

23.3 • Glycogen Catabolism

Dietary Glycogen and Starch Breakdown

As noted earlier, well-fed adult human beings normally metabolize about 160 g of carbohydrates each day. A balanced diet easily provides this amount, mostly in the form of starch, with smaller amounts of glycogen. If too little carbohydrate is supplied by the diet, glycogen reserves in liver and muscle tissue can also be mobilized. The reactions by which ingested starch and glycogen are digested are shown in Figure 23.14. The enzyme known as α -amylase is an important component of saliva and pancreatic juice. (β -Amylase is found in plants. The α - and β -designations for these enzymes serve only to distinguish the two, and do not refer to glycosidic linkage nomenclature.) α -Amylase is an *endoglycosidase* that hydrolyzes α -(1 \rightarrow 4) linkages of amylopectin and glycogen at random positions, eventually producing a mixture of maltose, maltotriose [with three α -(1 \rightarrow 4)-linked glucose residues], and other small oligosaccharides. α -Amylase can cleave on either side of a glycogen or amylopectin branch point, but activity is reduced in highly branched regions of the polysaccharide and stops four residues from any branch point.

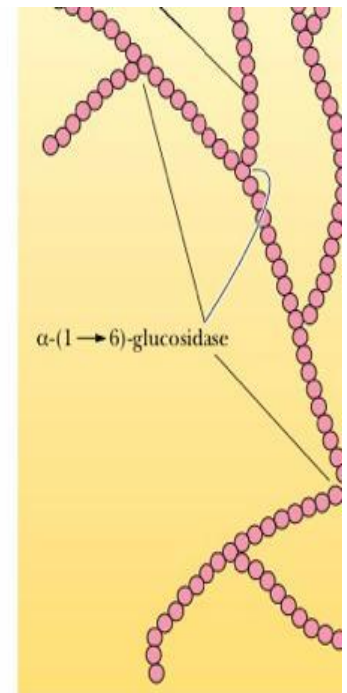
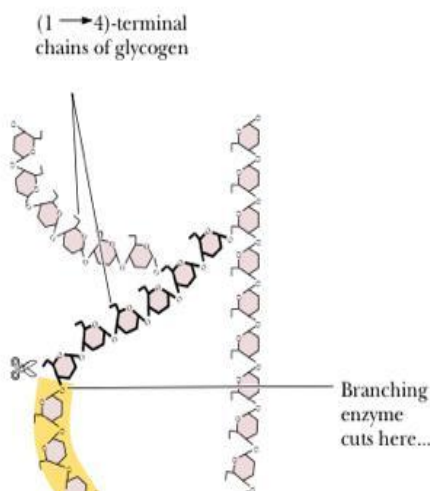


FIGURE 23.14 • Hydrolysis of gly starch by α -amylase and β -amylase.

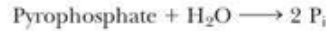


Glycogen Branching Occurs by Transfer of Terminal Chain Segments

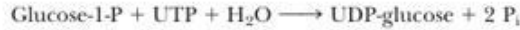
Glycogen is a branched polymer of glucose units. The branches arise from α -(1 \rightarrow 6) linkages which occur every 8 to 12 residues. As noted in Chapter 7, the branches provide multiple sites for rapid degradation or elongation of the polymer and also increase its solubility. Glycogen branches are formed by **amylo-(1,4 \rightarrow 1,6)-transglycosylase**, also known as *branching enzyme*. The reaction involves the transfer of a six- or seven-residue segment from the non-reducing end of a linear chain at least 11 residues in length to the C-6 hydroxyl of a glucose residue of the same chain or another chain (Figure 23.20). For each branching reaction, the resulting polymer has gained a new terminus at which growth can occur.

23.5 • Control of Glycogen Metabolism

The reaction proceeds via attack by a phosphate oxygen of glucose-1-phosphate on the α -phosphorus of UTP, with departure of the pyrophosphate anion. The reaction is a reversible one, but—as is the case for many biosynthetic reactions—it is driven forward by subsequent hydrolysis of pyrophosphate:



The net reaction for sugar nucleotide formation (combining the preceding two equations) is thus



Sugar nucleotides of this type act as donors of sugar units in the biosynthesis of oligo- and polysaccharides. In animals, UDP-glucose is the donor of glucose units for glycogen synthesis, but ADP-glucose is the glucose source for starch synthesis in plants.

Glycogen Synthase Catalyzes Formation of α -(1 \rightarrow 4) Glycosidic Bonds in Glycogen

The very large glycogen polymer is built around a tiny protein core. The first glucose residue is covalently joined to the protein **glycogenin** via an acetal linkage to a tyrosine-OH group on the protein. Sugar units are added to the glycogen polymer by the action of **glycogen synthase**. The reaction involves transfer of a glucosyl unit from UDP-glucose to the C-4 hydroxyl group at a nonreducing end of a glycogen strand. The mechanism proceeds by cleavage of the C—O bond between the glucose moiety and the β -phosphate of UDP-glucose, leaving an oxonium ion intermediate, which is rapidly attacked by the C-4 hydroxyl oxygen of a terminal glucose unit on glycogen (Figure 23.19). The reaction is exergonic and has a ΔG° of -13.3 kJ/mol .

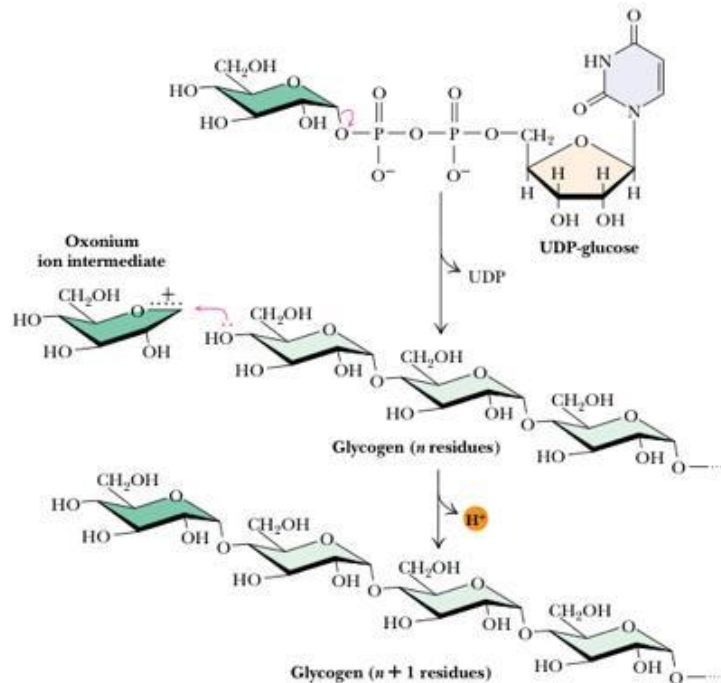


FIGURE 23.19 • The glycogen synthesis. Cleavage of the C—O bond of glucose yields an oxonium intermediate; the hydroxyl oxygen of the terminal glycogen molecule completes the



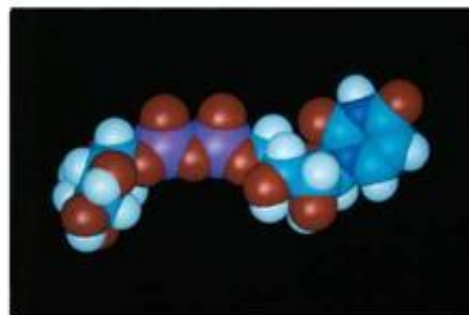
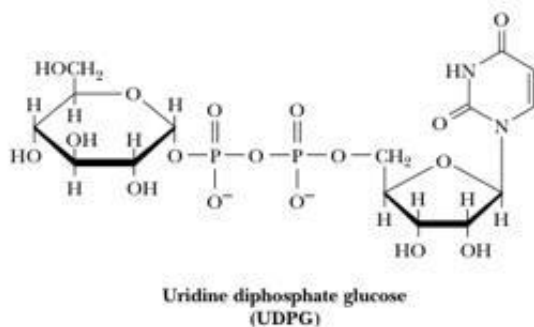


FIGURE 23.17 • The structure of UDP-glucose, a sugar nucleotide.

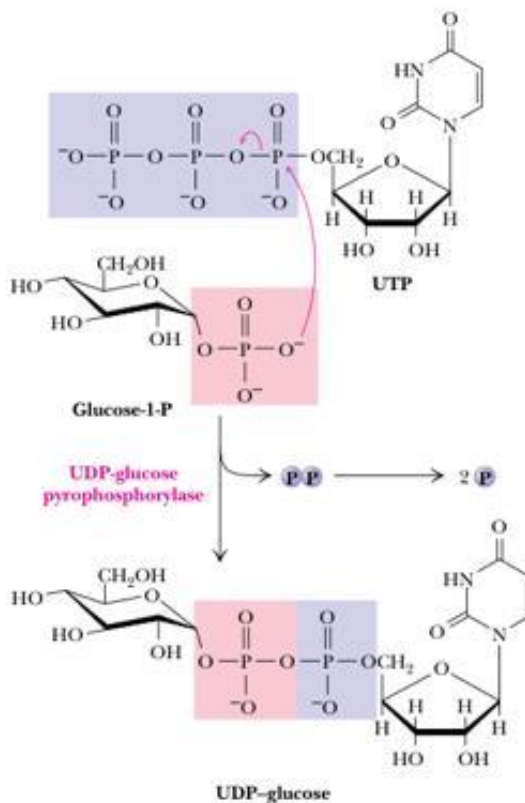
thought of as activated forms of sugar units (Figure 23.17). For example, formation of an ester linkage between the C-1 hydroxyl group and the β -phosphate of UDP activates the glucose moiety of **UDP-glucose**.

UDP-Glucose Synthesis Is Driven by Pyrophosphate Hydrolysis

Sugar nucleotides are formed from sugar-1-phosphates and nucleoside triphosphates by specific **pyrophosphorylase** enzymes (Figure 23.18). For example, **UDP-glucose pyrophosphorylase** catalyzes the formation of UDP-glucose from glucose-1-phosphate and uridine 5'-triphosphate:



FIGURE 23.18 • The UDP-glucose pyrophosphorylase reaction is a phosphoanhydride exchange, with a phosphoryl oxygen of glucose-1-P attacking the α -phosphorus of UTP to form UDP-glucose and pyrophosphate.



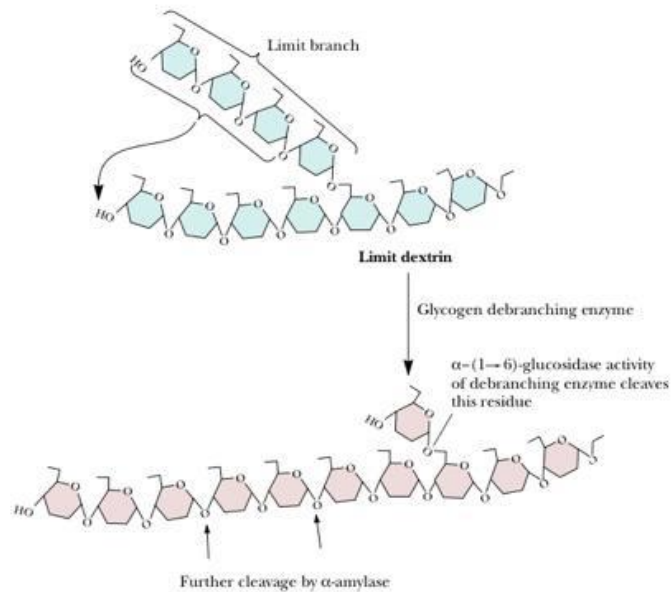
The highly branched polysaccharides that are left after extensive exposure to α -amylase are called **limit dextrins**. These structures can be further degraded by the action of a **debranching enzyme**, which carries out two distinct reactions. The first of these, known as **oligo(α 1,4 \rightarrow α 1,4) glucantransferase** activity, removes a trisaccharide unit and transfers this group to the end of another, nearby branch (Figure 23.15). This leaves a single glucose residue in α -(1 \rightarrow 6) linkage to the main chain. The **α -(1 \rightarrow 6) glucosidase** activity of the debranching enzyme then cleaves this residue from the chain, leaving a polysaccharide chain with one branch fewer. Repetition of this sequence of events leads to complete degradation of the polysaccharide.

β -Amylase is an *exoglycosidase* that cleaves maltose units from the free, nonreducing ends of amylopectin branches, as in Figure 23.14. Like α -amylase, however, β -amylase does not cleave either the α -(1 \rightarrow 6) bonds at the branch points or the α -(1 \rightarrow 4) linkages near the branch points.

Metabolism of Tissue Glycogen

Digestion itself is a highly efficient process in which almost 100% of ingested food is absorbed and metabolized. Digestive breakdown of starch and glycogen is an unregulated process. On the other hand, tissue glycogen represents an important reservoir of potential energy, and it should be no surprise that the reactions involved in its degradation and synthesis are carefully controlled and regulated. Glycogen reserves in liver and muscle tissue are stored in the cytosol as granules exhibiting a molecular weight range from 6×10^6 to 1600×10^6 . These granular aggregates contain the enzymes required to synthesize and catabolize the glycogen, as well as all the enzymes of glycolysis.

FIGURE 23.15 • The reactions of glycogen debranching enzyme. Transfer of a group of three α -(1 \rightarrow 4)-linked glucose residues from a limit branch to another branch is followed by cleavage of the α -(1 \rightarrow 6) bond of the residue that remains at the branch point.



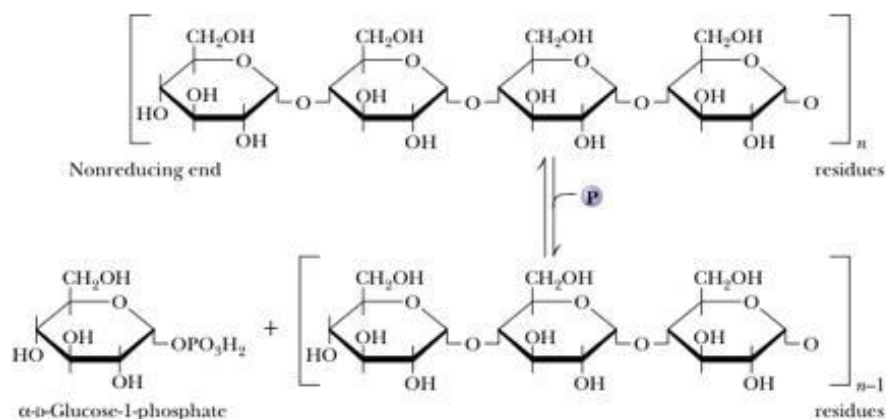


FIGURE 23.16 • The glycogen phosphorylase reaction.

The principal enzyme of glycogen catabolism is **glycogen phosphorylase**, a highly regulated enzyme that was discussed extensively in Chapter 15. The glycogen phosphorylase reaction (Figure 23.16) involves phosphorolysis at a nonreducing end of a glycogen polymer. The standard-state free energy change for this reaction is $+3.1$ kJ/mol, but the intracellular ratio of $[P_i]$ to $[\text{glucose-1-P}]$ approaches 100, and thus the actual ΔG *in vivo* is approximately -6 kJ/mol. There is an energetic advantage to the cell in this phosphorolysis reaction. If glycogen breakdown were hydrolytic and yielded glucose as a product, it would be necessary to phosphorylate the product glucose (with the expenditure of a molecule of ATP) to initiate its glycolytic degradation.

The glycogen phosphorylase reaction degrades glycogen to produce limit dextrins, which are further degraded by debranching enzyme, as already described.

23.4 • Glycogen Synthesis

Animals synthesize and store glycogen when glucose levels are high, but the synthetic pathway is not merely a reversal of the glycogen phosphorylase reaction. High levels of phosphate in the cell favor glycogen breakdown and prevent the phosphorylase reaction from synthesizing glycogen *in vivo*, in spite of the fact that ΔG° for the phosphorylase reaction actually favors glycogen synthesis. Hence, another reaction pathway must be employed in the cell for the net synthesis of glycogen. In essence, this pathway must activate glucose units for transfer to glycogen chains.

Glycogen Units Are Activated for Transfer by Formation of Sugar Nucleotides

We are familiar with several examples of chemical activation as a strategy for group transfer reactions. Acetyl-CoA is an activated form of acetate, biotin and tetrahydrofolate activate one-carbon groups for transfer, and ATP is an activated form of phosphate. Luis Leloir, a biochemist in Argentina, showed in the 1950s that glycogen synthesis depended upon **sugar nucleotides**, which may be