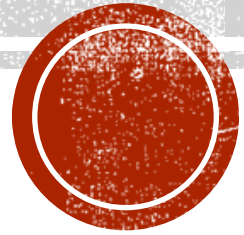
Glycogen Metabolism

1. Glycogenesis
2. Glycogenolysis



Students Learning Outcomes

❖ **By the end of this lecture, the students should be able to:**

1. Discuss glycogen synthesis (definition, site, importance, and steps).
2. Discuss glycogenolysis (definition, importance, and steps).
3. Summarize reciprocal regulation of both glycogenesis and glycogenolysis.
4. Differentiate between liver and muscle glycogen.
5. Describe glycogen storage diseases.
6. Clarify pathogenesis of Von Gierke's manifestations.

Content

1. Glycogen
2. Glycogen metabolism
    a. Glycogenesis
    b. Glycogenolysis
3. Glycogen storage diseases

Glycogen

❖**Definition**: It is the **storage** form of carbohydrate **in animal**

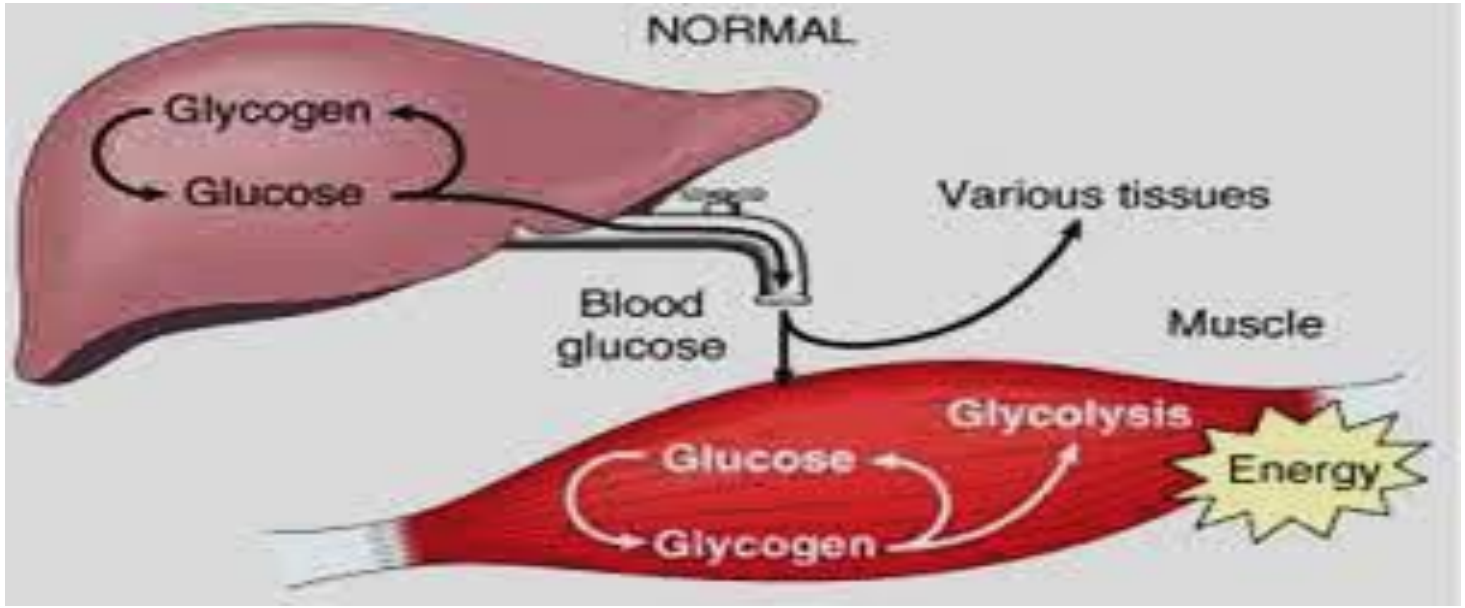
❖**Location:** cytoplasm of many tissue but mainly:

- ✓ **Liver (8-10% of liver weight)**
- ✓ **Muscle (2 % of its weight)**

▪

Function of Glycogen

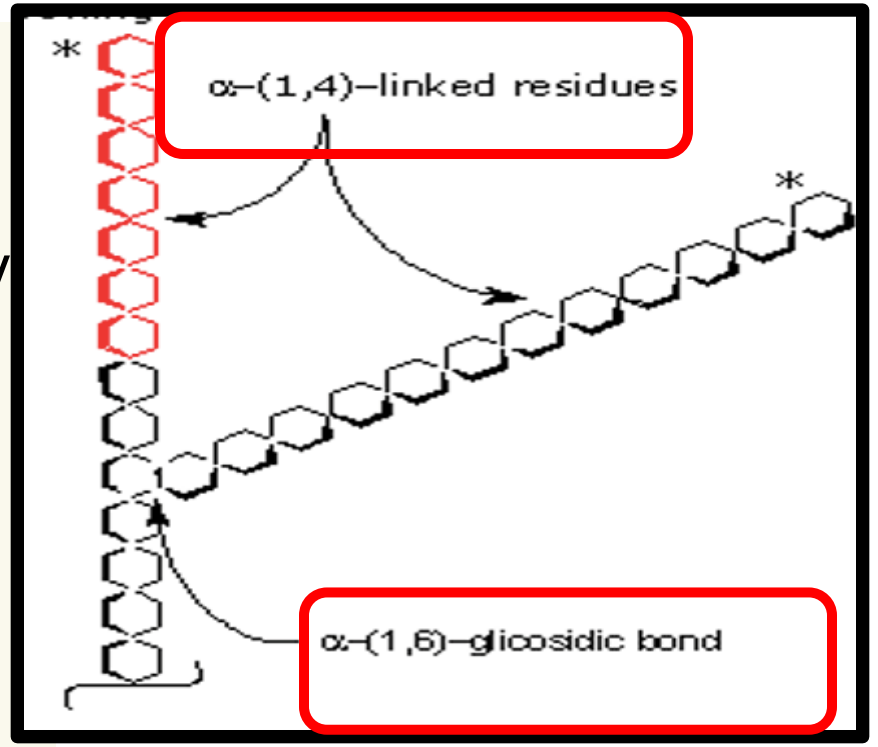
	Liver glycogen	Muscle glycogen
Function	The liver breaks down to **maintenance blood glucose** between meals, or during fasting	**Reserve fuel:** muscle breaks down it to glucose → undergo glycolysis→ **Energy** for muscle during **contraction**
Depleted	**After 12-18** hours **fasting**	After **muscular exercise**



Structure of glycogen

❖ Structure

- It is a **branched Polymer** of glucose units linked by
  - ✓ α 1,4 glycosidic linkage within the main branches
  - ✓ α 1,6 glycosidic linkage at the branched points
- With about 8-12 glucose residue in the branch
- A protein **glycogen primer (=** Glycogenin protein containing tyrosine aa) forming the core of glycogen particle.

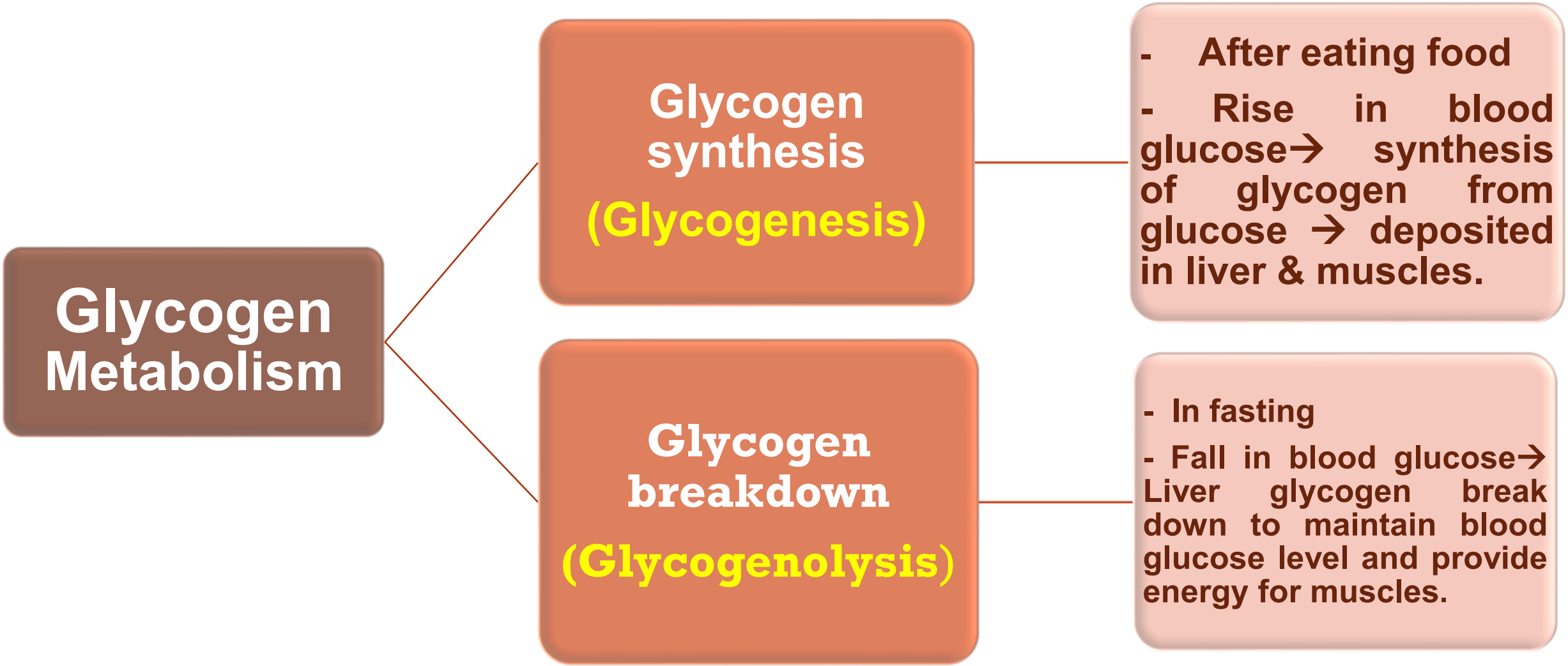


Clinical application:

Marathon runners need glycogen

1. Many runners use **high carbohydrate diet** in preparation for racing to increase **glycogen stores**
2. **Training** increased muscle glycogen content
3. Exhaustion and collapse caused by **depletion of glycogen**

Glycogen metabolism



After about 12-18 hours fasting→ depletion of liver glycogen

Glycogenesis

1. Definition
2. Site
3. Importance
4. Steps
5. Regulation

Glycogenesis

1.Definition of glycogenesis

It is the process of synthesis of glycogen from glucose

2.Sites of glycogenesis

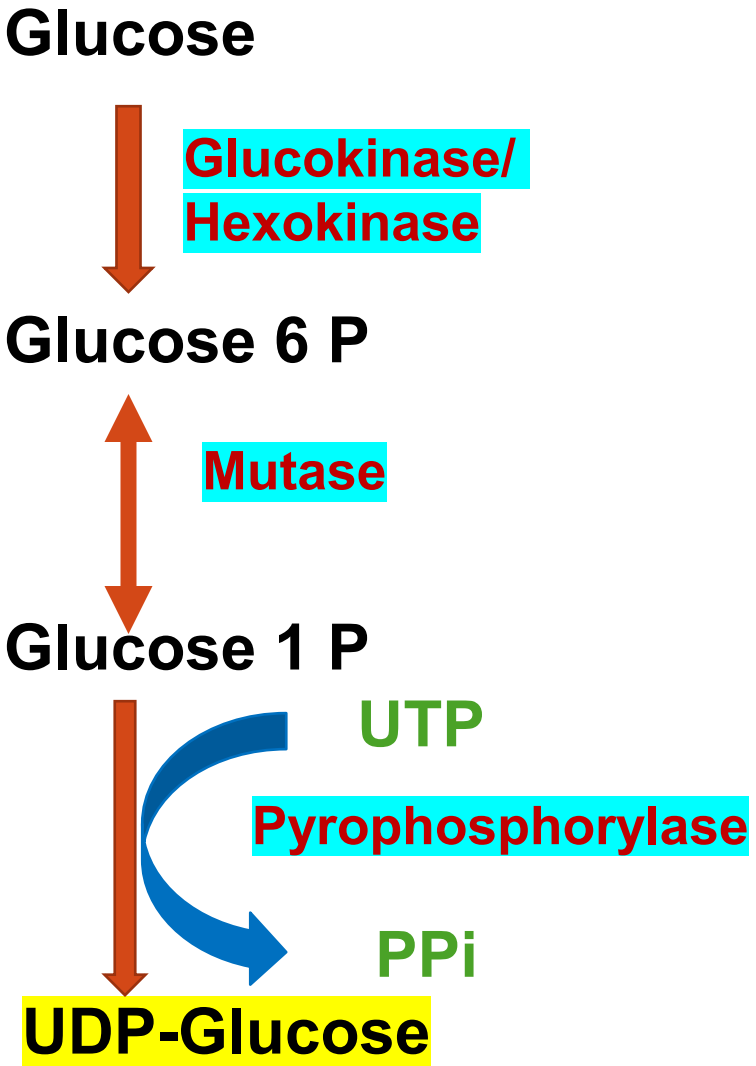
In the cytosol of all tissues, mainly in liver & skeletal muscles.

3.Importance of glycogenesis

It stores excess glucose after high carbohydrate meal

4.Steps of glycogenesis

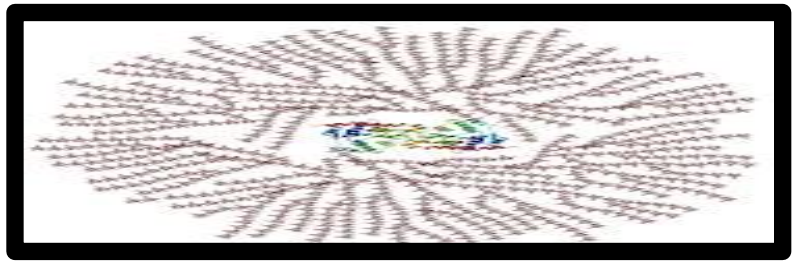
I- Activation of glucose to UDP-Glucose by pyrophosphorylase



In case of excess glucose

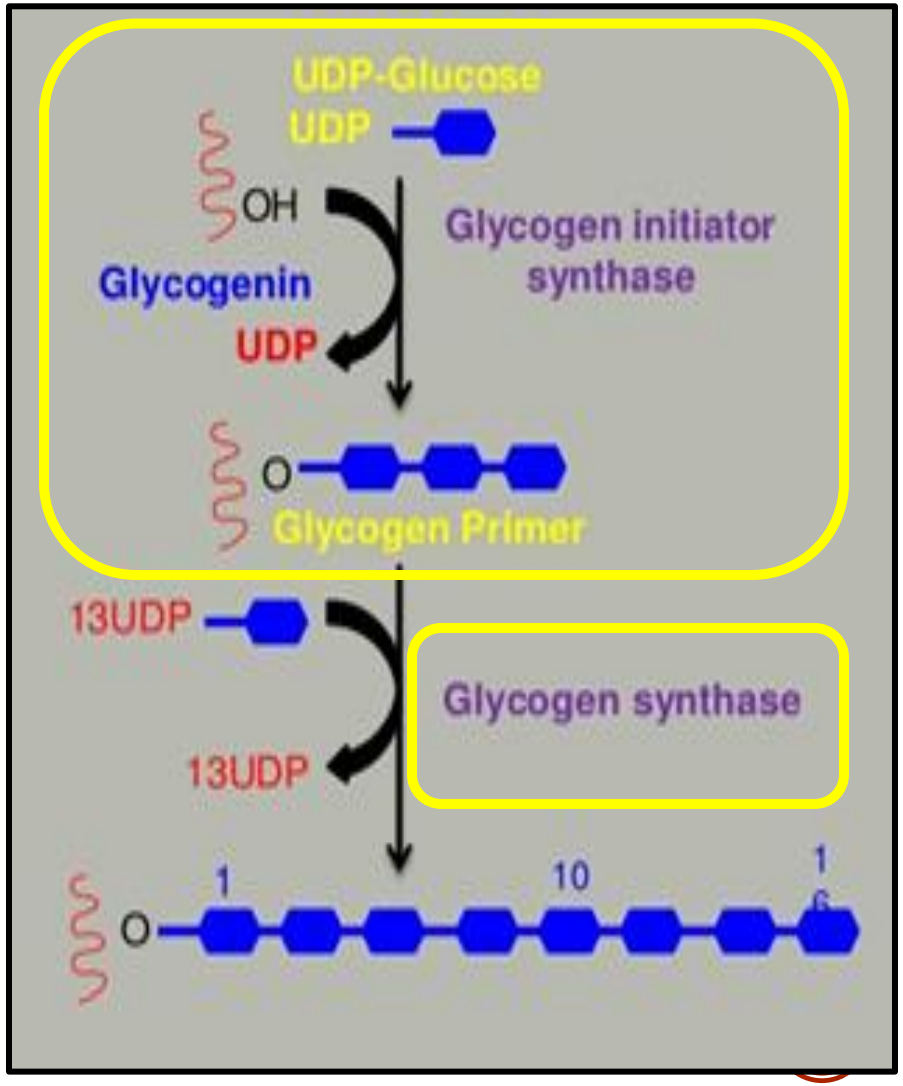
1. Glucose → G6P by **glucokinase/ hexokinase**
2. G6P → G1P by **mutase**
3. G1P then activated by UTP → form UDP-Glucose by **pyrophosphorylase**

II. Initiation of glycogen synthesis

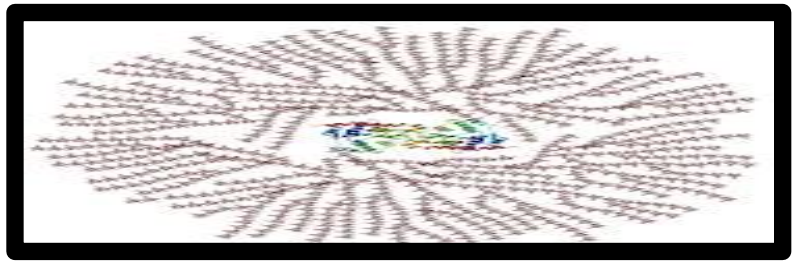


Addition of UDP-Glucose to glycogen primer

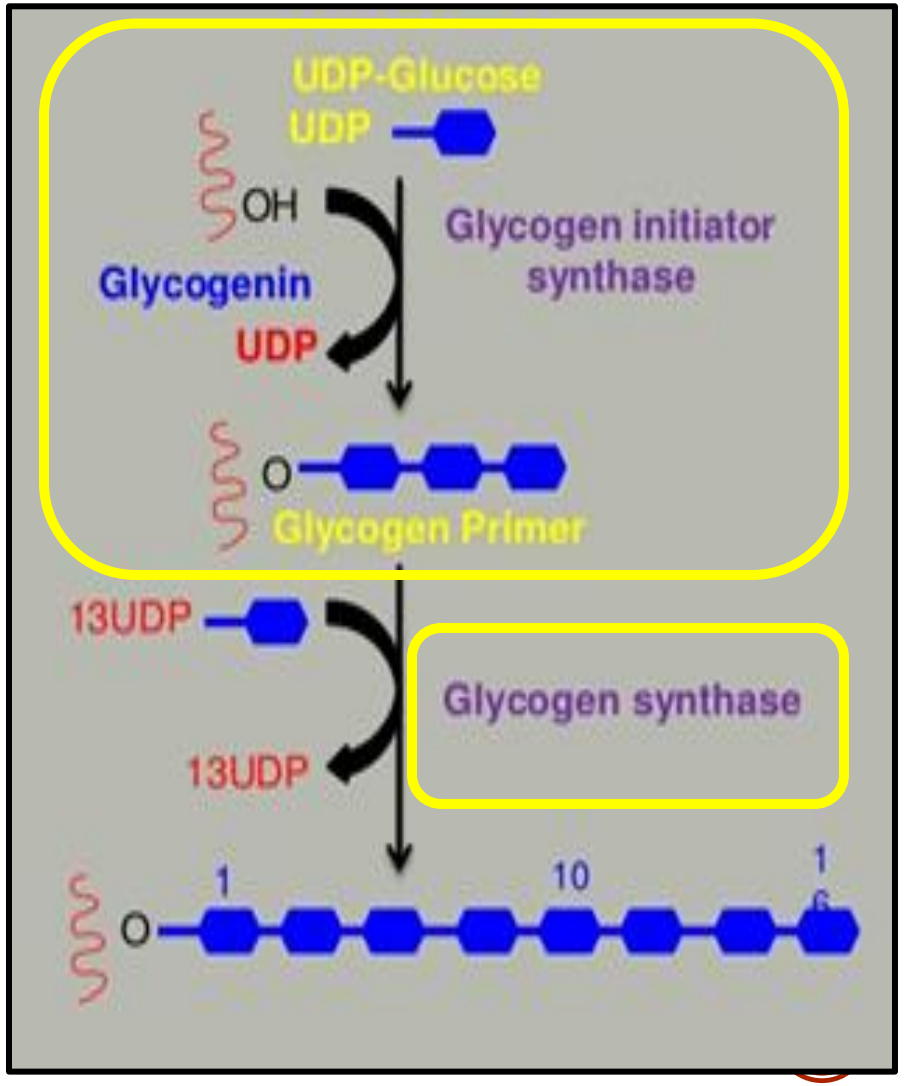
1. It requires the presence of **glycogen primer** (**Glycogenin**)
2. Glycogenin is a protein that has tyrosine amino acids with an OH group.
3. An enzyme called **Glycogen initiator synthase** then adds **UDP glucose** to the **tyrosine OH** group of glycogenin primer several times.



III. Elongation of the glycogen chain



- By **Glycogen Synthase**
- It continuous adding UDP-glucose to the glycogen primer linking the glucose residues by **α-1,4 bonds** till reaching 10-12 residue in the chain

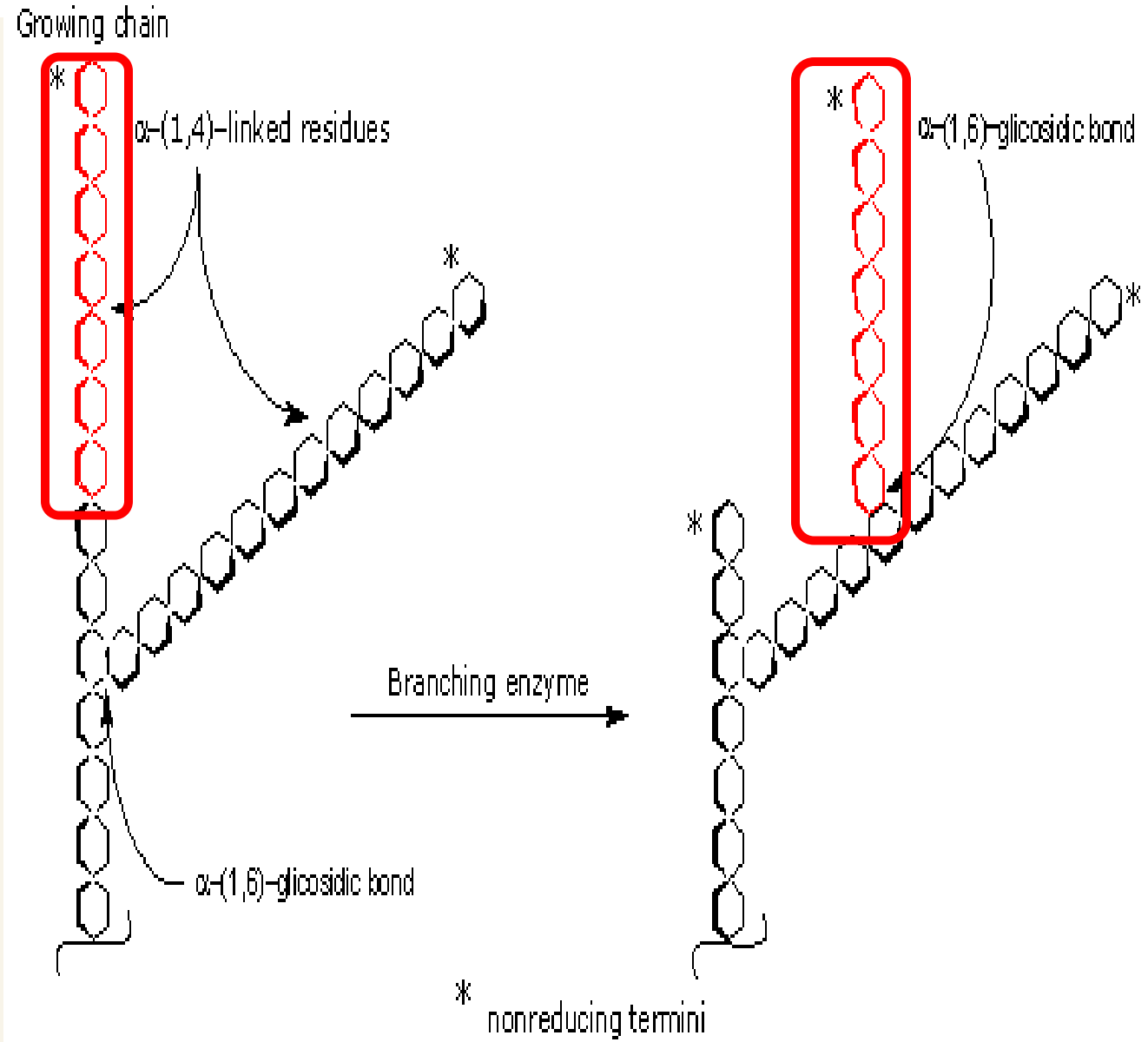


IV. Branching of the glycogen polymer

- Catalyzed by **Branching (transferase) enzyme**

- **Branching enzyme works by:**

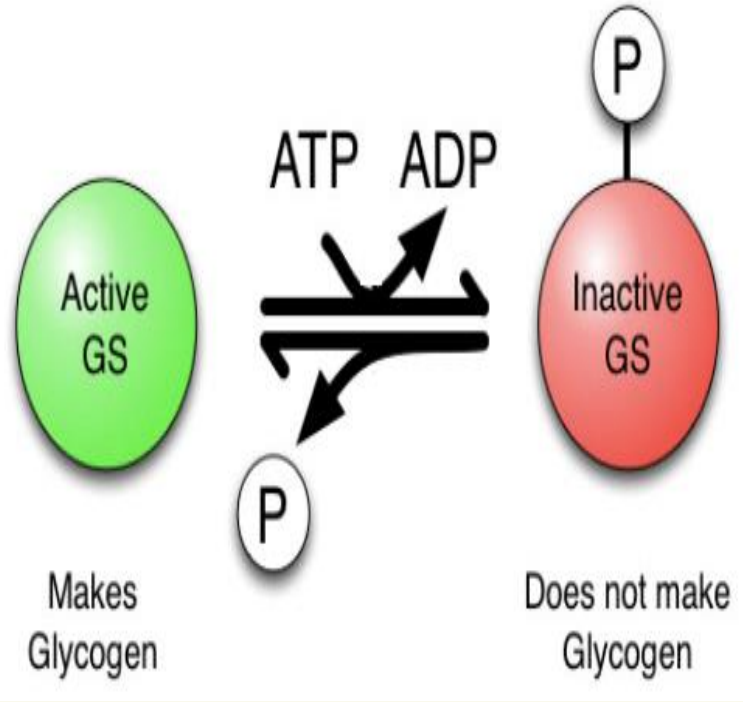
1) **Breaking α-1,4** bonds
2) **Removing** block of **7 glucose** residues
3) **Transferring** them to nearby branch→ creating **1,6 bonds** at branching point



5. Regulation of glycogenesis

- The key regulatory enzyme is **Glycogen Synthase (GS)**

- GS is present in two forms:
  a) **active form** : is the **dephosphorylated GS**
  b) **Inactive form**: is the **phosphorylated GS**



I. Hormonal regulation of glycogen synthesis

a. **In Well fed state :Insulin** **dephosphorylation** of GS→ **activating** it→ ↑ glycogenesis in liver and muscles → ↓ blood glucose level.

b. **In Fasting state: Glucagon and epinephrin** → **phosphorylation** of GS→ **inactivating** it→ ↓ glycogen synthesis in liver and muscle→ ↑ blood glucose.

II. Glucose & Glucose 6 P→ also **activate** glycogen synthase

Glycogenolysis

1. Definition
2. Site
3. Importance
4. Steps
5. End products & fate of G-1-P
6. Regulation

Glycogenolysis

1. Definition of glycogenolysis

It is the breakdown of glycogen into **glucose** (in the liver) and **glucose 6 phosphate** (in muscles).

2. Sites of glycogenolysis

In the cytosol of many tissue especially liver cells and muscles.

Glycogenolysis

3. Importance of glycogenolysis

(1) Liver glycogenolysis: It is the main source of blood glucose in **fasting** conditions for less than 18 hours.

(2) Muscle glycogenolysis: The source of energy in muscles during muscle **contractions.**

4. Steps of Glycogenolysis :

Glycogenolysis is catalysed by 2 enzymes

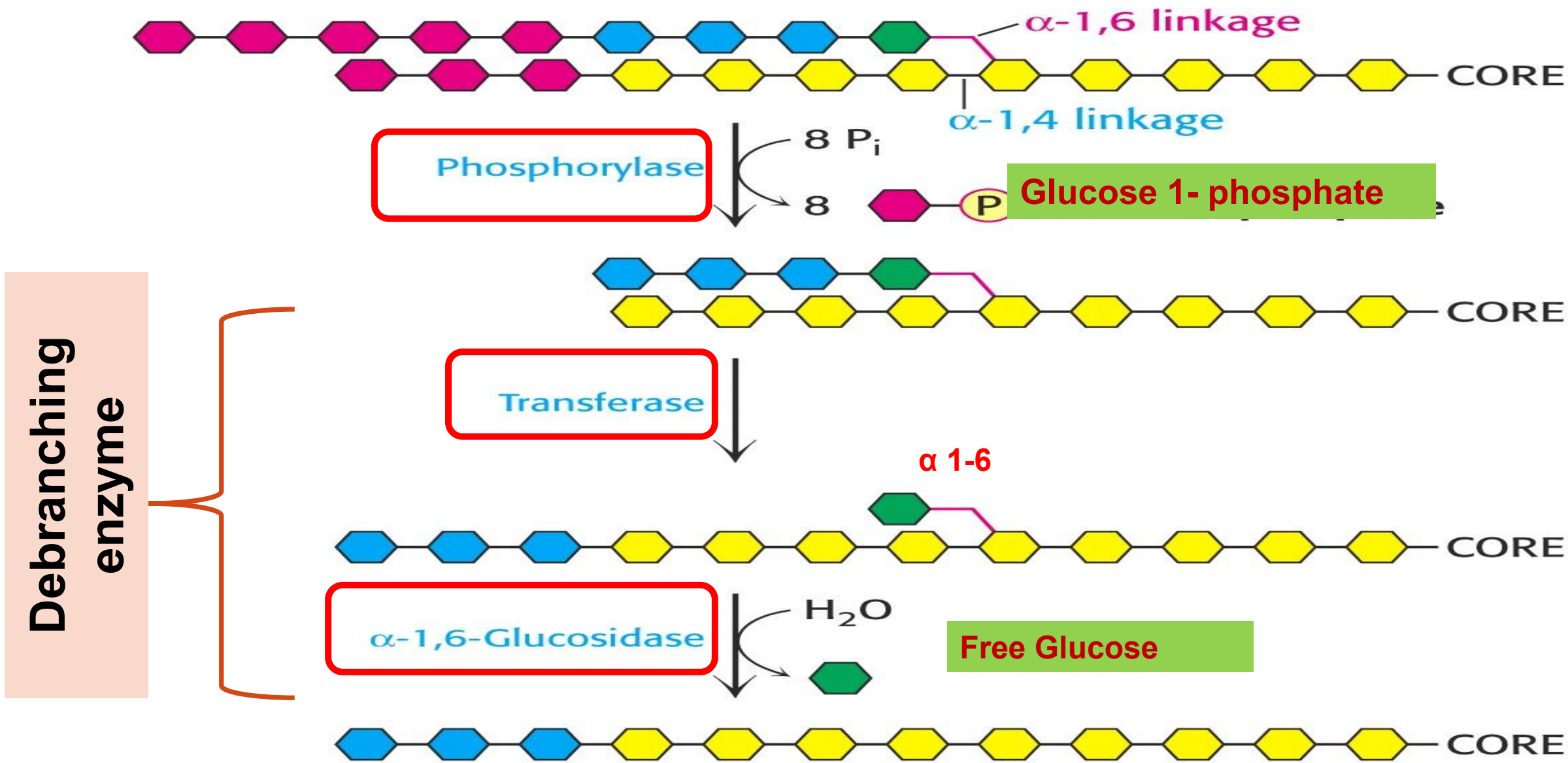
I. Glycogen phosphorylase:

Break **α 1-4 bond** by **adding P** to Glucose →releasing **glucose 1 P** & leaving 4 glucose residues in the chain.

II. Debranching enzyme : bifunctional enzyme (has 2 actions)

1. **Glucotransferase:** **transfer 3 glucoses** from one branch → to main branch leaving the **last glucose** at the branching point.
2. **Glucosidase:** **break** the **last glucose at α 1-6** branching bond by **adding H2O** → releasing **free glucose**

Enzymes catalysing glycogenolysis:



5. End products of glycogenolysis

I. Glucose 1 P: (many)

- ✓ Released from the main branches
- ✓ G1P is converted to **G6P** *** by mutase enzyme

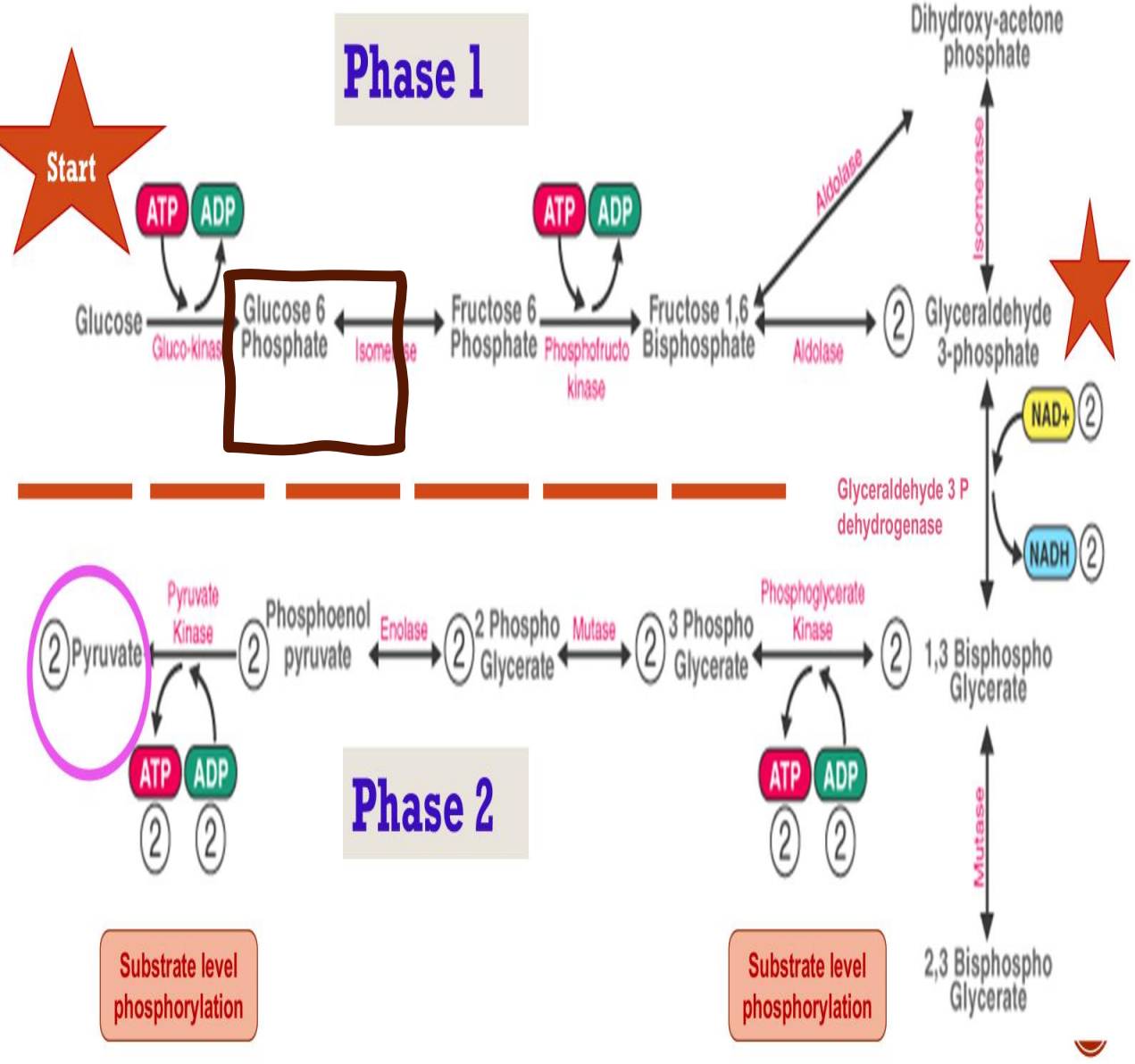
II. Free glucose: (little)

- ✓ released only from the branching points

Fate of G6P

1. **In the liver**: it convert to glucose (**by glucose 6 phosphatase**) → **glucose** released to the blood to maintain **blood glucose level**.
2. **In the muscle** → free glucose is not formed as the muscles don't have Glucose 6 Phosphatase , so G6P join glycolysis → **pyruvate → lactate &** give **energy for muscle** contraction.
3. **Join HMP pathway → NADPH & ribose 5 P**

2 Phases of glycolysis (10 enzymatic reactions)

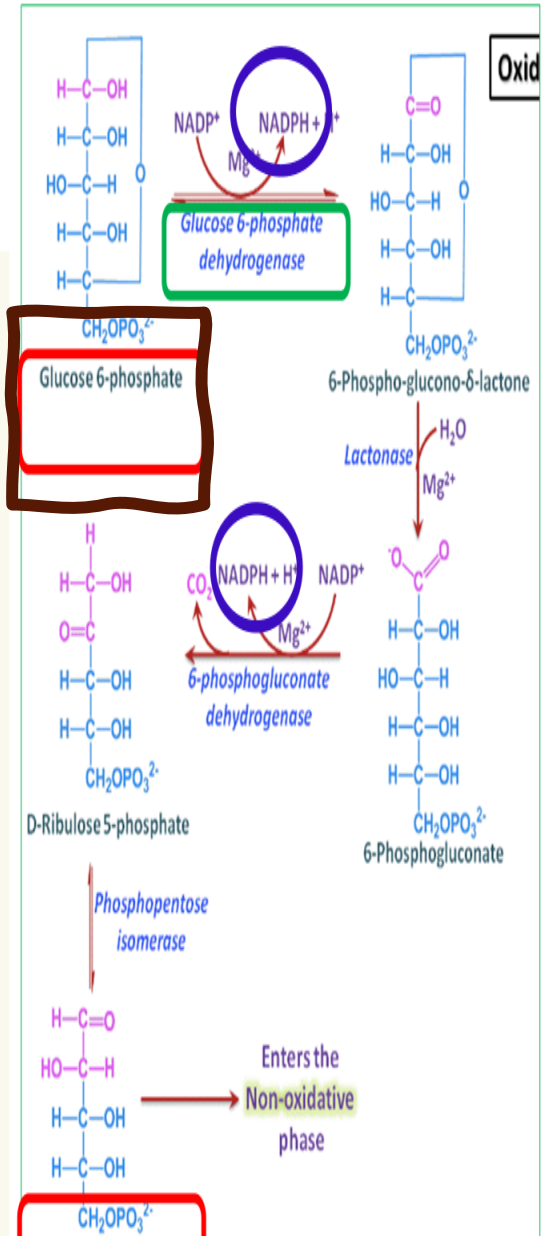


Phases of HMP

I. Oxidative phase

- ✓ **Irreversible**
- ✓ **Start by**: Glucose 6 phosphate (G6P)
- ✓ **End by formation of** : **Ribose 5 P** → enter nonoxidative step
- ✓ **Produce: 2 NADPH**
- ✓ Imp enzyme: **G-6-P dehydrogenase** (G6PD)

(The key regulatory enzyme) catalysing 1st reaction



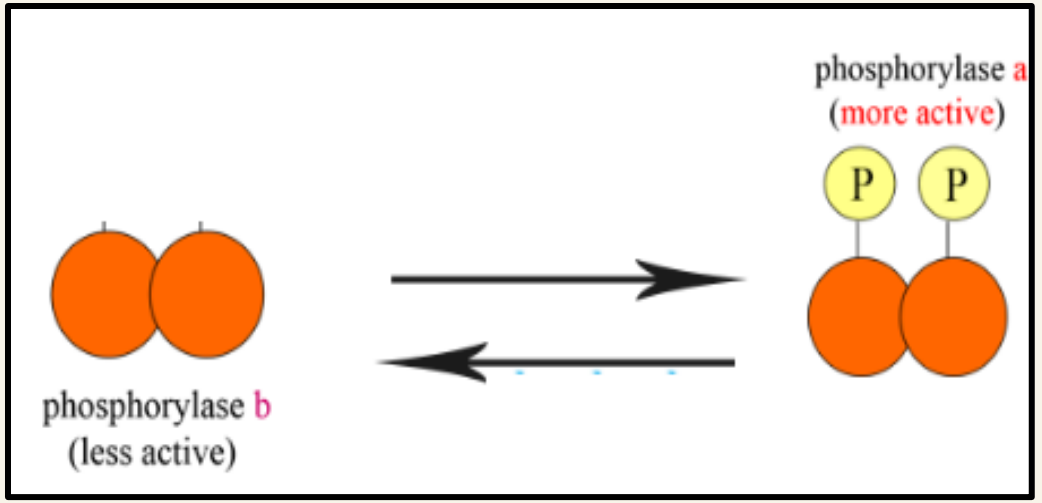
6. Regulation of glycogenolysis

- **Key regulatory enzyme of glycogenolysis**: **glycogen phosphorylase**

- **Glycogen phosphorylase** It has two forms:

  a) The active form is **phosphorylated.**

  b) The inactive form is **dephosphorylated**



- **Hormonal regulation of glycogen phosphorylase activity:**

  a. In Well fed state :Insulin dephosphorylating glycogen phosphorylase → inactivating it→ ↓ glycogen breakdown in liver and muscles.

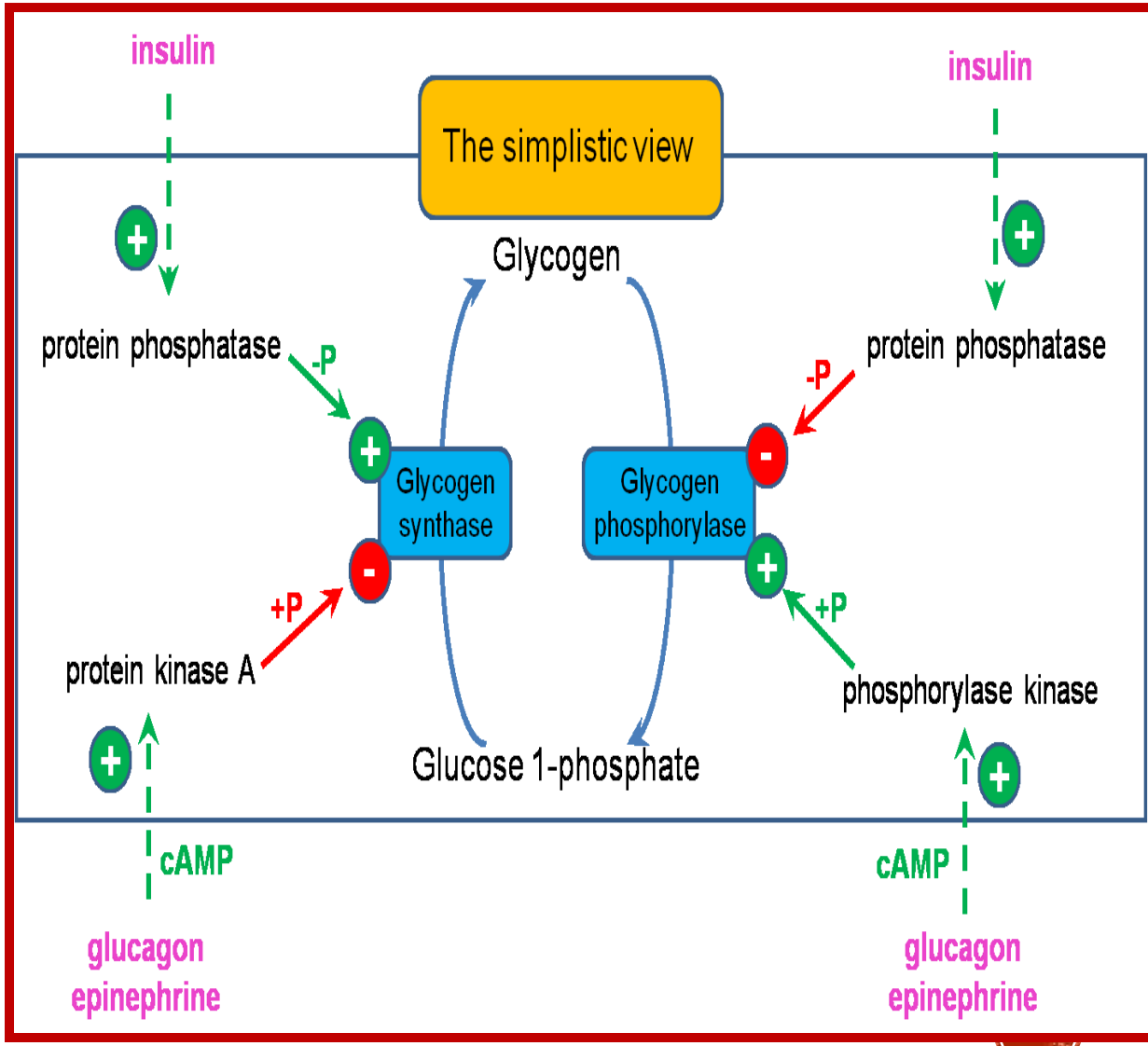
  b. In Fasting state: Glucagon and epinephrin → phosphorylation of glycogen phosphorylase → activating it→ ↑ glycogen breakdown in liver and muscle

.

Reciprocal regulation of glycogenesis and glycogenolysis

- **Insulin→ always dephosphorylate enzymes→ so, it** stimulate glycogenesis & inhibit glycogenolysis

- **Glucagon & epinephrin→ always phosphorylate enzymes →** so, it stimulate glycogenolysis & inhibit glycogenesis



Differences between liver and muscle glycogen

	Liver glycogen	Muscle glycogen
Amount	- 8 % of liver weight - 120 gm	- 2% of muscle weight - 300 gm
Function	Source of blood glucose during early fasting	Source of energy for muscle contraction
Fate	Glucose	Glucose 6-phosphate
Starvation	Decreases liver glycogen	No effect on muscle glycogen
Exercise	Has no effect	Decrease muscle glycogen
Insulin	Increase	Increase
Glucagon	Decrease	Has no effect

Glycogen storage diseases (Glycogenosis)

Glycogen Storage diseases (GSD) = Glycogenosis

- **Definition:** **Inherited** metabolic disorders characterized by deposition of abnormal amounts of glycogen in liver and muscle due to deficiency of enzymes of glycogen metabolism .
- **Types** : There are more than 13 types depending on which enzyme is deficient.
- **General symptoms:**

1- Hypoglycaemia : if deficiency is in liver enzyme

2- Muscle weakness and difficulty in exercise: if deficiency is in muscle enzyme

3- Additional symptoms: differ depending on which enzyme is deficient

Glycogen Storage diseases (GSD) = Glycogenosis

❖ Type I glycogen storage disease: Von Gierek's disease

- ✓ **Most important** glycogen storage disease.
- ✓ **Due to deficiency of glucose-6-phosphatase** → accumulation of **glucose-6-phosphate** and **glycogen** in **liver.**
- ✓ **Characterized by:**

1. Fasting hypoglycaemia: liver cannot release enough free glucose by glycogenolysis, only the **free glucose** from **debranching** enzyme is available.

2. Hyperlipidaemia: due to **increased lipolysis** in adipose tissues.

MCQs

Which one of the following processes is stimulated by Insulin?

a) Hepatic glycogenolysis
b) Muscle glycogenolysis
c) Hepatic glycogenesis
d) Lipolysis
e) Gluconeogenesis

MCQs

For glycogenesis, glucose should be converted to:

a) Glucuronic acid
b) Pyruvic acid
c) UDP-glucose
d) Sorbitol
e) Lactic acid

MCQs

In glycogenolysis, the enzyme which transfers a trisaccharide unit from one branch to the other exposing 1→ 6 branch point is:

a) Phosphorylase
b) Glucosyl transferase
c) Amylo [1→ 6] glucosidase
d) Amylo[1→ 4]→ [1→ 6] transglucosidase


Life
isn't about
finding yourself.
...
Life
is about
creating yourself.