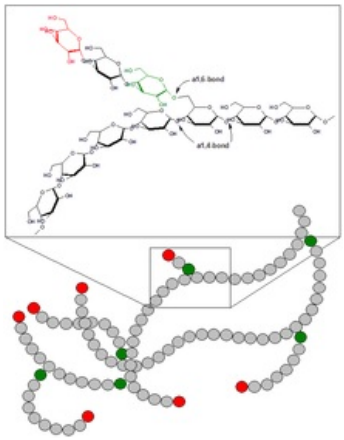
Glycogen metabolism



Glycogen Structure

Glycogen is a **branched homopolymer'** of glucose molecules. Most of the glucose residues are linked by **α 1→4 linkages**. Every twelfth glucose residue is connected to the next residue by an **α 1→6 bond** - a branching point of the glycogen molecule is created. These branches are extended by additional glucose residues connected by α 1→4 linkages. This creates insoluble glycogen molecules resembling tree branches in their structure. All reactions during glycogen metabolism take place only at the "non-reducing ends" of its molecule - these can be shortened or lengthened.

Function of glycogen

In animals, glycogen serves as a "carbohydrate storehouse" from which glucose esters can be released by cleavage. Richly hydrated ``glycogen granules *are found in the cytoplasm of* ``*all cells*. The human body can store approximately 450 g of glycogen. Of this amount, 80-100 g is found in the liver - the so-called **liver glycogen**, which is used to maintain a constant level of glucose in the blood (glycemia). Another 300 g is in the muscle cells - the so-called *muscle glycogen*. It serves rather as an internal muscle energy reserve during muscle work. Muscle cells **do not contain glucose-6-phosphatase** and therefore muscles cannot release pure glucose into the bloodstream. The rest (about 50 g of glycogen) goes to other cells of the human body.

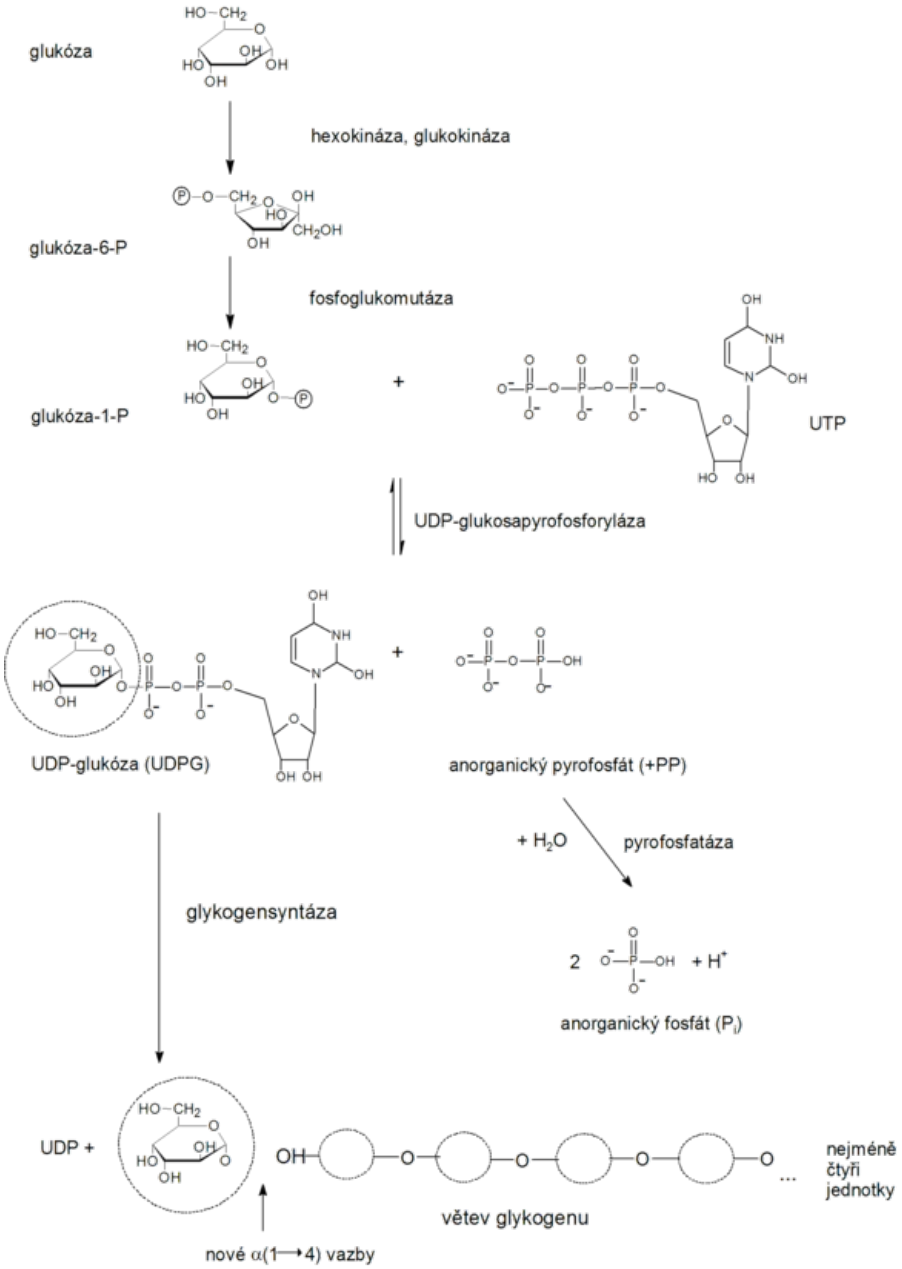
Glycogen as an energy store

As mentioned above, glycogen is '*not the main energy store* of the body (liver glycogen is depleted within 12-24 hours of starvation). This is because it is a ``polar*,* ``*richly hydrated molecule*, and the bound water only "takes up space" and does not bring energy gain. The energy supply in adipose tissue is much more economical – it is not hydrated (TAGs have a hydrophobic character) and at the same time fatty acids are made up of a more reduced carbon skeleton $-CH_2$ – compared to carbohydrates $-CH(OH)-$. By oxidizing them, a larger amount of energy is released. However, glycogen represents a storehouse of glucose, which is important, for example, for glucose-dependent cells (e.g. brain, erythrocytes).

Histochemical evidence

In histochemistry, its presence is proven by the so-called **PAS-reaction** (oxidation of two adjacent hydroxyl groups with periodic acid and subsequent reaction of the aldehyde groups thus formed with Schiff's reagent).

Glycogenesis (glycogen synthesis)



The process of glycogen synthesis takes place **in the cytosol**. It is intense mainly in the liver and skeletal muscle. Glycogen synthesis is based on glucose molecules and additionally requires a so-called *primer* - i.e. a molecule that contains a chain of several glucoses connected by glycosidic bonds (most often it is the rest of the glycogen present in the cell, or the protein *glycogenin*)).

Progress

1. Phosphorylation of glucose to Glc-6-P

- "glucokinase" catalyzes this reaction in the liver,
- in muscles **hexokinase**'.

2. Conversion of Glc-6-P to Glc-1-P

- using **glucose phosphate isomerase**'.

3. Glc-1-P reacts with UTP

- catalyzed by UDP-glucose pyrophosphorylase,

  UDP-Glc is formed, or the activated form of glucose (UDP binds to C1).

  The formation of glycosidic bonds between glucose molecules is an **endergonic process**' and therefore energy-rich substrates are required. The transfer of glucose residues from UDP-Glc is direct ($\Delta G < 0$).

4. UDP-Glc with its C1 attaches '*to the C4 non-reducing end* of glycogen

- catalyzed by the enzyme "glycogen synthase" and at the same time releases UDP.

  Thus, an α 1→4 bond O-glycosidic bond is formed.

5. Once the growing chain reaches a certain length (> 11 glucose residues), the molecule branches.

A branching enzyme, amylo-(1,4-1,6)-transglycosylase) removes an oligosaccharide graft consisting of 6–7 glucose residues from the chain, which is subsequently attached to The −OH group located at C6 of the molecule glucose molecules located inside the glycogen chain - an α 1→6 bond is formed. These branches can be newly elongated by the action of glycogen synthase (see above).

Regulation of glycogen synthesis

Glycogen synthesis takes place at a time when the organism has a *sufficient supply of energy substrates* from food, i.e. it can create energy reserves for worse times. The main regulatory enzyme is **glycogen synthase**'. Its activity is regulated by means of phosphorylation - if the enzyme is phosphorylated, it is inactivated, dephosphorylation, on the contrary, leads to the activation of the enzyme. Phosphorylation is influenced by the **insulin / glucagon ratio**' (e.g. through the intracellular concentration of cAMP). Increasing the ratio activates glycogen synthesis (insulin is an anabolic hormone). A decrease in the ratio or catecholamines, on the contrary, inhibit it.

Glycogenolysis (degradation of glycogen)

Scheme of glycogenolysis Glycogen is **never completely degraded*, its degradation takes place in the cytosol of cells. This happens gradually in the form of so-called phosphorolytic cleavage (phosphorolysis, binding of inorganic phosphate), when with the help of the enzyme "glycogen phosphorylase" (phosphorylase for short) individual glucose monomer units are released from the non-reducing ends in the form of "Glc-1-P"*** - *the so-called **Cori ester**'. During the splitting of a glycogen molecule, phosphorylated glucose is produced directly, **without the consumption of ATP**':*

N glucose residues + HPO_4^{2-} → Glc-1-P + (N−1) glucose residues

The richly branched glycogen molecule has many non-reducing ends, which is why glycogen is broken down quickly. At this point it is useful to mention that the breakdown of polysaccharides in the digestive tract takes place quite differently. Polysaccharides are first cleaved inside their chains to form shorter polysaccharides and oligosaccharides. Subsequently, free (not phosphorylated) glucose is released.

The course of glycogenolysis

1. Glycogen phosphorylase can only cleave α-1→4 glycosidic bonds.

Starts to cleave glycogen from the non-reducing end and Glc-1-P are formed.

2. Glc-1-P is converted to Glc-6-P

- by '*phosphoglucomutase* activity.

3. Glycogen breakdown

- stops at the 4th glucose residue before the branching point where the **α 1→6 linkage** occurs.

4. The so-called branching enzyme (glucanotransferase, transglycosidase)

separates a graft consisting of three glucose residues from the side chain and transfers it to the end of the linear (main) chain. There, it connects it using an α 1→4 bond.

5. At the point of the original branching, there is only one residue bound by an α 1→6 bond

- is cleaved by the enzyme **amylo-α1→6-glucosidase**'.

  As a result, an **unbranched chain** is formed with the possibility of further cleavage by glycogen

phosphorylase.

6. Glc-6-P is converted to glucose

- using **glucose-6-phosphatase'** (catalyzes the cleavage of phosphate).

  This enzyme is found in liver and kidney cells and in enterocytes, where it binds to smooth endoplasmic reticulum membranes.

7. Glc-6-P

- is transported to the ER by the enzyme "translocase".

  This separation into the ER serves to ensure that the resulting glucose is not immediately phosphorylated back to Glc-6-P.

8. Free glucose is then released into the blood, where it can serve as a source of energy.

Regulation of glycogenolysis

If the concentration of glucose in the blood falls, there is a **decrease in the insulin/glucagon ratio *in the plasma. Liver glycogen is broken down under these conditions. If the glycogen content in the liver decreases during starvation or under stressful conditions of the organism, glucose is synthesized de novo by ``gluconeogenesis from non-sugar sources*. The main regulatory enzyme of glycogenolysis is glycogen phosphorylase, one of those enzymes whose activity is regulated by covalent modification of the molecule. Here it is true that** phosphorylase is active phosphorylated**.**

- Activated phosphorylase is referred to as '*phosphorylase a*.
- Inactive phosphorylase (does not have a phosphate group attached) is called ``phosphorylase b*.*

Phosphorylation of glycogen phosphorylase is catalyzed by the enzyme ``phosphorylase kinase*, while dephosphorylation is catalyzed by ``protein phosphatases*. Glycogenolysis is activated by **counterregulatory hormones - glucagon, catecholamines and glucocorticoids** (e.g. cortisol), while insulin inhibits it.

In muscle cells, the regulation of glycogenolysis is also associated with a change in the concentration of Ca^{2+} ions. An increase in their intracellular concentration results in the activation of phosphorylase kinase and glycogen phosphorylase – activation of glycogenolysis. Mediators of their effect are, on the one hand, the binding protein "calmodulin" and, on the other hand, calmodulin-dependent protein kinases.

Clinical correlation

Congenital disorders of glycogen metabolism are called **glycogenoses'**. In them, glycogen accumulates in cells (mainly in liver and muscle cells), which can result in a varied spectrum of symptoms - e.g. liver enlargement, hypoglycemia or developmental delay. Their incidence is approximately 1:10,000. The best-known type is type I – the so-called *von Gierke's disease*, when the defective glu kose-6-phosphatase.

Summary of Glycogen Metabolism Regulation

It clearly follows from the above that the regulation of both processes, glycogen synthesis and degradation, is contradictory. The individual effects are summarized in the following table:

Regulatory enzyme	Activation	Inhibition
Glycogen phosphorylase (glycogenolysis)	Glucagon, adrenaline (phosphorylation), decrease in ATP/AMP ratio Ca^{2+} (in muscle)	Increase in ATP/AMP ratio Insulin
Glycogen synthase (glycogen synthesis)	Insulin (induction)	Glucagon, adrenaline (phosphorylation)

- ws:Metabolismus glykogenu