GLYCOGEN SYNTHESIS AND DEGRADATION

FUNCTION
To store glucose equivalents and retrieve them on demand

LOCATION
Major deposits in liver for maintaining blood glucose
Deposits in muscle for providing glucose for muscle energy requirements
The synthesis and degradation of glycogen provide control of the availability of glucose equivalents. Conditions that reflect low-glucose and/or low-energy levels turn on glycogen degradation and turn off glycogen synthesis (Fig. 11-1). Regulation is principally through a cascade of phosphorylation that begins with increases in the concentration of cAMP brought about by the stimulation of adenylate cyclase by hormones for low-glucose (glucagon) and low-energy (epinephrine) levels. Glycogen phosphorylase, the enzyme that degrades glycogen to glucose 1-phosphate, is activated through phosphorylation catalyzed by phosphorylase kinase. The phosphorylase kinase is, in turn, activated by cAMP-dependent protein kinase. In the absence of cAMP signals, the activity of protein phosphatases keeps phosphorylase inactive and activates glycogen synthase. Glycogen synthesis is inactivated by phosphorylation of glycogen synthase, the enzyme responsible for making glycogen.

Regulation of glycogen synthesis and degradation is essentially the same in the liver and muscle, but there are a couple of wrinkles. Glycogen degradation is also activated in muscle in response to the rise in intracellular calcium levels that accompanies contraction. This is achieved by
Figure 11-1  Glycogen Synthesis and Degradation
The short form shows the major control features. The long form indicates the number of glucose residues required around the branch points to make the various synthesis and degradation steps work correctly.
a stimulation of phosphorylase kinase that occurs when calmodulin (a regulatory protein associated with phosphorylase and some other proteins) binds calcium. In addition, glycogen synthesis can be activated by high levels of glucose 6-phosphate. Glycogen synthase, even when it’s phosphorylated and inactive, can be stimulated by glucose 6-phosphate.

### ATP YIELD

No ATP is required to remove glucose from glycogen stores.

**Degradation:**

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(Glycogen)_n + P_i \longrightarrow \text{glucose 1-phosphate} + (glycogen)_{n-1}
\]

Glucose 1-phosphate + H₂O \(\longrightarrow\) glucose + P_i

Net: \( (Glycogen)_n + H_2O \longrightarrow (glycogen)_{n-1} + \text{glucose} \)

### ATP COST

2 ATPs are required to store each glucose as glycogen.

**Synthesis:**

Glucose + ATP \(\longrightarrow\) glucose 6-phosphate + ADP

Glucose 6-phosphate \(\longrightarrow\) glucose 1-phosphate

Glucose 1-phosphate + UTP \(\longrightarrow\) UDP-glucose + 2P_i

UDP-glucose + (glycogen)ₙ \(\longrightarrow\) UDP + (glycogen)ₙ₊₁

UDP + ATP \(\longrightarrow\) UTP + ADP

Net: \( (Glycogen)_n + \text{glucose} + 2\text{ATP} \longrightarrow (glycogen)_{n+1} + 2\text{ADP} + 2P_i \)

### MOLECULAR FEATURES

Glycogen is a branched polymer (1-4 and 1-6 connections) of glucose connected in an α linkage at the anomeric carbon.

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¹ To get the net reaction, molecules that occur on the right side of one reaction and on the left side of another reaction can be canceled (crossed through).
If there’s plenty of glucose 6-phosphate around, there’s no need to make more, so it might as well be stored as glycogen.

The branched structure of glycogen poses some special problems for the synthesis and degradation of the molecule and for remembering how it’s done (Fig. 11-2). Glycogen is a polymer of glucose in which linear strings of glucose molecules connected at the ends (through the 1 and 4 carbon atoms of the glucose) are strung together in a branched fashion. Branches occur where one glucose in the chain that’s already connected 1-4 has another glucose attached at the 6 position. Another linear string of glucoses (attached 1-4) then takes off from the branch. This type of structure has directions as does DNA. At one end (called the reducing end), you have a glucose with nothing attached to carbon 1. Since each branch creates an extra end, glycogen has lots of ends that have nothing attached to carbon 4. The glucose with things attached at carbons 1, 4, and 6 is called a branch point. Special enzymes, branchers and debranchers, are involved in making and destroying the branch points. Like much else in biology, these enzymes take what would appear to be a relatively simple task and complicate it beyond belief.

The degradation of glycogen is accomplished by the combined action of phosphorylase and glycogen debrancher. Phosphorylase can make glucose 6-phosphate only out of unbranched glucose residues that are connected to glycogen in a 1-4 linkage. If the glucose has a branch on it, phosphorylase won’t touch it. Phosphorylase cleaves the glycosidic bond of the glucose residues at the multiple, nonreducing ends and nibbles down the outer limbs of the glycogen molecule, releasing glucose 1-phosphates as it goes, until it gets to a structure that has 4 glucose molecules attached to each side of the branch. Then the debrancher takes over. The debrancher takes 3 glucose residues from one side (C-6) of the branch and attaches them in a 1-4 linkage to the other side of the branch, leaving a structure in which a lone glucose is attached to the branch on the 1-6 side. The other side is now linear but is 7 glucoses long. The other activity of the debrancher (yes, it has two activities in the same molecule) then takes the glucose off the 1-6 side and releases it as free

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2 The reducing end is basically the end that doesn’t have another glucose residue attached at carbon 1 (the anomeric carbon). It’s called the reducing end because sugars that don’t have anything attached at C-1 can be easily oxidized by specific chemicals that change colors, and such reactions fascinated early sugar chemists. If the end becomes oxidized, it must have reduced something . . . hence, the reducing end.

3 Debrancher is given a terrible name in many texts—something like gluc something or other, or glyco, and maybe transferase stuck in there somewhere (actually it’s amylo-1,6-glucosidase/4—glucanotransferase). You’ll probably recognize it when you see it.
glucose. You’re left with a linear molecule (at least at this branch point), and phosphorylase is off and running again.

The synthesis of glycogen gets so complicated, it’s hovering somewhere around 22 on the trivia sorter. Glycogen synthase adds a glucose from a UDP-glucose to the C-4 end of the preexisting glycogen molecule. To put in branch points, the branching enzyme takes a block of 7 glucoses and transfers them to a site closer to the interior of the glycogen molecule . . . if the block of residues contains a free C-4 end, if it is contained in a block that’s at least 11 long, and if the new branch point is at least 4 glucoses away from another branch. Got it?

4 Some free glucose (not glucose 1-phosphate) is released from glycogen, even in muscle. So the idea that muscle can’t make any glucose is not quite right. However, this glucose is not really enough to count on.

5 UTP + glucose $\rightarrow$ UDP-O-glucose + PP. The oxygen from C-1 of glucose is attached to the UDP. The pyrophosphate is hydrolyzed to 2 P, by pyrophosphatase to drive the reaction to completion.