BIO TEAM 429

بسم الله الرحمن الرحيم

MUSCULOSKELETAL BLOCK

GLYCOGEN METABOLISM

إعداد الطالبات:

بدور آل قدره – ساره بن حسين – رهام الحناكي

ساره محاسن – ألاء الأحمري

شكر خاص لبدراء المحارب

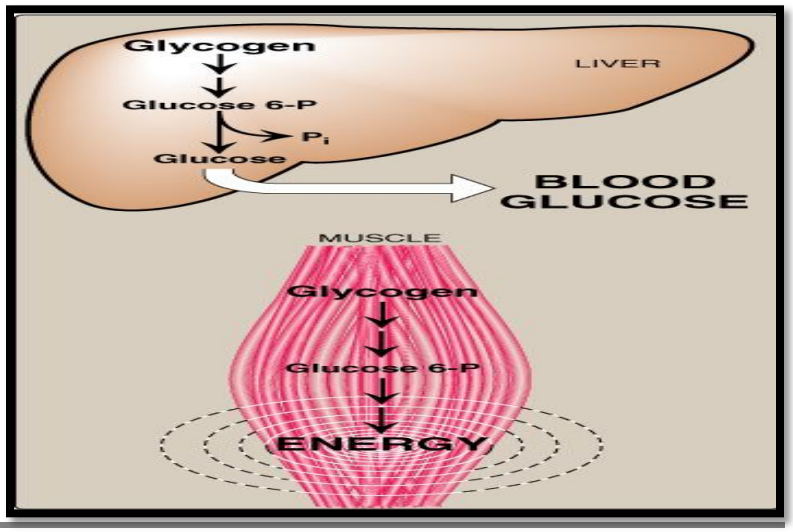
❖ Energy source:

1. **Glucose: preferred energy source for the brain + essential source for cells with few or no mitochondria (as RBCs) + exercising muscles (substrate for anaerobic glycolysis)**
   - **Sources of Glucose to human Body:**
     1) **DIET: sporadic (depends on the diet) → is not always a reliable source of glucose**
     2) **GLYCOGEN DEGRADATION (Glycogenolysis)**
     3) **GLUCONEOGENESIS: can provide sustained synthesis of glucose BUT slow in responding to falling in blood glucose level**

2. **Glycogen: storage of glucose used in the absence of a dieting source of glucose ⟶ released from liver and kidney during exercise ⟶ muscle glycogen**
   - **Depletion of glycogen stores (e.g. in prolonged fasting) ⟶ gluconeogenesis using amino acids to synthesize glucose de novo**

❖ Location of glycogen in the body:

In skeletal muscle & liver
- **400 gram in muscles (1-2% of resting muscle weight)**
- **100 grams in liver (~ 10% of well-fed liver)**



Functions of glycogen

muscle glycogen

Fuel reserve for the muscle (ATP production)

(During muscular exercise)

liver glycogen

A source for blood glucose

(Especially during early stages of fasting)

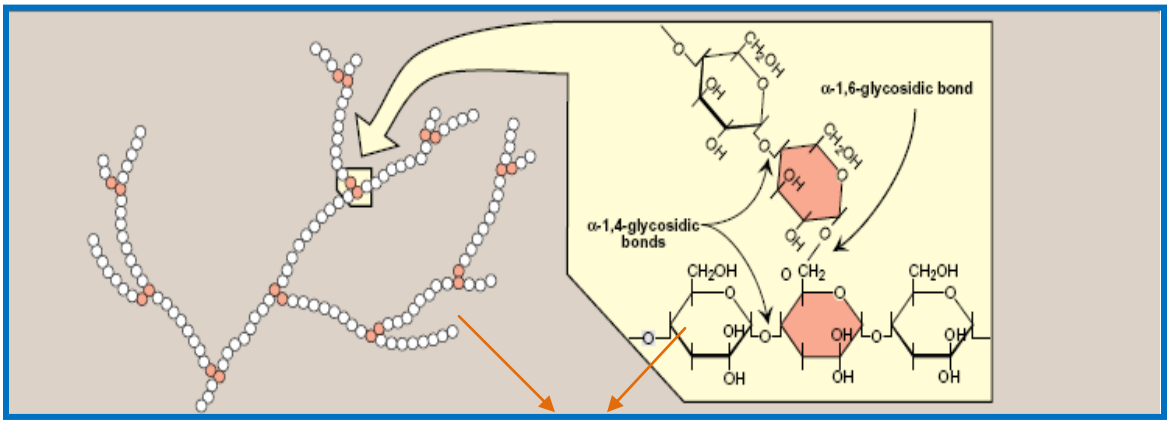
✓ Chemical Structure of Glycogen:

Branched-chain homopolysaccharide made exclusively from α- D-glucose

✓ **Linkage:** - Glucose residues ⟶ α (1-4) glycosidic linkage
- At the Branch (every 8-10 residue) ⟶ α (1-6) glycosidic linkage

✓ **Glycogen is present in the cytoplasm in the form of granules which**

contain most of the enzymes necessary for glycogen synthesis & degradation



α- D-glucose

Metabolism of Glycogen

Glycogenesis
(Synthesis of Glycogen from Glucose)

A mechanism to store glucose in Liver & Skeletal Muscles

Glycogenolysis
(Breakdown of Glycogen to Glucose)

✓ GLYCOGENESIS:

- Occurs in the cytosol of liver & skeletal muscles

1) UDP-GLUCOSE Synthesis : Glucose 1-phosphate + UTP (uridine triphosphate) ⟶ UDP-glucose (is the building block for glycogen synthesis)+ PP_i (pyrophosphate)
   - Enzyme: UDP-glucose pyrophosphorylase

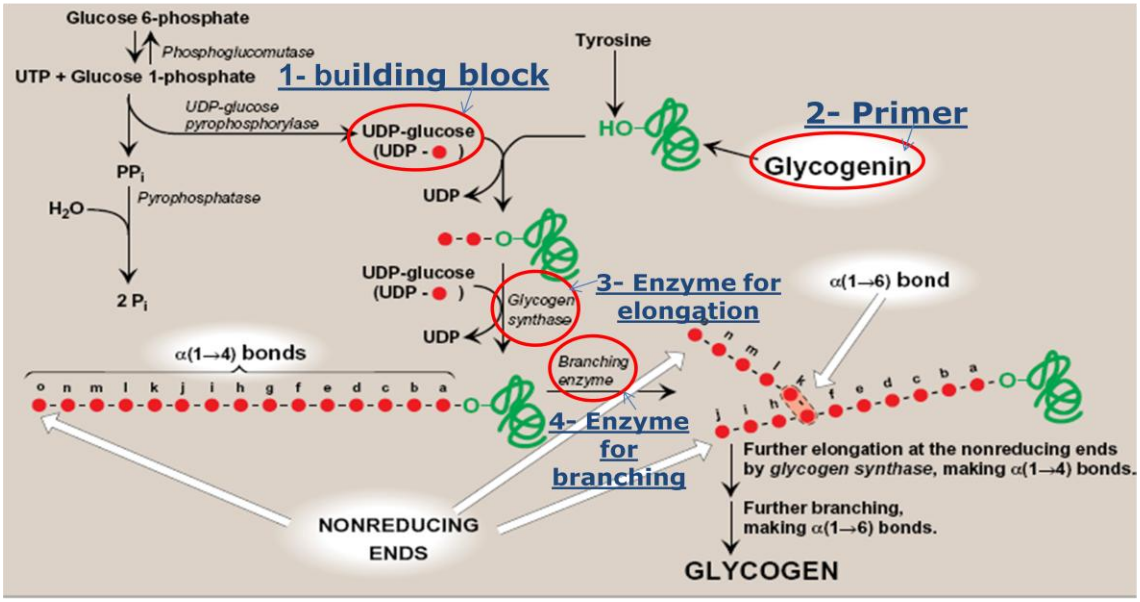
2) PRIMER for synthesis are either: a- Glycogen fragment (if cellular glycogen store in not depleted totally)or
   b- glycogenin (used when glycogen stores are depleted)
   + UDP-glucose ⟶ glycogenin to which the initial glucosyl unit is attached

3) ELONGATION of a primer: more glucose is transfered from UDP – glucose to the growing end of the chain
   - α (1-4) linkage are formed .
   - Enzyme: glycogen synthase.

4) Branches are synthesized
   - Enzyme : " branching enzyme "

On average, a branch point is formed every eight glucosyl residues and at this point the bond is α (1- 6) linkage .

GLYCOGENESIS
Synthesis of Glycogen



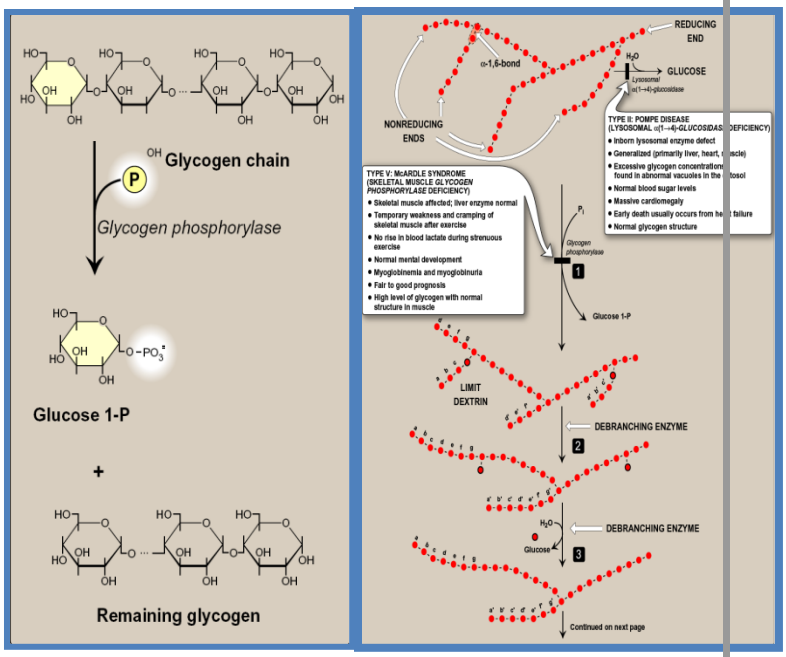
❖ Glycogenolysis:

(Breakdown of glycogen in liver & skeletal muscles).

In the cytosol, NOT the reverse reaction of the glycogen synthetic reaction .

1) **Glycogen is cleaved at the - α (1- 4) Glycosidic bound.**

Continues until four glucosyl residues remain on each branch → this is called a " limit dextrin . because the glycogen phosphoryase cannot degrade it any further i.e. it limits the action of the phosphorylase, and another enzyme has to solve the branch-point problem: the debranching enzyme .



Enzyme : glycogen phosphorylase.

Deficiency : glycogen storage disease

(type v Mc Ardle's disease). - - -▸ the enzyme is deficient from skeletal muscle

Product: dextrin + glucose 1- phosphate .

Glucose 1-phosphate is converted to glucose 6-phosphate.

2) α (1-6) linkage cleaved by debranching enzyme → remove branches .
Product: free glucose.

3) A small amount of glycogen degraded by lysosomal enzyme .
Purpose of pathway unknown .
Enzyme : - α (1-4) – glucosidase.
Deficiency: GSD type II (Pompe disease) .
Accumulation of glycogen in vacuoles in lysosomes.
- Pompe disease is the Only glycogen storage disease that is lysosomal .

4)- Glucose 1-phosphate is converted to glucose 6-phosphate

Enzyme: phosphoglucomutase

a. In the liver: glucose 6-phosphate is translocated to the ER
Enzyme: glucose 6-phosphate translocase
Deficiency : GSD type Ib
In the ER: glucose 6-phosphate →free glucose
Enzyme: glucose 6-phosphatase
Deficiency : GSD Type Ia (Von Gierke Disease)

b. In the muscle: (no glucose 6- phosphatase) so the glucose 6-phosphate will enter glycolysis

- Fate of glucose 6-phosphate:
  - In liver:
    - G-6P is converted to *free glucose* (by *glucose 6-phosphatase*)
    - Free Glucose is transported to blood (blood glucose)
  - In skeletal muscles:
    - G-6P is *not* converted to free glucose
    - So, it is not transported to blood
    - BUT: it is used only as a source of energy inside sk. muscles (by glycolysis that yields lactic acid)

❖ REGULATION OF GLYCOGEN SYNTHESIS & DEGRADATION:

- Synthesis & degradation of glycogen are tightly regulated

✓ **In the liver:**

- Glycogen degradation accelerates during fasting
- Glycogen synthesis accelerates during well-fed status

✓ **In Skeletal Muscles:**

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

- Regulation is accomplished on *two levels:*

1- Within individual cells (*allosteric regulation*)

2- All over the body (*hormonal regulation*)

➢ Regulation within individual cells:

1- Regulation in the well-fed state:

in wel-fed state → Glucose 6-phosphate, Glucose & ATP ↑

- *Glycogen synthase* is allosterically ACTIVATED by:
  G-6-P
- *Glycogen phosphorylase* is allosterically INHIBITED by :
  G-6-P *(in liver & sk. ms.)*
  ATP *(in liver & sk. ms.)*
  Glucose *(in liver only)*

2- During muscular contraction:

During muscular contraction → Calcium & AMP ↑

- *Glycogen phosphorylase is ACTIVATED by calcium & AMP → ↑ Glycogen degradation*

Summary of regulation within individual

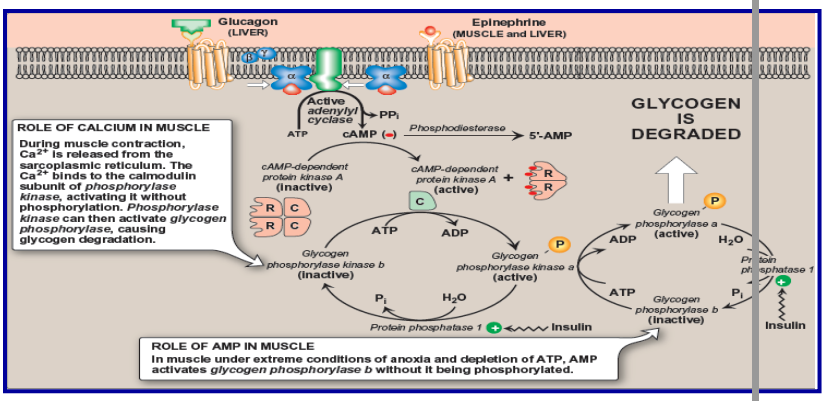
1- in well-fed state:

- ✓ G 6-P, glucose & ATP ↑
- ✓ *stimulation* of synthase → ↑ synthesis
- ✓ *inhibition* of phosphorylase → ↓ degradation

2- In muscular contraction (activity):

- ✓ Ca_2^+ & AMP ↑
- ✓ *stimulation* of phosphorylase → ↑ degradation

❖ Hormonal regulation:

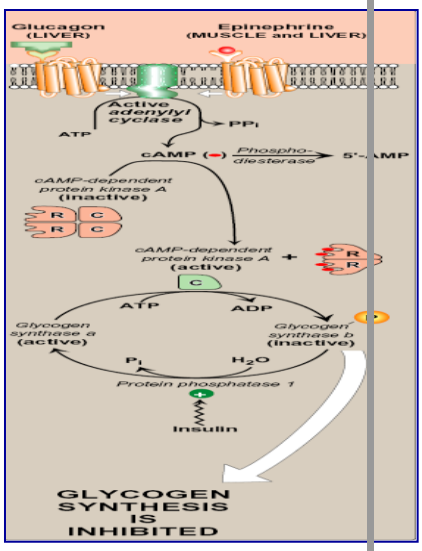


➢ **Activation** of glycogen phosphorylase (i.e. ***glycogen degradation***) by <u>cAMP-directed pathway</u>

- The binding of hormones to membrane receptors signals the need for glycogen degradation either to :
  - elevate blood glucose (by glyogenolysis of liver glycogen)
  - provide the sk. muscle by energy (by glyogenolysis of skeletal muscles)

✓ <u>hormones</u> :

- glucagon: for liver glycogen <u>only</u>
- epinephrine: for liver & muscle glycogen



➢ **Inhibition** of glycogen synthase (glycogen synthesis) <u>by cAMP-directed pathway</u>

- The regulated enzyme in glycogen synthesis is glycogen synthase
  - Glycogen synthase
    dephosphorylated (active, a form)
    phosphorylated (inactive, b form)

- Glycogen synthase a is converted to the inactive form by phosphorylation by cAMP-dependent protein kinase A by the cAMP pathway
- Glycogen synthase b can be converted to the active form (dephosphorylated) by protein phosphatase 1 (which is activated by insulin)

1. Decrease in glucose levels or need for energy →release glucagon and epinephrine →bind to specific cell-membrane receptors → activation of cAMP-dependent protein kinase→phosphorylates inactive glycogen phosphorylase → glycogenolysis
   Result: activation of glycogen degeneration

2. Glucagon and epinephrine → activates cAMP-dependent protein kinase A →phosphorylates glycogen synthase →inactive (Also other kinases e.g the protein kinase C can phosphorylate and hence inactivate glycogen synthase)
   Result: inhibition of glycogen synthesis

3. Insulin→activates protein phosphatase 1 → dephosphorylates glycogen synthase →activates
   Result: glycogen synthesis

❖ Glycogen Storage Diseases

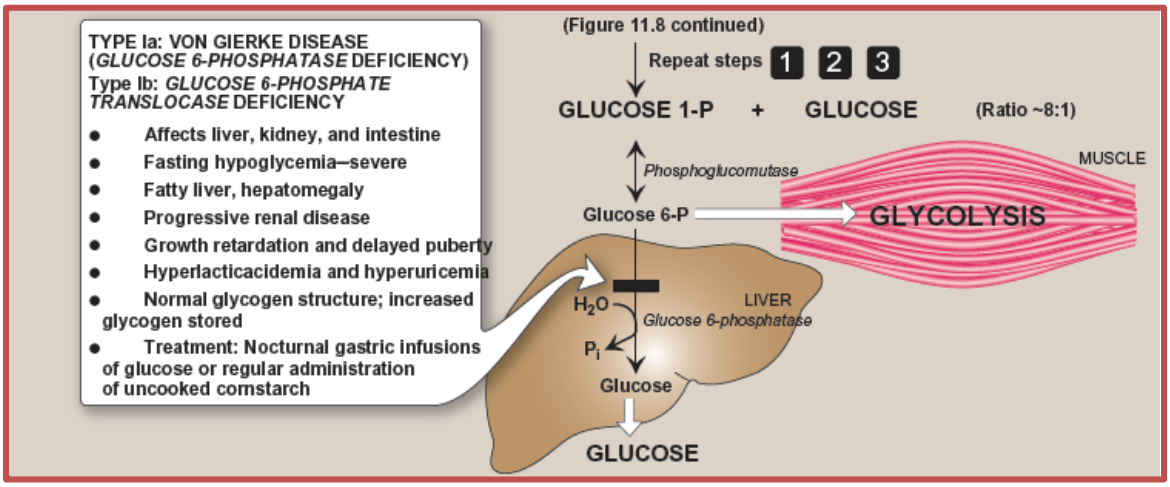
- GSD Ia (Von Gierke disease) & Ib
  - Glucose 6-phosphatase & glucose 6-phosphate translocase deficiency in the liver respectively
- GSD II (Pompe's disease)
  - Failure to lysosomal breakdown of glycogen (1-4 glucosidase def.)
- GSD V (Mc Ardle' disease)
  - Deficiency of glycogen phosphorylase in skeletal muscle (of glycogenolysis)

✓ Von Gierke's Disease

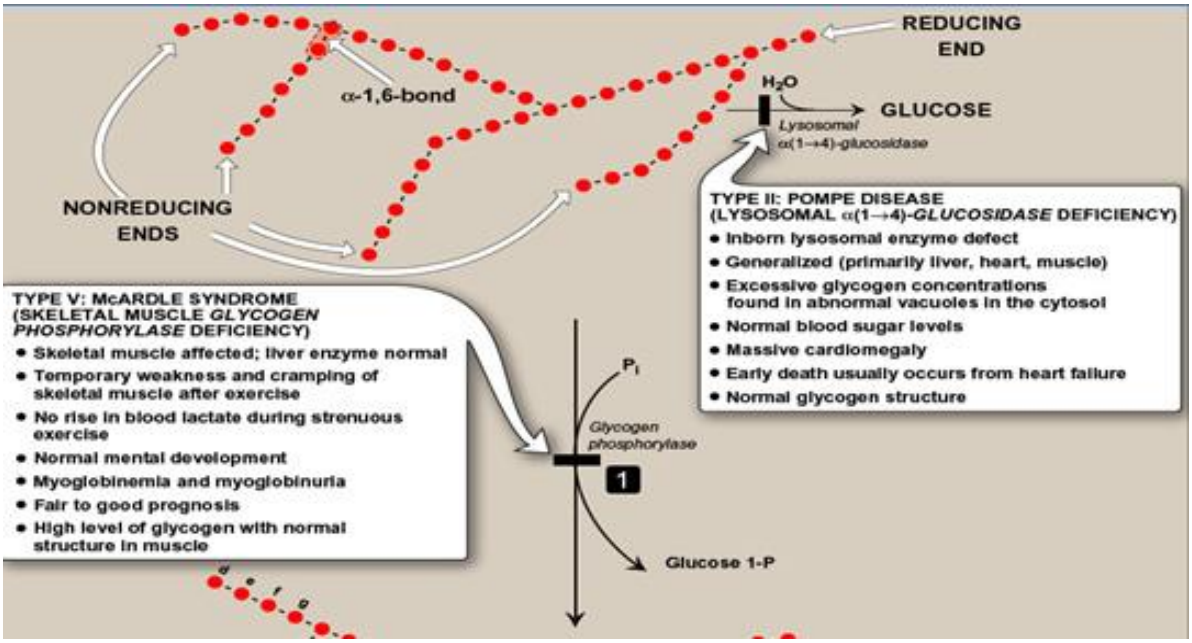
- Caused by deficiency in glucose 6-phosphatase
- Glucose 6-phosphate is trapped inside liver cells
- No glucose is transported to blood from glycogenolysis

▪ Clinical Manifestations:

- Hypoglycemia (severe, fasting): due to impaired glucose release from cells of liver
- Hepatomegaly: due to accumulation of glycogen in the liver, , fatty liver, hepatomegaly, renomegaly → progressive renal disease
- Hyperuricaemia (and Gout): due to increased metabolism of G-6-P via pentose phosphate pathway, forming ribose 5-phosphate --- purines --- uric acid
- Hyperlacticacidemia & Metabolic (lactic) Acidosis



✓ **McArdle Syndrome & Pompe disease**



Summary (most imp. Points about diseases):

✓ the 3 diseases discussed in details → abnormal amount of normal glycogen structure.

- Type 1 : sever fasting hypoglycemia ,liver diseases" hepatomegaly, fatty liver" , gout.
- Type 2 : the only GSD that is lysosomal, affects many organs, normal blood sugar level (as opposed to the severe fasting hypoglycemia of Von Gierke disease), fatal disease especially in infant: death due to heart failure ,cardiomegaly, cardiomyopathy
- Type 5: Liver enzyme is normal, skeletal muscle is affected, benign condition (relative to the others), muscle disease, severe pain after exercise, no rise in lactic acid after exercise, patient at rest is fine, myoglobinemia, myoglobinuria, normal mental development