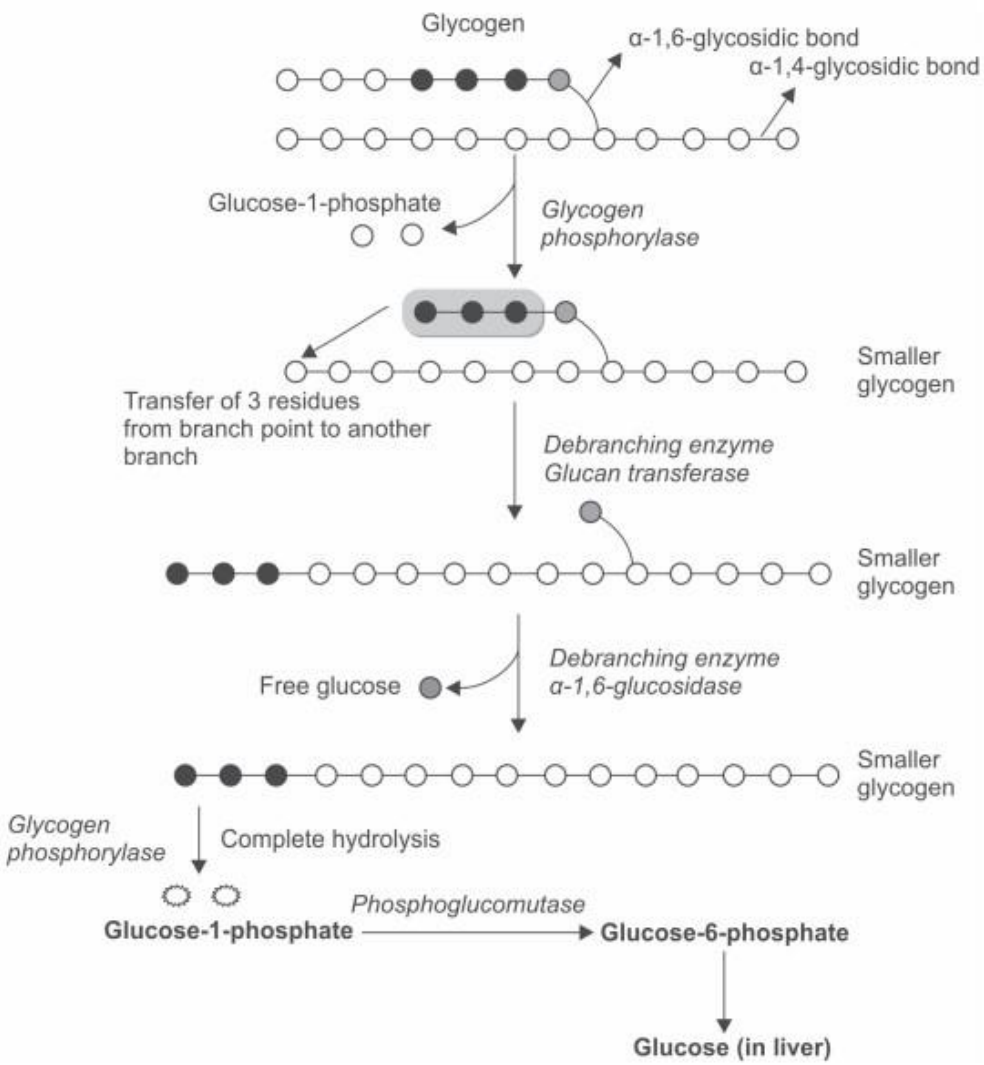


Fig. 4.10: Steps in glycogenolysis

Glycogenolysis (Breakdown of Glycogen)

- **Step-by-Step Mechanisms**
- **1- Glycogen Phosphorylase**:
  - Catalyzes the cleavage of α-1,4 glycosidic bonds by **phosphorolysis** (not hydrolysis).
  - Uses inorganic phosphate (Pi) to generate **glucose-1-phosphate (G1P)**.
- **2- Debranching Enzyme**:
  - Multi-functional enzyme with:
    - **4-α-glucanotransferase activity**: Transfers three glucose residues from a branch to the main chain.
    - **Amylo-α-1,6-glucosidase activity**: Hydrolyzes the α-1,6 bond, releasing free glucose.

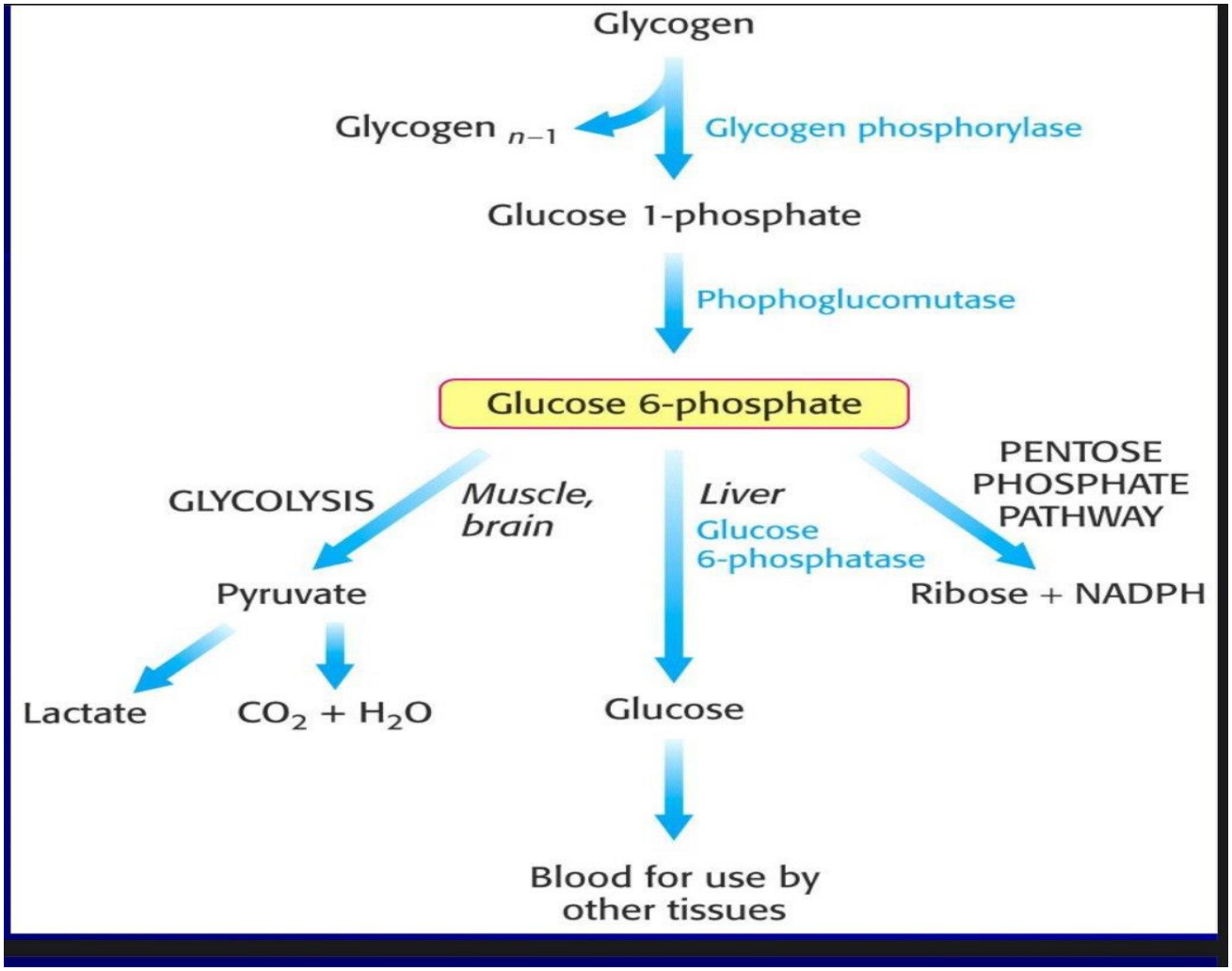
3- Phosphoglucomutase:

- Converts G1P to G6P for downstream utilization:
  - **Liver**: G6P is dephosphorylated by glucose-6-phosphatase to free glucose.
  - **Muscle**: G6P enters glycolysis for ATP generation.

4- **Glucose-6-Phosphatase** (Liver-specific):

- Found in the endoplasmic reticulum membrane.
- Hydrolyzes G6P to glucose and inorganic phosphate.
- **Absent in muscle, limiting its glycogen use to local energy production.**

Glucose 6-phosphate has 3 fates



Regulation of Glycogen Metabolism

- **A. Hormonal Regulation**
- **Insulin**:
  - Activates **protein phosphatase-1 (PP1)**:
    - activates **glycogen synthase**.
    - inhibits **glycogen phosphorylase**.
  - Stimulates glucose uptake in muscle by recruiting **GLUT4** to the plasma membrane.
- **Glucagon**:
  - Activates **adenylyl cyclase**, increasing **cAMP** levels.
  - cAMP activates **protein kinase A (PKA)**:
    - PKA phosphorylates and activates **glycogen phosphorylase kinase**, which then activates glycogen phosphorylase.
    - PKA **inactivates** **glycogen synthase**.
- **Epinephrine**:
  - Acts via ß-adrenergic receptors in muscle (cAMP/PKA pathway).

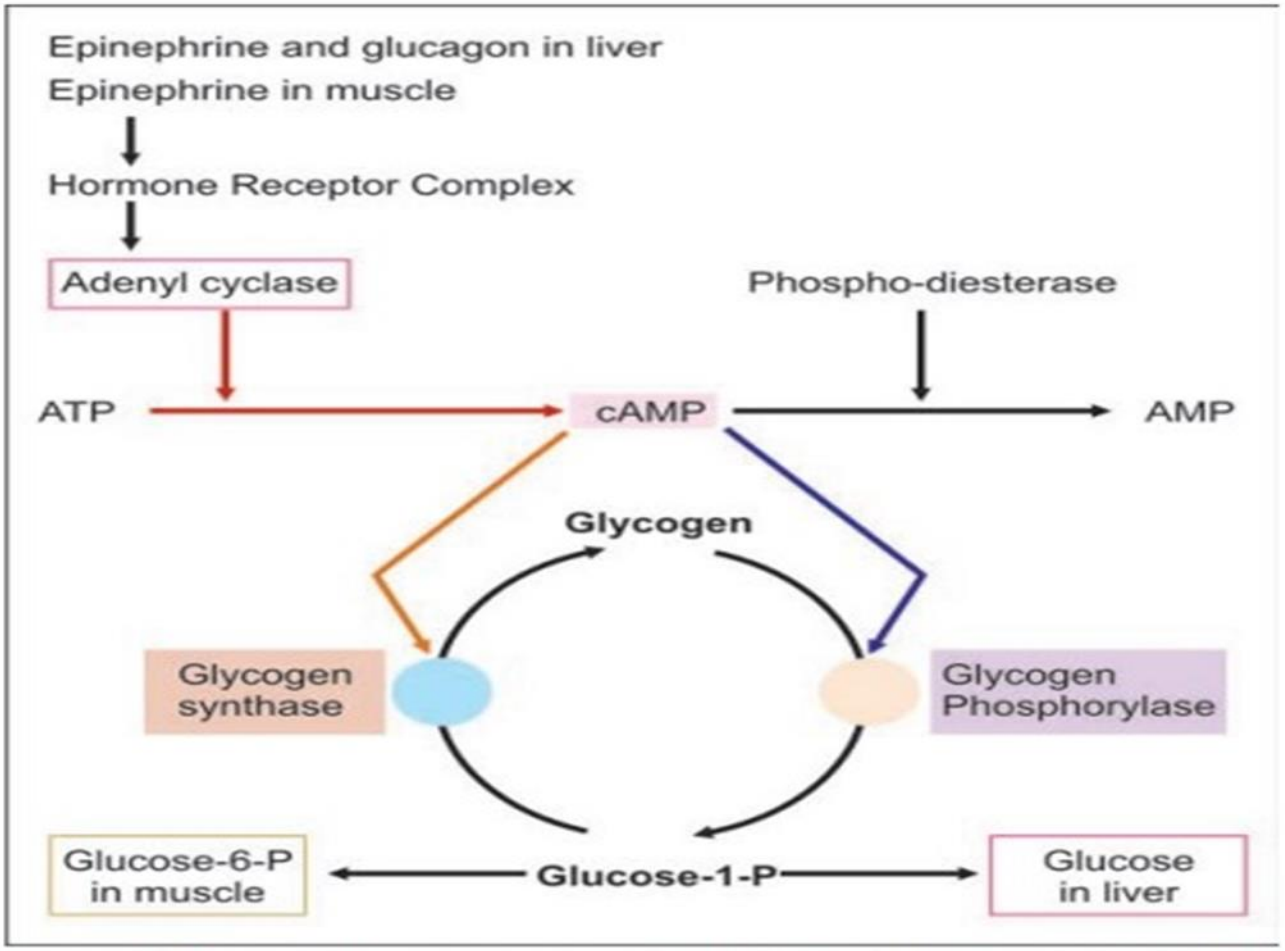


Fig. 9.39. Reciprocal regulation of glycogenolysis and glycogen synthesis by cyclic AMP

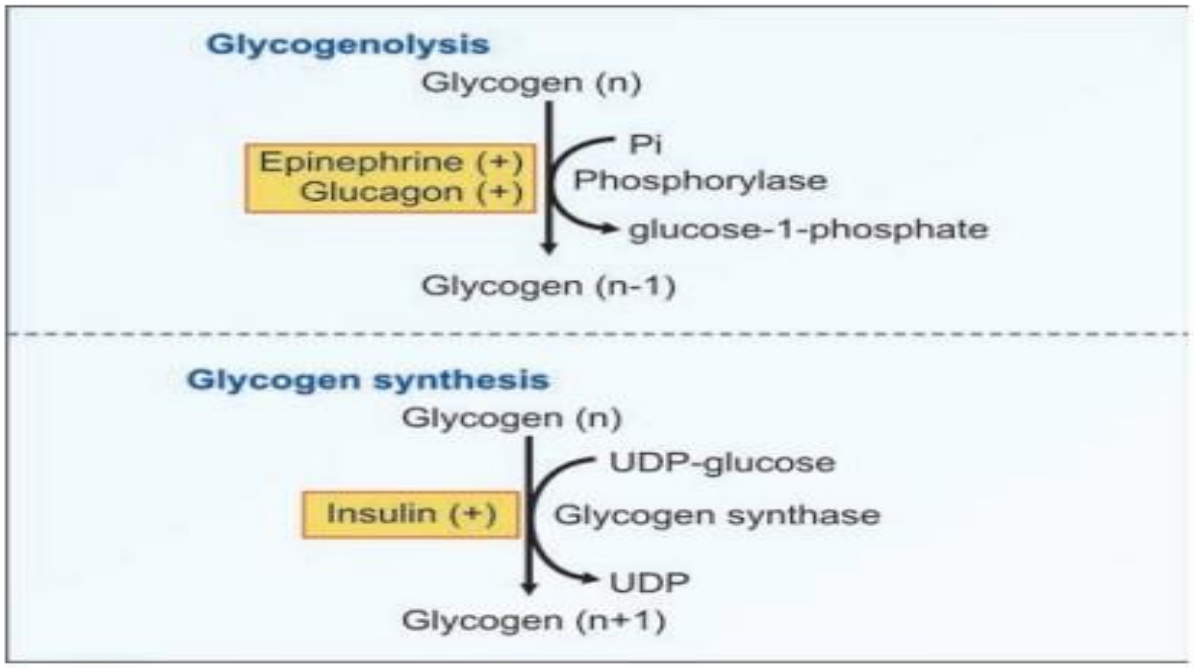


Fig. 9.40. Effects of hormones on glycogen

B. Allosteric Regulation

- **Glycogen Phosphorylase**:
  - Activated by **AMP** (signals low energy in muscle).
  - Inhibited by **ATP** and **G6P** (high energy state).
- **Glycogen Synthase**:
  - Activated by **G6P**, a signal of excess glucose.

Clinical applications
GLYCOGEN STORAGE DISEASES

- These are inborn-errors of metabolism
- **Glycogen Storage Disease Type-I**
- It is also called Von Gierke's Disease.
- It's the Most common type of glycogen storage disease .
- **Glucose-6-phosphatase is deficient.**
- . Fasting hypoglycemia that does not respond to stimulation by adrenaline.
- The glucose cannot be released from liver during over night fasting
- Treatment is to give small quantity of food at frequent intervals.

- **Type III**
- **Deficiency of Debranching enzyme**
- Highly branched dextrin accumulates in the liver
- Symptoms :-Fasting hypoglycemia; hepatomegaly

- **Type V** :-
- **Deficiency of Muscle phosphorylase**
  Symptoms Excercise intolerance; accumulation of glycogen in muscles
- **Type VI** :-
- **Deficiency of Liver phosphorylase**
- Symptoms :hypoglycemia; hepatomegaly

. Summary of Regulation

- The key enzyme for glycogenolysis is phosphorylase, which is activated by glucagon and adrenaline under the stimulus of hypoglycemia.

- The key enzyme for glycogen synthesis is glycogen synthase, the activity of which is decreased by adrenaline but is enhanced by insulin, under the stimulus of hyperglycemia

Thank you

Any questions ?