BIOCHEMISTRY

Fourth Class-First Couse

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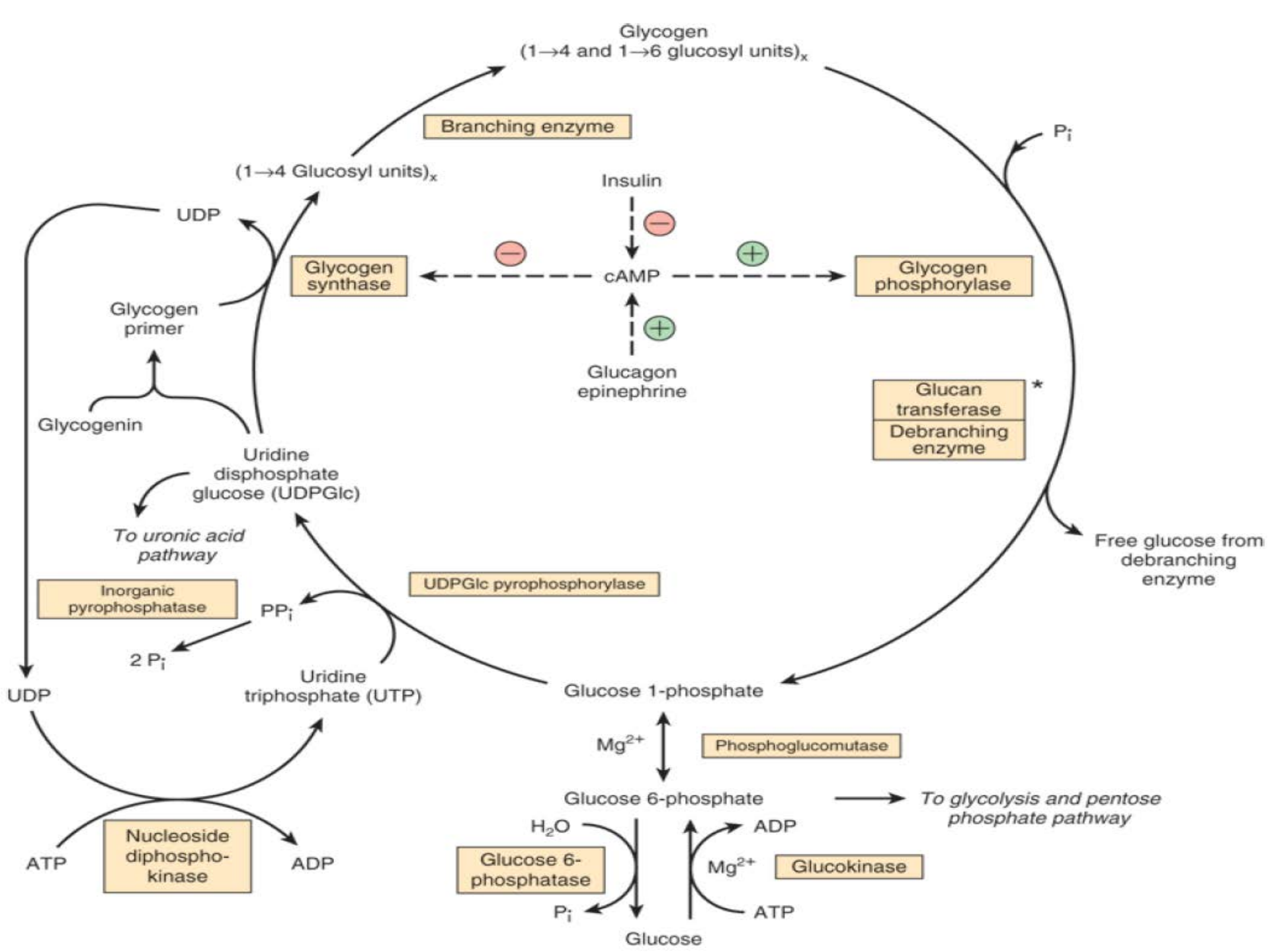
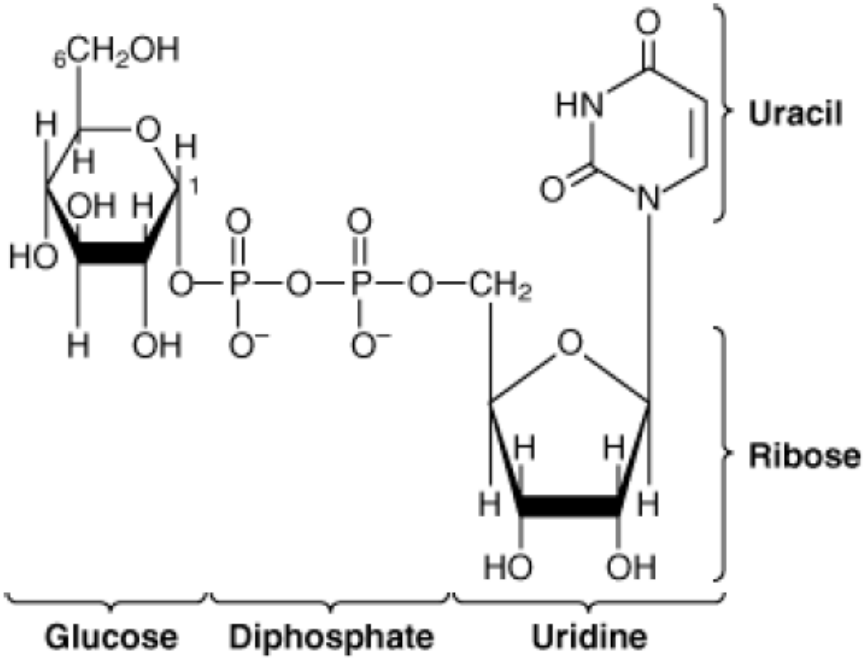
Glycogen metabolism

The Pathway of Glycogen Biosynthesis Involves a Special Nucleotide of Glucose

As in glycolysis, glucose is phosphorylated to glucose 6-phosphate, catalyzed by **hexokinase in muscle and glucokinase in liver (Figure 19–1). Glucose 6-phosphate is isomerized to glucose 1-phosphate by phosphoglucomutase. The enzyme itself is phosphorylated, and the phospho-group takes part in a reversible** reaction in which glucose 1,6-bisphosphate is an intermediate. Next, glucose 1-phosphate reacts with uridine triphosphate (UTP) to form the active nucleotide **uridine diphosphate glucose (UDPGlc) and pyrophosphate** (Figure 19–2), catalyzed by **UDPGlc pyrophosphorylase. The reaction proceeds in the direction of UDPGlc** formation because **pyrophosphatase catalyzes hydrolysis of pyrophosphate to 2 x phosphate, so removing one of** the reaction products.


Glycogen
(1→4 and 1→6 glucosyl units)x
Branching enzyme
Pi
(1→4 Glucosyl units)x
Insulin
UDP
Glycogen synthase
cAMP
Glycogen phosphorylase
Glycogen primer
Glucagon epinephrine
Glucan transferase
Debranching enzyme
*
Glycogenin
Uridine disphosphate glucose (UDPGlc)
To uronic acid pathway
Free glucose from debranching enzyme
Inorganic pyrophosphatase
UDPGlc pyrophosphorylase
PPi
2 Pi
UDP
Uridine triphosphate (UTP)
Glucose 1-phosphate
Mg2+
Phosphoglucomutase
Glucose 6-phosphate
To glycolysis and pentose phosphate pathway
H2O
ADP
Glucose 6-phosphatase
Mg2+
Glucokinase
Pi
ATP
Glucose
ATP
Nucleoside diphospho-kinase
ADP



Uridine diphosphate glucose (UDPGlc).

Glycogen synthase catalyzes the formation of a glycoside bond between C-1 of the glucose of UDPGlc and C-4 of

a terminal glucose residue of glycogen, liberating uridine diphosphate (UDP). A preexisting glycogen molecule, or "glycogen primer," must be present to initiate this reaction. The glycogen primer in turn is formed on a protein primer known as **glycogenin. Glycogenin is a 37 kDa protein that is glucosylated on a specific tyrosine residue by**

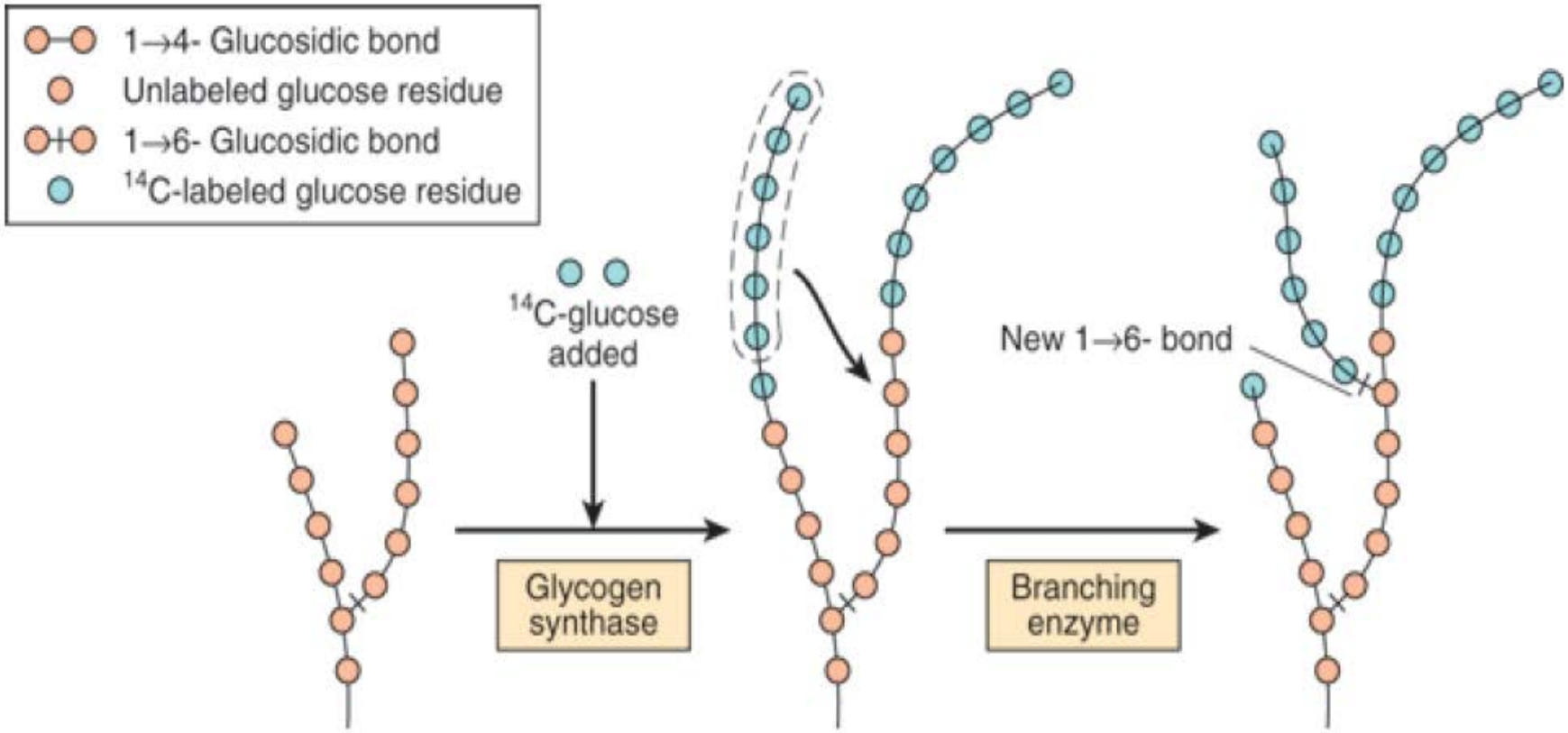
UDPGlc. Further glucose residues are attached in the 1 4 position (catalyzed by glycogenin itself) to form a short chain that is a substrate for glycogen synthase. In skeletal muscle, glycogenin remains attached in the center of the glycogen molecule (Figure 14–13); in liver the number of glycogen molecules is greater than the number of glycogenin molecules.

Branching Involves Detachment of Existing Glycogen Chains

The addition of a glucose residue to a preexisting glycogen chain, or "primer," occurs at the nonreducing, outer end

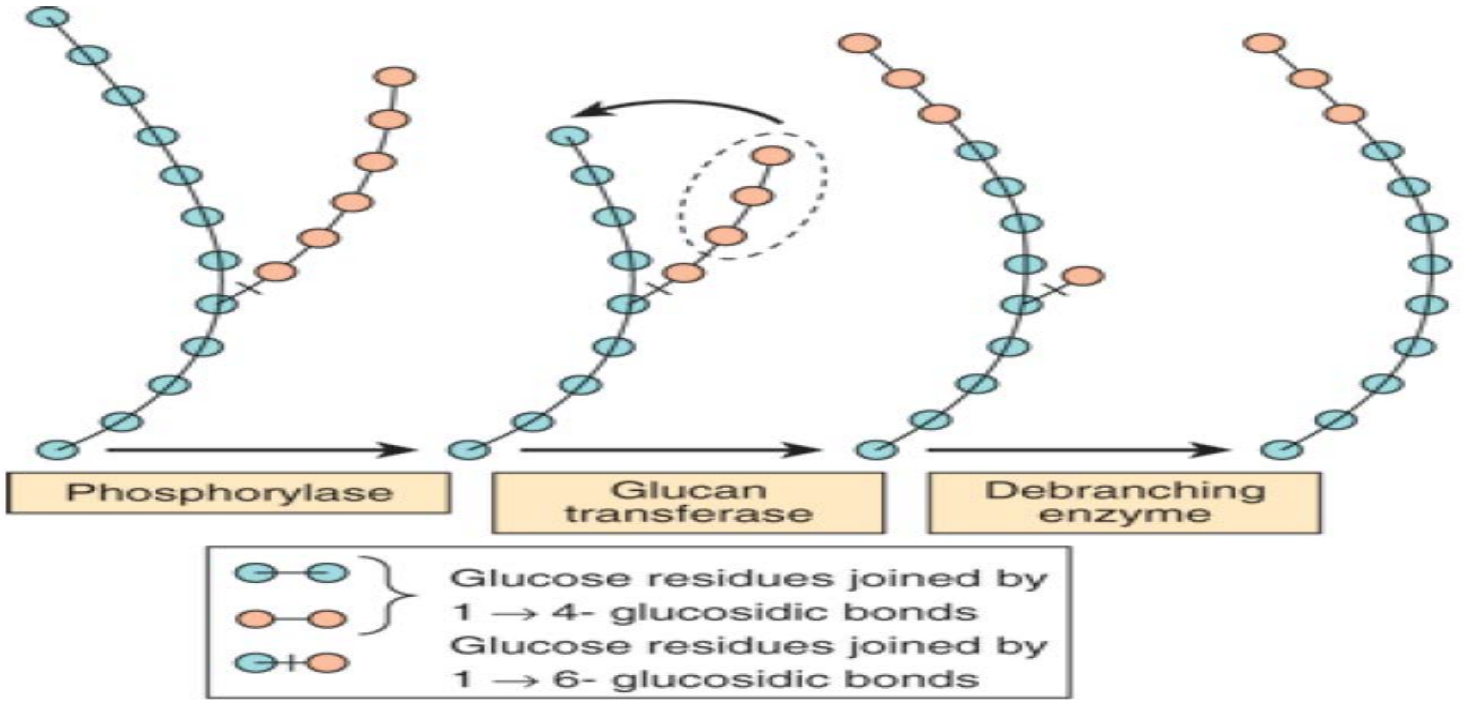
of the molecule, so that the branches of the glycogen molecule become elongated as successive 1 4 linkages are formed (Figure 19–3). When the chain is at least 11 glucose residues long, **branching enzyme transfers a part of**

the 1 4-chain (at least six glucose residues) to a neighboring chain to form a 1 6 linkage, establishing a **branch point. The branches grow by further additions of 1 4-glucosyl units and further branching.**



GLYCOGENOLYSIS IS NOT THE REVERSE OF GLYCOGENESIS, BUT IS A SEPARATE PATHWAY

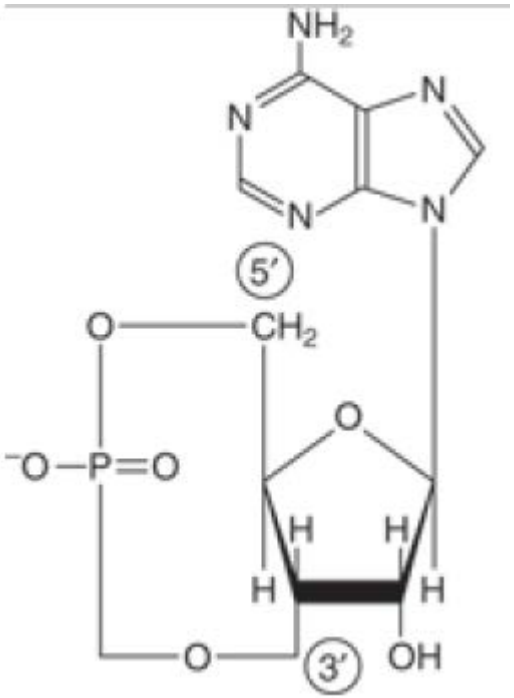
Glycogen phosphorylase catalyzes the rate-limiting step in glycogenolysis by catalyzing the phosphoroylytic cleavage (phosphorolysis; of hydrolysis) of the 1 4 linkages of glycogen to yield glucose 1-phosphate (Figur. Glycogen phosphorylase requires pyridoxal phosphate (see Chapter 44) as its coenzyme. Unlike the reactions of amino acid metabolism (Chapter 29), in which the aldehyde is the reactive group, in phosphorylase it is the phosphate group that it catalytically active. The terminal glucosyl residues from the outermost chains of the glycogen molecule are removed sequentially until approximately four glucose residues remain on either side of a 1 6 branch (Figure 19–4). Another enzyme**(-[1 4] -[1 4] glucan transferase) transfers a trisaccharide** unit from one branch to the other, exposing the 1 6 branch point. **Hydrolysis of the 1 6 linkages requires the debranching enzyme; glucan transferase and the debranching enzyme are separate activities of a single protein** with two catalytic sites. Further phosphorylase action can then proceed. The combined action of phosphorylase and these other enzymes leads to the complete breakdown of glycogen. The reaction catalyzed by phosphoglucomutase is reversible, so that glucose 6-phosphate can be formed from glucose 1-phosphate. In **liver (and kidney), but** not in muscle, **glucose 6-phosphatase hydrolyzes glucose 6-phosphate, yielding glucose that is exported, leading** to an increase in the blood glucose concentration. Glucose 6-phosphatase is in the lumen of the smooth endoplasmic reticulum, and genetic defects of the glucose 6-phosphate transporter can cause a variant of type I glycogen storage disease (see Table 19–2).



CYCLIC AMP INTEGRATES THE REGULATION OF GLYCOGENOLYSIS & GLYCOGENESIS

The principal enzymes controlling glycogen metabolism—glycogen phosphorylase and glycogen synthase—are regulated by allosteric mechanisms and covalent modification by reversible phosphorylation and dephosphorylation of enzyme protein in response to hormone action (Chapter 9).

Phosphorylation is increased in response to cyclic AMP (cAMP) (Figure 19–5) formed from ATP by **adenylyl cyclase** at the inner surface of cell membranes in response to hormones such as **epinephrine, norepinephrine, and glucagon. cAMP is hydrolyzed by phosphodiesterase, so terminating hormone action; in liver insulin increases** the activity of phosphodiesterase.



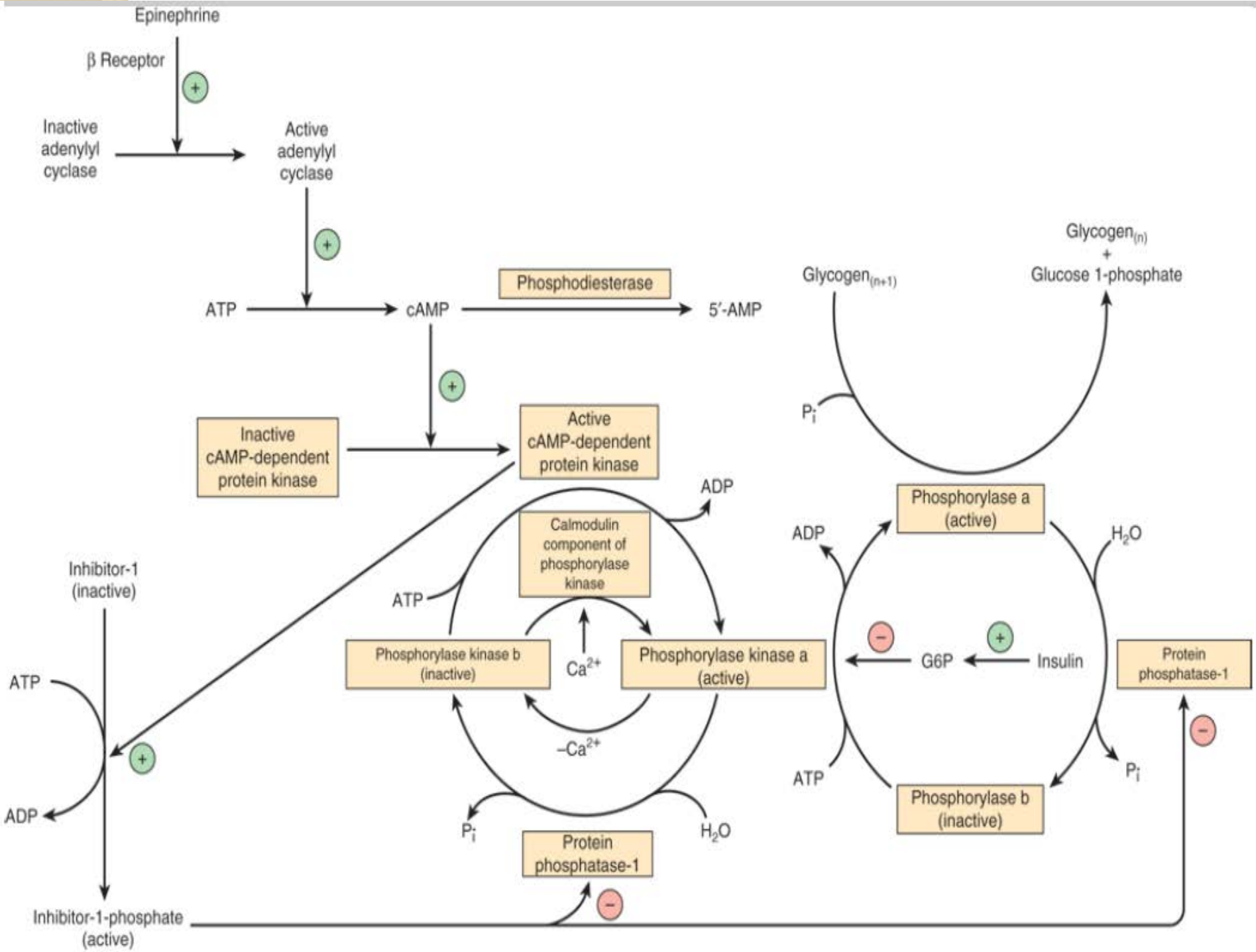
The Control of Phosphorylase Differs between Liver & Muscle

In the liver the role of glycogen is to provide free glucose for export to maintain the blood concentration of glucose; in muscle the role of glycogen is to provide a source of glucose 6-phosphate for glycolysis in response to the need for ATP for muscle contraction. In both tissues, the enzyme is activated by phosphorylation catalyzed by phosphorylase kinase (to yield phosphorylase a) and inactivated by dephosphorylation catalyzed by phosphoprotein phosphatase (to yield phosphorylase b), in response to hormonal and other signals.

There is instantaneous overriding of this hormonal control. Active phosphorylase a in both tissues is allosterically inhibited by ATP and glucose 6-phosphate; in liver, but not muscle, free glucose is also an inhibitor. Muscle phosphorylase differs from the liver isoenzyme in having a binding site for 5'AMP, which acts as an allosteric activator of the (inactive) dephosphorylated b-form of the enzyme. 5'AMP acts as a potent signal of the energy state of the muscle cell; it is formed as the concentration of ADP begins to increase (indicating the need for increased substrate metabolism to permit ATP formation), as a result of the reaction of adenylate kinase: 2 x ADP ATP + 5'AMP.

cAMP Activates Phosphorylase

Phosphorylase kinase is activated in response to cAMP (Figure 19–6). Increasing the concentration of cAMP activates **cAMP-dependent protein kinase, which catalyzes the phosphorylation by ATP of inactive phosphorylase kinase b to active phosphorylase kinase a, which in turn, phosphorylates phosphorylase b to** phosphorylase a. In the liver, cAMP is formed in response to glucagon, which is secreted in response to falling blood glucose. Muscle is insensitive to glucagon; in muscle, the signal for increased cAMP formation is the action of norepinephrine, which is secreted in response to fear or fright, when there is a need for increased glycogenolysis to permit rapid muscle activity.


Epinephrine
β Receptor
+
Inactive adenylyl cyclase
Active adenylyl cyclase
+
ATP
cAMP
Phosphodiesterase
5′-AMP
+
Inactive cAMP-dependent protein kinase
Active cAMP-dependent protein kinase
Glycogen(n+1)
Pi
Glycogen(n)
+
Glucose 1-phosphate
ADP
Calmodulin component of phosphorylase kinase
ATP
Phosphorylase kinase b (inactive)
Ca2+
Phosphorylase kinase a (active)
–Ca2+
Pi
H2O
Protein phosphatase-1
Inhibitor-1 (inactive)
ATP
+
ADP
Inhibitor-1-phosphate (active)
−
Phosphorylase a (active)
ADP
H2O
−
G6P
+
Insulin
Protein phosphatase-1
−
ATP
Pi
Phosphorylase b (inactive)

Ca2+ Synchronizes the Activation of Phosphorylase with Muscle Contraction

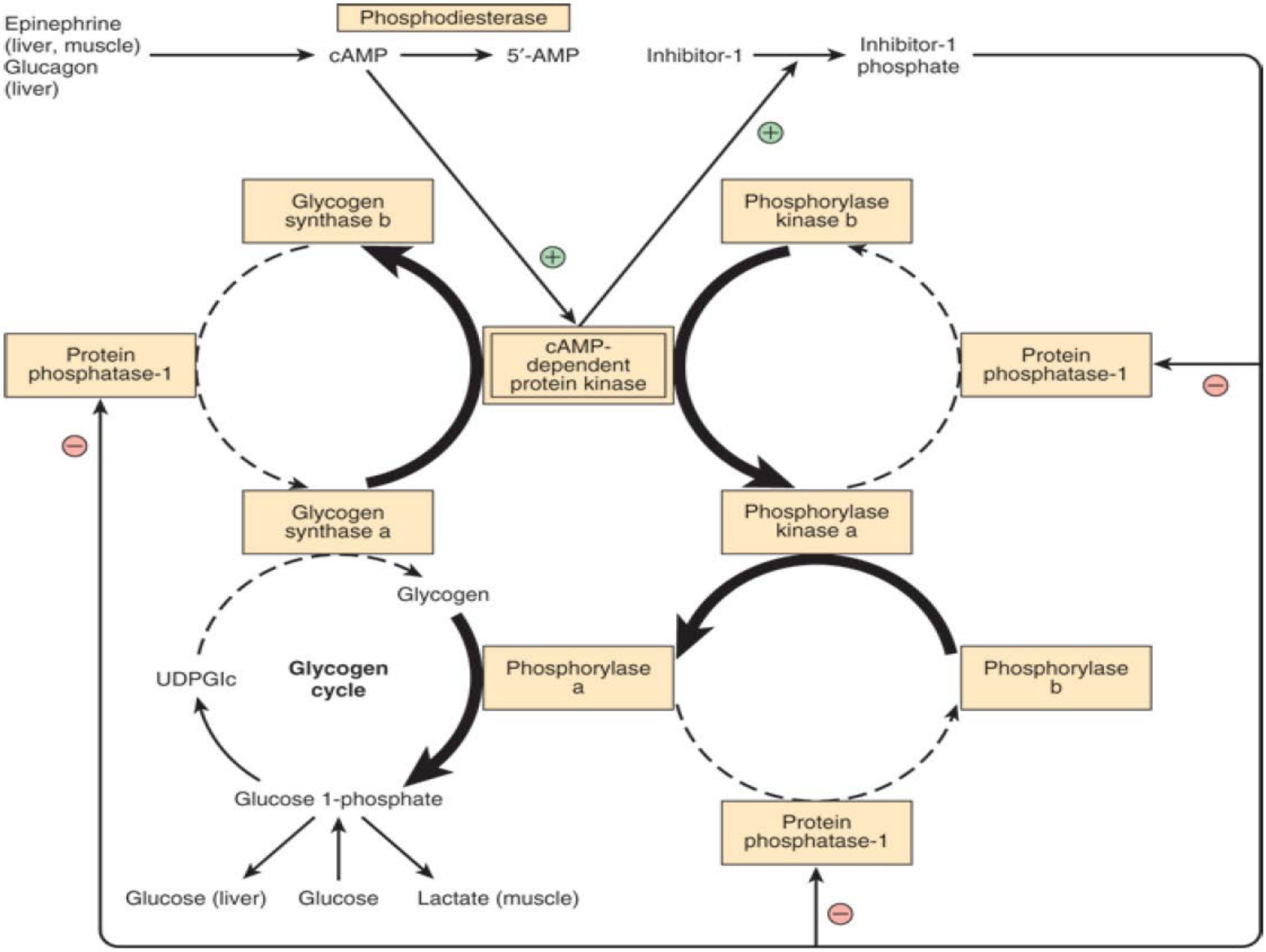
Glycogenolysis in muscle increases several 100-fold at the onset of contraction; the same signal (increased cytosolic Ca2+ ion concentration) is responsible for initiation of both contraction and glycogenolysis. Muscle phosphorylase kinase, which activates glycogen phosphorylase, is a tetramer of four different subunits, , , , and . The and subunits contain serine residues that are phosphorylated by cAMP-dependent protein kinase. The subunit is identical to the Ca2+ -binding protein **calmodulin (Chapter 42), and binds four Ca2+ . The binding of** Ca2+ activates the catalytic site of the subunit even while the enzyme is in the dephosphorylated b state; the phosphorylated a form is only fully activated in the presence of high concentrations of Ca2+ .

Glycogenolysis in Liver Can Be cAMP-Independent

In the liver, there is cAMP-independent activation of glycogenolysis in response to stimulation of 1 **adrenergic** receptors by epinephrine and norepinephrine. This involves mobilization of Ca2+ into the cytosol, followed by the stimulation of a **Ca2+ /calmodulin-sensitive phosphorylase kinase. cAMP-independent glycogenolysis is also** activated by vasopressin, oxytocin, and angiotensin II acting either through calcium or the phosphatidylinositol bisphosphate pathway (Figure 42–10).

REGULATION OF GLYCOGEN METABOLISM IS EFFECTED BY A BALANCE IN ACTIVITIES BETWEEN GLYCOGEN SYNTHASE & PHOSPHORYLASE

At the same time as phosphorylase is activated by a rise in concentration of cAMP (via phosphorylase kinase), glycogen synthase is converted to the inactive form; both effects are mediated via **cAMP-dependent protein kinase (Figure 19–8). Thus, inhibition of glycogenolysis enhances net glycogenesis, and inhibition of glycogenesis** enhances net glycogenolysis. Also, the dephosphorylation of phosphorylase a, phosphorylase kinase, and glycogen synthase b is catalyzed by a single enzyme with broad specificity—**protein phosphatase-1. In turn, protein** phosphatase-1 is inhibited by cAMP-dependent protein kinase via inhibitor-1. Thus, glycogenolysis can be terminated and glycogenesis can be stimulated, or vice versa, synchronously, because both processes are dependent on the activity of cAMP-dependent protein kinase. Both phosphorylase kinase and glycogen synthase may be reversibly phosphorylated at more than one site by separate kinases and phosphatases. These secondary phosphorylations modify the sensitivity of the primary sites to phosphorylation and dephosphorylation **(multisite phosphorylation). Also, they allow insulin, by way of increased glucose 6-phosphate, to have effects that act** reciprocally to those of cAMP (see Figures 19–6 & 19–7).


Epinephrine
(liver, muscle)
Glucagon
(liver)
Phosphodiesterase
cAMP
5′-AMP
Inhibitor-1
Inhibitor-1
phosphate
Glycogen
synthase b
Phosphorylase
kinase b
Protein
phosphatase-1
cAMP-
dependent
protein kinase
Protein
phosphatase-1
Glycogen
synthase a
Phosphorylase
kinase a
Glycogen
UDPGlc
Glycogen
cycle
Phosphorylase
a
Phosphorylase
b
Glucose 1-phosphate
Protein
phosphatase-1
Glucose (liver)
Glucose
Lactate (muscle)