5. Glycogen metabolism

A constant source of blood glucose is essential for human life. Glucose is the preferred energy substrate for the brain, and a fundamental energy source cells without mitochondria, such as red blood cells. Skeletal muscles, which contract rapidly, require a significant supply of glucose, which alone, through glycolysis, provides the necessary energy. Blood glucose comes from three sources:

- Dietary glucose ingested with meals,
- Gluconeogenesis,
- Glycogen (glucose polymer) from the liver

The source of dietary glucose (disaccharides, starch, and glycogen) is sporadic and unreliable. Gluconeogenesis is often too slow to meet immediate demand. In contrast, the animal body has developed a rapid mobilization process in the liver and striated muscles in response to immediate demand in the absence of dietary glucose. This process is glycogenolysis, or glycogen breakdown.

While hepatic glycogen is mobilized to maintain blood glucose levels and supply peripheral tissues, glycogen stored in muscles is mobilized and consumed locally for muscle function. Liver glycogen stores increase when animals are well fed and can decrease during prolonged fasting until depleted. Muscle glycogen stores are minimally affected by prolonged fasting and can be replenished after activity that has depleted some of them. Whether in the liver or muscles, glycogen is synthesized from glucose 6-phosphate as a precursor. Glycogen synthesis is called glycogenesis.

5.1. Glycogenolysis

5.2.1 Sequences of enzymatic reactions

The main enzyme in the breakdown of endogenous glycogen (hepatic and muscular) is glycogen phosphorylase, which releases glucose-1-phosphate and limiting dextrin. Two other enzymes, a glycosyltransferase and an α(1-6) glucosidase, are involved in the complete conversion of glycogen to glucose-6-phosphate. Only the liver can convert glucose-6-phosphate into glucose, which is then excreted into the bloodstream.

- **Glycogen Phosphorolysis**

Phosphorolysis itself is catalyzed by glycogen phosphorylase. This enzyme cleaves the α(1-4) bond from the non-reducing end and attaches a phosphate group, supplied by ATP, to carbon 1 of the released glucose, yielding glucose 1-phosphate. Phosphorolysis is repeated sequentially on glycogen up to four glycolytic residues on each chain before the α(1-6) bond. The residual structure is called limit dextrin, which resists further action by phosphorylase (Figure 14).

- **Debranching enzyme**

Debranching enzyme acts on limit dextrin by removing an oligosyl group of three glucose residues from each limit dextrin chain. This oligosyl group is then used to extend another limit dextrin chain, thus allowing phosphorolysis to resume on that chain. After the action of this enzyme, a glucose linked by the α (1-6) bond remains in place of the side chain.

- **α(1-6) Glucosidase**

Finally, α-glucosidase hydrolyzes the glucose residues linked by the α (1-6) bond and releases the glucose. After the action of these three enzymes, glycogen releases primarily glucose 1-phosphate (via phosphorolysis) and a small amount of glucose (via hydrolysis). Glucose 1-phosphate is isomerized to glucose 6-phosphate by phosphoglucomutase. Glucose 6-phosphate can enter glycolysis in the liver and muscle. However, the primary objective of hepatic glycogen degradation is to maintain blood glucose levels. To achieve this, only the liver, after glycogen degradation, possesses glucose 6-phosphatase, which hydrolyzes glucose 6-phosphate into glucose and excretes the latter into the bloodstream. The two catalyzed reactions are as follows:

Glucose 1-P → Glucose 6-P (Phosphoglucomutase)

Glucose 6-P + H_2O → Glucose + Pi(Glucose 6-phosphatase)

The entire sequence of glycogen degradation reactions is summarized in Figure.

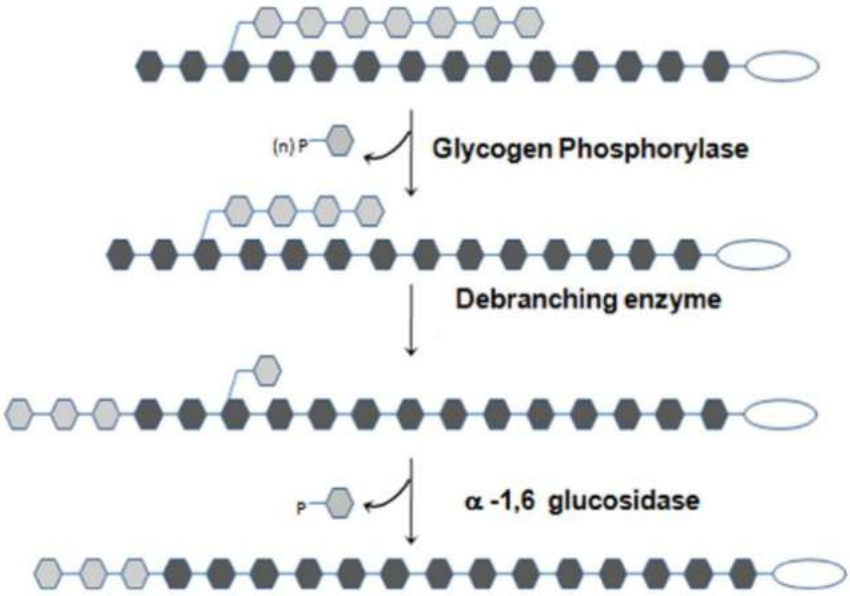

Figure 14: Glycogenolysis steps

5.3 Glycogenolysis regulation

Glycogen metabolism is an integral part of energy metabolism. It is under hormonal control. Adrenaline and glucagon direct catabolism and energy production; insulin controls anabolism, which is oriented towards energy storage. The effects of these two groups of hormones are antagonistic, which necessitates coordinated regulation, as we will see later. Regarding glycogen breakdown, we will distinguish between hormonal regulation and regulation by calcium ions.

5. 3.1. Hormonal regulation

Glucagon and adrenaline (epinephrine) are the two main hormones that control the breakdown or mobilization of glycogen. There are two glycogen phosphorylases, one muscular and the other hepatic. Each exists in two forms: the α form (active) and the β form (inactive). The inactive form (β) can be converted to the active form (α) by phosphorylation. The two forms, whether in muscle or in the liver, interconvert into one another through the action of two enzymes: phosphorylase kinase (transition from the inactive form to the active form by phosphorylation) and phosphorylase phosphatase (hydrolysis of the phosphate group) Figure 15.

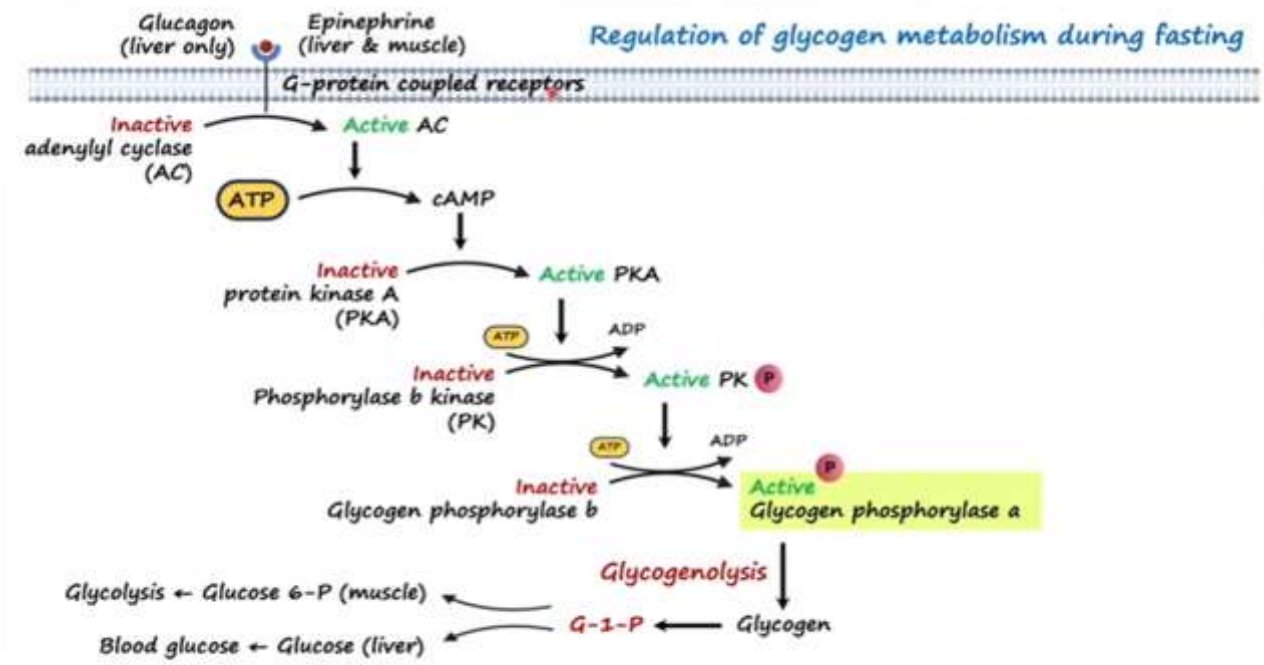

Figure 15: Hormonal regulation of glycogenolysis.

- Phosphorylase kinase, which phosphorylates hepatic or muscle phosphorylase, also exists in two forms: one active (phosphorylated) and the other inactive (dephosphorylated). The interconversion between the inactive and active forms is mediated by a protein kinase.
- Protein kinase is composed of two subunits, one catalytic (active) and the other regulatory. The inactive form is the assembly of the two subunits, with the regulatory subunit masking the catalytic site of the active subunit. Activation of protein kinase is mediated by cAMP (cyclic AMP), which, by combining with the regulatory subunit, releases the catalytic site of the active subunit.
- cAMP is produced in the cytosol from ATP by membrane adenylate cyclase, which is activated by two main hormones: adrenaline (epinephrine) or glucagon.

Hormonal regulation is actually the result of the transduction of a chemical signal leading to intracellular effects, which in this case corresponds to the mobilization of glycogen. The mechanisms of action of adrenaline and glucagon are similar, once each of these hormones binds to its specific membrane receptor.

- The binding of each hormone to its specific membrane receptor leads to the activation of a membrane adenylate cyclase.

- Activated adenylate cyclase catalyzes, through ATP hydrolysis, the formation of cyclic AMP (cAMP), considered a second messenger.
- c AMP binds to protein kinase A (cAMP-dependent) and combines with the regulatory subunit to release the catalytic subunit (active protein kinase A).
- Active protein kinase A phosphorylates, in the presence of ATP, glycogen phosphorylase kinase, which becomes active in its phosphorylated form.
- Finally, this phosphorylase kinase phosphorylates glycogen phosphorylase, converting it from the β form to the α form, which catalyzes the phosphorolysis of glycogen.

5.2.Glycogenesis

The purpose of glycogen synthesis is to store, in the liver, a portion of the excess glucose following a diet rich in carbohydrates and proteins, and in the muscles to regenerate glycogen stores, a fraction of which has been depleted by physical activity. Glycogen synthesis occurs primarily in the liver and muscles. The main enzyme is glycogen synthase. The precursor is glucose 6-phosphate.

5.2.1. Sequences of enzymatic reactions

- **Isomerization of glucose 6-phosphate to glucose 1-phosphate**

The enzyme that catalyzes this reaction is phosphoglucomutase.

Glucose 6-phosphate → glucose 1-phosphate

- Transfer of the glucosyl group onto UTP (formation of UDP-glucose).

The donor of the glucose group in the polymerization of glucose into glycogen is UDP-glucose. Its formation is ensured by UDP-glucose pyrophosphorylase, which transfers the glucosyl group onto UDP, releasing pyrophosphate (PPi). Hydrolysis of PPi by pyrophosphatase further promotes the reaction.

UTP + glucose → UDP-glucose + PPi

- **Synthesis of a primer to initiate glycogen synthesis**

Glycogen synthase, which is responsible for the formation of the α (1-4) linkage, is an elongation enzyme and cannot initiate de novo glycogen synthesis from glucose. A primer is required, which can be obtained in several ways:

✓ using a glycogen fragment in the form of dextrin

- ✓ In the absence of this fragment, a specific protein, glycogenin. It possesses a tyrosine side chain that acts as an acceptor, thanks to its -OH group, for the first glucosyl residue from UDP-glucose. The formation of the first glycosidic bond is catalyzed by an initiating glycogen synthase. Glycogenin itself can add a few glucose units linked by α (1-4) bond to complete the primer (8 glucose units) Figure 16.

- **Glycogen synthase chain elongation**

The glycogen chain is elongated by glycogen synthase, which transfers the glucosyl residue of UDP-glucose to the non-reducing end of the primer or elongating glycogen chain and sequentially forms the α (1-4) linkage according to the reaction:

Glycogen (n glucose) + UDP-glucose → glycogen [(n+1)] glucose + UDP

UDP is then converted back to UTP by a nucleoside diphosphate kinase in the presence of ATP.

ATP + UDP → UTP + ADP

- **Side chain formation**

At every 8 glucose residues on the linear chain synthesized by glycogen synthase, a branch forms, giving glycogen a highly branched structure. This increases the number of non-reducing ends, which are favorable to the activity of glycogen phosphorylase during the mobilization of glycogen reserves. This branching also ensures its much higher solubility compared to amylose, which has a purely linear structure. The branching is carried out by a branching enzyme r glycosyl transferase. It takes an oligosaccharide of 5 to 8 glucose residues from the non-reducing end of the elongating chain and attaches it to a glucosyl residue on the main chain via an (1-6) bond.

5.2.2. Regulation of glycogenesis

The regulation of glycogen synthesis is ensured by the ability of glycogen synthase to exist in two forms: an active (dephosphorylated) form and an inactive (phosphorylated) form. The interconversion between the two forms is controlled by an insulin-dependent protein phosphatase and protein kinase A. The activation of glycogen synthase results from a series of cascade reactions triggered by insulin, a polypeptide hormone secreted by the β cells of the islets of langerhans in the pancreas. The molecules essential to this mechanism are:

• A protein phosphatase: it becomes active through phosphorylation catalyzed by an insulin-dependent protein kinase.

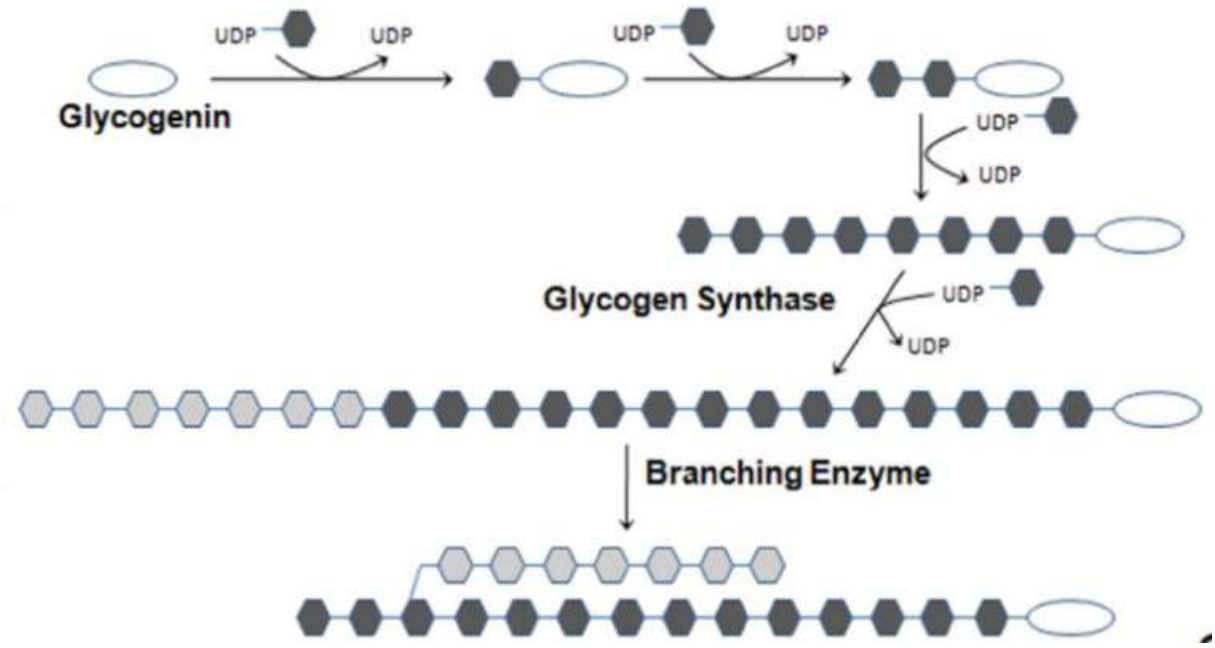

Figure 16: Glycogenesis steps

• The phosphatase kinase mentioned above: it is the penultimate step in a series of phosphorylation reactions initiated by the tyrosine kinase of the catalytic receptor of insulin. The insulin receptor, composed of four protein subunits embedded in the target cell membrane. The α2 dimer forms the hormone-binding domain. The β2 dimer has a tyrosine kinase on each subunit, on the inner face of the membrane.

• The mechanism of glycogen synthase activation can be summarized as follows:

- Insulin binds to its receptor and forms an insulin receptor-receptor complex. The receptor's tyrosine kinase phosphorylates a specific tyrosine residue on each β subunit (autophosphorylation).
- The tyrosine kinase then phosphorylates the tyrosine residue on a first protein substrate called IRS-1 (Insulin Receptor Substrate 1). IRS-1-P will initiate a series of cascade phosphorylation reactions, the last step of which is the activation, by phosphorylation, of a protein phosphatase (called insulin-dependent).
- This protein dephosphorylates glycogen synthase (which is inactivated by phosphorylation by protein kinase A) and restores its activity. Glycogen synthesis is thus initiated or restarted. Figure 17 below shows the mechanism of protein phosphatase activation by insulin.

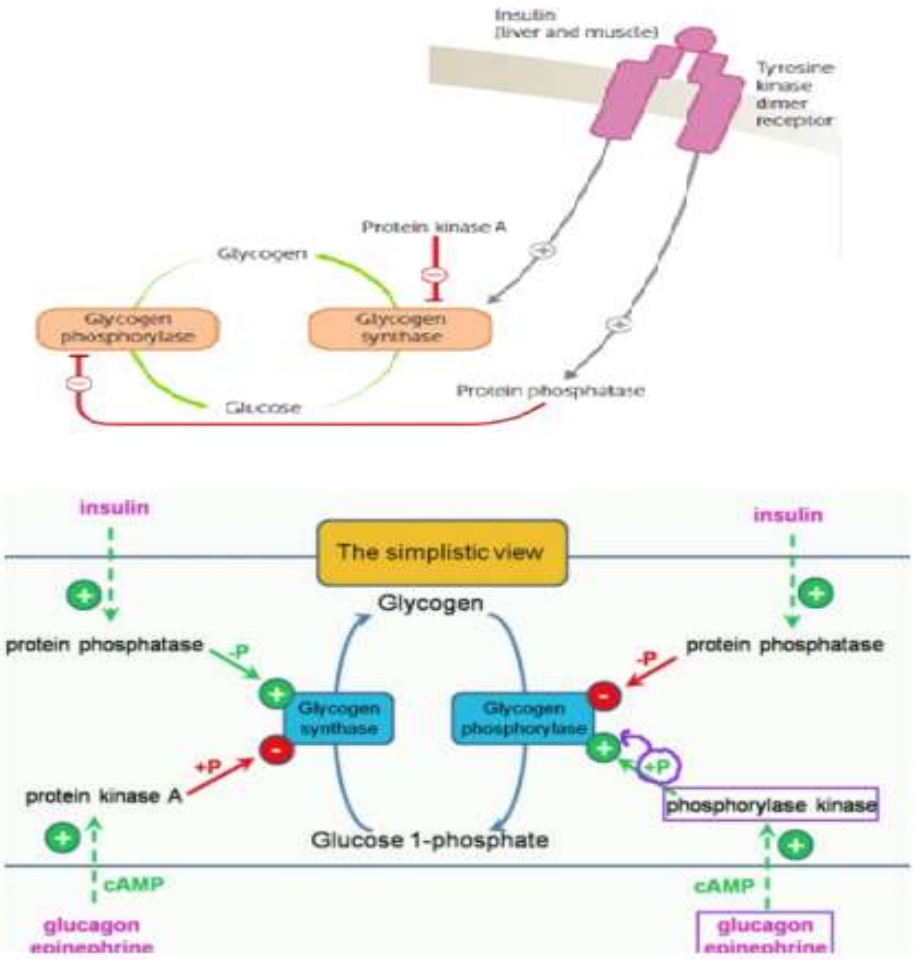

Figure 17: Hormonal regulation of glycogen synthase by insulin and glucagon