Metabolism of glycogen

Glycogen is the major storage form of carbohydrate in animal and corresponds to starch in plant. It occurs mainly in liver (up to 6%) and muscle (up to 1%). However, because of great mass, muscle represents some 3-4 times as much as glycogen store as liver. It is branched polymer of α-glucose.

The function of muscle glycogen is to act as a readily available source of hexose units for glycolysis within the muscle itself. Liver glycogen is largely concerned with storage and export of hexose units for maintenance of the blood glucose, particularly between meals. After (12-18 hours) of fasting, the liver becomes almost totally depleted of glycogen, whereas muscle glycogen is only depleted significantly after prolonged various exercise.

Why the cell can store glycogen but not glucose?

Because when glucose increased, osmotic pressure in the cell increase, causing water movement toward the cell and leading to burst so when glucose accumulates in the cell, it will convert to glycogen which consists of branched series of glucose.

Glycogenesis

The process of glycogenesis start when glucose-6-phosphat is changed to glucose-1-phosphate by mutase

\[
\text{mutase}\quad \text{glucose-6-phosphat} \rightarrow \text{glucose-1-phosphate}
\]

The reaction is reversible and depends on concentration of substrate (glucose-6-phosphat), if there is a large amount or quantities of glucose-6-phosphat will lead to formation of glucose 1-phosphate and the opposite is right. No loss in the energy in this reaction

- As glucose 1-phosphate formed, it will react with high energy compound UTP (uradin triphosphate), which react with glucose to give UDP glucose (uradin diphosphate glucose) and pyrophosphate released
- glucose 1-phosphate is high energetic compound and called (active glucose molecule), this reaction is carried by (UDP glucose pyrophosphorylase)
- One UDP glucose is formed, it can add already to exiting glycogen in the cell (glycogen primer) by addition of α1-4 linkage causing elongation of the chain is carried by glycogen synthase.

- In the same time (simultaneously) another enzyme will change α1-4 linkage to α1-6 linkage, this enzyme (Amylo α1-4 → α1-6 linkage transglucosidase or branching enzyme. The process continues by addition of more glucose molecules at α1-4 linkage and then changing this to α1-6 linkage as result a large glycogen molecule.
Glycogen synthase

Found in the cell in active or inactive form

Adenyl cyclase is activated by:
1- Adrenalin hormones
2- Glucagon hormones

- So the inactive glycogen synthase is activated by losing phosphate group and gives it to ADP molecule to form ATP

- The reaction is carried out by the glycogen synthase phosphatase enzyme which activated by insulin, so high concentration of glucose will cause activation of glycogen synthase

- Active glycogen synthase become inactive when it takes phosphate group and thus is converted to ADP

- The reaction is carried by the enzyme glycogen synthase kinase (active), this phosphate group is attached to (OH) group of enzyme

- Also glycogen synthase kinase is found active or inactive
Inactive one is activated by cAMP (cyclic AMP) or 3,5 cyclic AMP that is formed within the cell from ATP by the action of adenyl cyclase enzyme, its activated by adrenalin and glucagon hormones.

During exercise or emotional stress, adrenalin is released in very high concentration activating the formation of cAMP and then glycogen synthesis is inhibited while a high amount of glucose will be used by the body to produce high amount of energy, which necessary for the exercise or emotional stress.

\[
\text{cAMP} \xrightarrow{\text{Phosphodiesterase}} \text{5AMP} \\
\]

Glycogen synthase is activated by glucose-6 phosphate and inhibited by glycogen (allosteric enzyme).

**Glycogenolysis**

When there’s a lack of energy, glycogen will be broken down to give glucose molecule, this process is carried out by 3 enzymes:

- *Phosphorylase*: hydrolyze α1-4 linkage in glycogen and liberating glucose-1-phosphate
• Oligo α 1-4 → α 1-4 glucantransferase: take chain of α1-4 and transfer it to another α1-4 causing elongation in the glucose chain

- Oligo α 1-4 – α 1-4 glucan transferase

• Amylase α1-6 glucosidase (debranching enzyme): hydrolyse α 1-6 linkage to facilitate the work of phosphorylase (become α1-4 linkages)

All these enzymes activate at the same time as a result glycogen is converted to glucose 1 phosphate, these reactions are irreversible

About phosphorylase enzyme
It’s found in the cell in active and inactive forms
active → inactive by losing a phosphate group and this carried out by phosphorlyase phosphatase
Inactive → active by taking phosphate group (ATP ADP) and this carried out by phosphorylase kinase
Phosphorylase enzyme has 2 immunologically different isoenzyme, one from liver and the other from muscles, and there are some similarities and differences between them

- Both are allosteric enzymes
- Both require pyridoxal-phosphate (vit B6 phosphate) as cofactor
- Both are interconverted into active and inactive form
- Both are activated by adrenalin

**Differences**

- Liver phosphorylase is a dimer (activated by 2 ATP) while muscle phosphorylase is tetramer (activated by 4 ATP)
- Liver phosphorylase is activated also by glucagon hormone while muscle phosphorylase is not activated by this hormone
- Liver phosphorylase has ½ molecular weight of muscle type

**Muscle phosphorylase** : 4 subunit + 4 ATP → active

**Liver phosphorylase** is a dimer: 2 subunits + 2 ATP → active

- Liver phosphorylase enzyme is activated by phosphorylase kinase (active), which take a phosphate group from ATP giving it to inactive phosphorylase phosphatase and activating it, and also converting ATP into ADP
Schematic representation of glycogenesis and glycogenolysis
Glycogen storage diseases:

The level of glycogen in muscle at rest and well fed is about 1% of tissue weight, while in the liver its range is between 5-7% of tissue weight. In severe exercise for 1-5 hours, the liver glycogen drops to 1% while the muscle glycogen drops to 0-0.1% and therefore the function of glycogen in the cell is to provide energy and store it. Since in certain disease leads to abnormal cell’s function, abnormal metabolism and glycogen structure, these may occur when enzyme of glycolysis or glycogenesis are affected.

In some inheritable diseases, deficiency of enzyme of glycolysis, glycogenesis and glycogenolysis lead to abnormal level of glycogen in the cell.

300 gm of liver contain 15 gm of glycogen

10 kg of muscle contain 100 gm of glycogen

So liver contains lower amount but higher percentage

- **Type I (Von Gierke’s diseases)**

Due to the deficiency of enzyme glucose-6-phosphatase (convert glucose-6-phosphat into glucose) its deficiency in the liver and tubules of kidney (glucose-6-phosphat $\rightarrow$ glucose) then glucose-6-phosphat will converted to glucose-1-phosphate $\rightarrow$ glycogenesis and leads to accumulation of glycogen and decrease in its breakdown.

- **Type II (Pope’s disease)**

Due to the deficiency of lysosomal (oligo $\alpha_1-4$ $\rightarrow$ $\alpha_1-4$ glucantransferase (hydrolyze glycogen in the lysosomes) it will cause accumulation of glycogen within organ and result in an increase level of glycogen in the cell containing lysosomes.

- **Type III (limited dextrinosis or Cori’s syndrome)**

Due deficiency of debranching enzyme (amylase $\alpha_1-6$ glucosidase), this cause excessive branching in glycogen ($\alpha_1-6$ linkage is high) but $\alpha_1-4$ linkage is short and abnormal glycogen will be formed in the cell.
- **Type IV: Amylopectnosis (Anderson’s diseases)**
  Due to deficiency of branching enzyme oligo α1-4 → α1-6 glucantransferase, abnormal glycogen similar to amylopectin with long chain and short branches.

- **Type V Macardal’s disease**
  Due to deficiency in muscle phosphorylase (myophosphorylase) → increase level of glycogen and deposition in the muscles and may reach 10-15% causing pain in movements, so inability to tolerate exercises with tiring. In this case, a decrease in lactic acid in blood because glycogen → glucose which is used by glycolysis and converted into lactic acid.

- **Type VI (Her’s diseases)**
  Due to deficiency of phosphoglucomutase which convert glucose 1-phosphate to glucose 6-phosphate so a decrease in concentration of glucose and increase of glycogen in cell will be result.

- **Type VII**
  Due to deficiency of phosphofructokinase, which convert fructose-6-phosphate → fructose 1,6 diphosphate, fructose-6-phosphate will convert into glucose 6-phosphate, the latter will continue the cycle in backward manner to form glycogen.

- **Type VIII**
  Due to deficiency of liver phosphorylase, glycogen level is high in liver and in the muscle is normal.
1. Glycogen synthase
2. Amylo α1-4 and α1-6 transglucosidase (debranching enzyme Type IV)
3. UTP-pyrophosphorylase

Glycogen

1. Phosphorylase (type V and VIII)
2. Oligo α1-4-→ α1-4 glucan transferase type II
3. Amylase α1-6 glycosidase debranching enzyme (type III, limited dextrinosis)

Glucose-1-phosphate

Mutase (type VI)

Glucose-6-phosphate

Phosphohexoisomerase

Fructose-6-phosphate

Phosphofructokinase (type VII)

Fructose1-6-diphosphate

Glycolysis → CO₂ + H₂O₂ + ATP