Glycogen is the principal storage form of glucose in animal cells, which can be quickly mobilized. What is the structure of glycogen? Which organs store glycogen, synthesize it, and which ones are responsible for its breakdown? How is glycogen metabolism regulated?

Glycogen: the Storage Form of Glucose

Significance and Localization of Glucose

Carbohydrates are key components of our diet. They provide energy, are precursors of lipids and amino acids, and they store energy in the form of glycogen.

The storage form of glucose in plants is starch, which resembles the glycogen stored in human or animal cells. The special chemical structure of glycogen allows for rapid synthesis and breakdown, which means that the body can respond quickly when glucose is in short supply.
Glycogen is present in cells in the form of **cytosolic granules**. Glycogen granules contain both the enzymes for synthesis and breakdown. Glycogen is present in all cells – except in erythrocytes. The quantities used for the energy requirements of the cells themselves are minimal.

Significant amounts of glycogen are stored in only two organs: in the liver (approximately 150 g) and in **skeletal muscles** (approximately 300 g).

**Function of Glycogen Storage**

The **function of glycogen** differs greatly between the two major sites of glycogen storage, i.e., in the liver and in the skeletal muscles:

- **Liver glycogen** is the first and immediate source of glucose for the maintenance of blood-glucose levels to meet the needs of the organism as a whole, especially of the brain and red blood cells.
- The **glycogen in skeletal muscles** serves exclusively as an energy source for the muscle itself.

**Structure of Glycogen**

Glycogen is a branched polymer consisting of residues of glucose, which are linked by **α-1,4 O-glycosidic** bonds with **α-1,6 branches** every 8 to 10 residues.

These linkages create a tree-like polymer consisting of up to 50,000 glucose monomers, which appear as cytosolic grains when examined with an electron microscope. Glycogen provides energy storage **with minimum effect on cellular osmolarity**. It is only minimally osmotic active due to its small size. Free glucose cannot be stored due to its high osmotic activity.

**Note:** Free glucose would cause each cell to burst due to its osmotic activity.

Another advantage is the branched structure of glycogen. The resulting numerous non-reducing ends ensure rapid mobilization and maintenance of the blood-glucose level.

**Glycogenesis**

The synthesis of glycogen does not usually involve the **de novo** formation of glycogen, but consists in lengthening of existing glycogen molecules by adding glucosyl residues.
Every glycogen molecule has, at its core, a **glycogenin** protein, a glycoprotein which remains attached to the reducing end of glycogen during its degradation.

**Figure 3 provides an overview of the most important reactions of glycogen synthesis.**

**Step 1 of Glycogenesis**

The first step corresponds to the first reaction of glycolysis. Glucose is phosphorylated to **glucose-6-phosphate**. In skeletal muscles, this reaction is catalyzed by the enzyme **hexokinase** and, in the liver, by the enzyme **glucokinase**.


**Step 2 of Glycogenesis**

The second step consists of the isomerization to **glucose-1-phosphate** by the enzyme **phosphoglucomutase**.

**Step 3 of Glycogenesis**

In order to produce an O-glycosidic compound for the synthesis of glycogen, a high level of energy is required. For this reason, glucose-1-phosphate is initially activated by a reaction with UTP (**uridine triphosphate**). This produces **UDP-glucose** and **pyrophosphate**, which is hydrolytically cleaved into two phosphates by the enzyme **pyrophosphatase**.

**Step 4 of Glycogenesis**

Now, the glucose can be transferred to the **C4-OH group** on one of the non-reducing ends of glycogen to form an α-1,4 glycosidic bond. This reaction is catalyzed by the enzyme **glycogen synthase**, liberating UDP which is then recycled by conversion to UTP with **ATP**.

**De novo Synthesis of a Glycogen Molecule**

New glucose residues can attach only to an existing glycogen molecule if the straight chain of the existing glycogen molecule is at least four glucose units long. For de novo synthesis, a **primer** (starter substrate) is essential; in this case, it is the protein **glycogenin** with its activity as a glycosyltransferase.
The glycosyltransferase links the tyrosine residue of the protein with UDP-glucose. UDP is cleaved and a glucose molecule attached. If eight glucose units attach to the tyrosine residue of the glycogenin, the glycogen synthase can elongate the chain.

**Incorporation of Branch Points in Glycogen**

The characteristic α-1,6 branches of glycogen are the products of an enzyme called amylo-(1,4→1,6)-transglycosylase = branching enzyme.

The amylo-(1,4→1,6)-transglycosylase adds branches to the growing glycogen molecule by forming α-1,6 linkages by binding to a linear α-1,4 chain that consists of at least eleven glucose monomers. Of these, a chain of seven glucose monomers is removed and transferred to the OH group of the C6 of a glucose residue. Thus, located between two branch points are at least four glucose monomers.

**Note:** The high density of branches characteristic for glycogen gives rise to a great number of non-reducing ends, which determines the possible rates of synthesis and breakdown and enables maximum speed of glucose release. It is thus possible, to quickly access glycogen stores to lower or increase blood-glucose levels, when required.

**The Breakdown of Glycogen: Glycogenolysis**

Glycogenolysis follows a different pathway than glycogenesis. Glucose-1-phosphate, a high-energy compound is released. The steps of glycogenolysis are as follows:

At the free non-reducing ends of glycogen, glycogen phosphorylase catalyzes phosphorolytic cleavage of the α-1,4-glycosidic linkages of glycogen, releasing glucose-1-phosphate as the reaction product. For this purpose, free inorganic phosphate is required. Glucose-1-phosphate can isomerize to glucose-6-phosphate and enter glycolysis.

The liver enzyme glucose-6-phosphatase converts glucose-6-phosphate to glucose, which regulates and maintains blood-glucose levels. Skeletal muscles lack this enzyme and can therefore not release glucose into the blood stream.

Glycogen phosphorylase is dependent on pyridoxal phosphate (PLP) and can only cleave α-1,4-glycosidic bonds. It stops cleaving α-1,4 linkages four glucose monomers away from an α-1,6 branch point.

**Degradation of Branching Points during Glycogenolysis**

The debranching enzyme (4-alpha-glucanotransferase) is a bifunctional enzyme, which is responsible for the degradation of branching points. It has the following functions:

- **Transferase activity:** 4-alpha-glucanotransferase transfers a segment of three glucose units from α-1,6 branched four-unit chains (the result of glycogen phosphorylase activity) to an adjacent branch of the glycogen chain.
- **Glucosidase activity:** 4-alpha-glucanotransferase hydrolytically cleaves the remaining α-1,6 linkage, producing glucose and a linear chain of glycogen.

**Regulation of Glycogen Metabolism**

Glycogen metabolism is regulated by two enzymes: glycogen phosphorylase and glycogen synthase. The co-ordination is mainly dependent on hormone-mediated and
partly also allosteric regulatory effects.

The **allosteric regulation** is a form of regulation of enzyme activity, which is carried out by certain enzymes (**allosteric enzymes**) which are almost always composed of multiple subunits. These may occur in more than one stable conformation.

A negative feedback mechanism leads to the inhibition of activity or synthesis of one or more enzymes through the end product. The inhibition of enzyme synthesis is called **enzyme expression**. The inhibition of enzyme activity is referred to as an allosteric effect.

**Regulation of the Breakdown of Glycogen (Glycogenolysis)**

Two distinct isoforms of glycogen phosphorylase exist; one is expressed in the liver and the other in skeletal muscle. As the process of glycogen metabolism is different in these two parts of the body, **muscles and liver are regulated separately**.

**Regulation of Glycogen Breakdown in Skeletal Muscle and all Non-Liver Cells**

Two forms of glycogen phosphorylase exist in skeletal muscle: **Phosphorylase a** (active form) and **phosphorylase b** (inactive form). The conversion of the inactive to the active form is catalyzed by the **phosphorylase kinase**. This enzyme is activated by hormones. The enzyme **protein kinase A** (PKA) regulates the phosphorylase kinase by phosphorylation. **Calcium ions** also have an activating effect in skeletal muscle. In a working muscle, the **sarcoplasmic reticulum** releases calcium ions, thus increasing the intracellular calcium concentration. The actual activation of glycogen phosphorylase is mediated by a **calcium-calmodulin complex**.

**Phosphorylase b** is also subject to allosteric effects. The inactive enzyme can become partially active, elevated levels of AMP can activate phosphorylase b. Even before phosphorylase kinase becomes active in order to meet specific demands of the cell (hormonally controlled), ATP and glucose-6-phosphate inhibit the activation of phosphorylase b, which means that the inactive state is favored. This mechanism prevents unnecessary depletion of muscle glycogen stores when the metabolic demands have already been met.

**Regulation of the Breakdown of Glycogen in the Liver**

In the liver, the enzyme phosphorylase kinase catalyzes the conversion of phosphorylase b to phosphorylase a. ATP and AMP are present in the liver, however, they are not relevant, as the liver does not degrade glycogen for its own use. Instead, **the liver covers its own energy requirements using fatty acids**.

**Regulation of the Synthesis of Glycogen (Glycogenesis)**

Regulatory mechanisms of glycogen synthesis in the liver and skeletal muscles are the same. Glycogen synthase exists in an active dephosphorylated form, called **glycogen synthase a**. The inactive phosphorylated form is referred to as **glycogen synthase b**. The conversion into the respective forms is mediated by protein kinase A, without further involvement of a kinase.

Also subject to allosteric regulation is the glycogen synthase b, which is activated by high
concentrations of glucose-6-phosphate.

**Note:** Don't be confused: Glycogen phosphorylase is activated by phosphorylation - glycogen synthase is activated by dephosphorylation.

**Hormonal Control of Glycogen Metabolism**

This important control mechanism prevents glycogen from being synthesized at the same time that it is being broken down. Three hormones play an important role here: glucagon, adrenaline, and insulin. Glucagon and adrenaline stimulate glycogen degradation, while insulin stimulates the synthesis of glycogen.

Upon activation of the insulin receptor, the phosphodiesterase is activated, decreasing cAMP levels and inactivating protein kinase (PKA). An inactive PKA decreases the level of phosphorylation of the phosphorylase kinase, which has an inhibitory effect on this enzyme. This, in turn, decreases the rate of glycogen degradation.

In addition, protein kinase B is activated, which reinforces the phosphorylation of glycogen synthase kinase 3 (GSK3) and thereby inactivates it. As a result, GSK3 phosphorylates the glycogen synthase to a lesser extent, causing the latter to become more active, which amplifies glycogen synthesis.

The phosphoprotein phosphatase 1 (PP1) catalyzes the key step, the dephosphorylation of glycogen synthase, which is responsible for glycogen synthesis. The latter can be inactivated by the downstream metabolic effects of adrenaline and glucagon (cAMP – PKA). Thus, adrenaline and glucagon contribute to the inactivation of glycogen synthesis.

**Note:** Adrenaline and glucagon have antagonistic effects on the mentioned signalling cascades, which are activated and inactivated by insulin.

The following illustrations show the different mechanisms at a glance:
Glycogen and Blood-Glucose Levels

Blood contains only very small amounts of glucose. The standard value of blood-glucose is 80—120 mg / 100 ml of blood. This corresponds to about 1 g/l of blood; accordingly, the total amount of glucose in circulating human blood is normally only about 5 g.

The liver is able to register the current blood-glucose concentration and adjust the glycogen metabolism accordingly. If blood-glucose level is too low, glucose is released. If blood-glucose levels are high, more glycogen is synthesized. Glucose stimulates the release of insulin, which triggers the activation of glycogen synthase and the inactivation of glycogen phosphorylase.

Within minutes after an intravenous administration of glucose, the enzymatic activity of glycogen phosphorylase decreases and the activity of glycogen synthase increases.

**Note:** Muscles and other tissues do not possess these special regulatory mechanisms. Adrenaline regulates and controls the wasteful depletion of glycogen during periods of starvation.

Clinical Relevance: Glycogen Storage Diseases

**Glycogenoses** are a group of hereditary diseases affecting the metabolism of glycogen, resulting in the extensive accumulation of glycogen deposits in organs and in muscle tissue. Responsible for this are deficient enzymes involved in the glycogen metabolism. Most common is the autosomal recessive defect of glucose-6-phosphorylase: Glycogen is synthesized, but cannot leave the cell.

The liver stores more and more glycogen, resulting in an enlarged liver (**hepatomegaly**) (up to 10 kg). Furthermore, glucose levels in the blood can no longer be maintained. This leads to severe **hypoglycemia** between meals.

So far, eleven distinct glycogen storage diseases and subforms have been identified. The typical symptoms and complications in addition to hepatomegaly include: hypoglycemia, nephromegaly, cirrhosis of the liver and myasthenia.

These are the **most common types of glycogenosis**:

- von Gierke’s disease (glycogen storage disease Type I)
- Pompe disease (glycogen storage disease Type II)
- Cori disease (glycogen storage disease Type III)

Treatment is aimed at maintaining a consistent blood-glucose level in order to avoid severe hypoglycaemia (especially at night).

Review Questions

The correct answers can be found below the references.

1. **Which of the following statements on the synthesis of glycogen is true?**

   A. An allosteric activation of the phosphoprotein phosphatase 1 (PP1) through high concentrations of glucose-6-phosphate results in the inactivation of glycogen synthase.
   B. The enzyme glycogen synthase catalyzes both, the formation of α-1,4-glycosidic and of α-1,6-glycosidic bonds.
C. The enzyme glycogen synthase links glucose monomers specifically with free reducing ends of glycogen.
D. Glycogen synthesis begins with the binding of a glucose monomer to a specific serine residue of the protein glycogenin catalyzed by the enzyme glycogen synthase.
E. A protein kinase A-dependent phosphorylation of active glycogen synthase inhibits glycogen synthesis.

2. Glycogen metabolism is regulated in different ways. Which of the following statements on the metabolism of glycogen is correct?

A. The enzyme glycogen phosphorylase a catalyzes the dephosphorylation of the hydrolytically linked glycosidic linkage between glucose units.
B. Glycogen synthase links the glucose units via 1,4-glycosidic bonds.
C. Glucagon regulates mainly the breakdown of glycogen in hepatocytes.
D. Glucose-6-phosphate is directly activated by UTP to UDP-glucose.
E. Through an increase of the concentration of cAMP, insulin stimulates the synthesis of glycogen in hepatocytes.

3. Which statement about glycogen is not true?

A. Glycogen is stored in the form of cytosolic granules.
B. The molecular structure of glycogen allows for rapid synthesis and breakdown.
C. Glycogen is stored primarily in the liver, and in smooth muscle cells.
D. Glycogen has a very low osmotic activity.
E. Glycogen represents the human equivalent to the starch in plants.

References


**Correct answers:** 1E, 2B, 3C

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