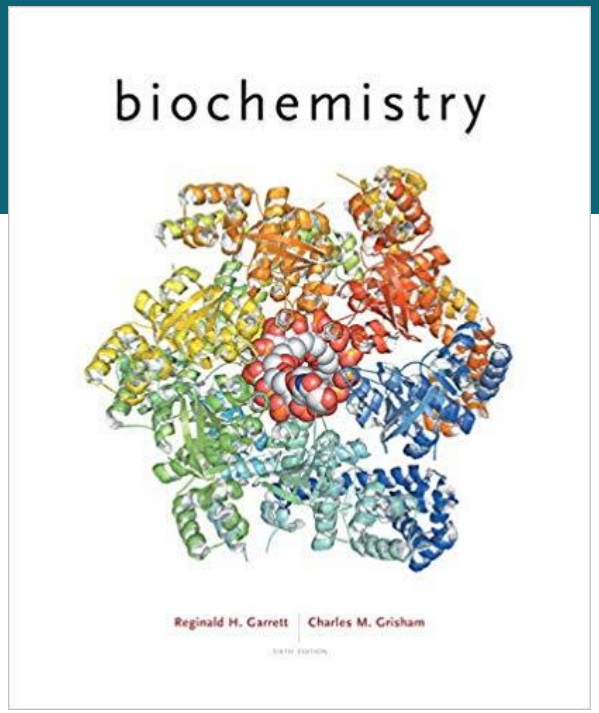

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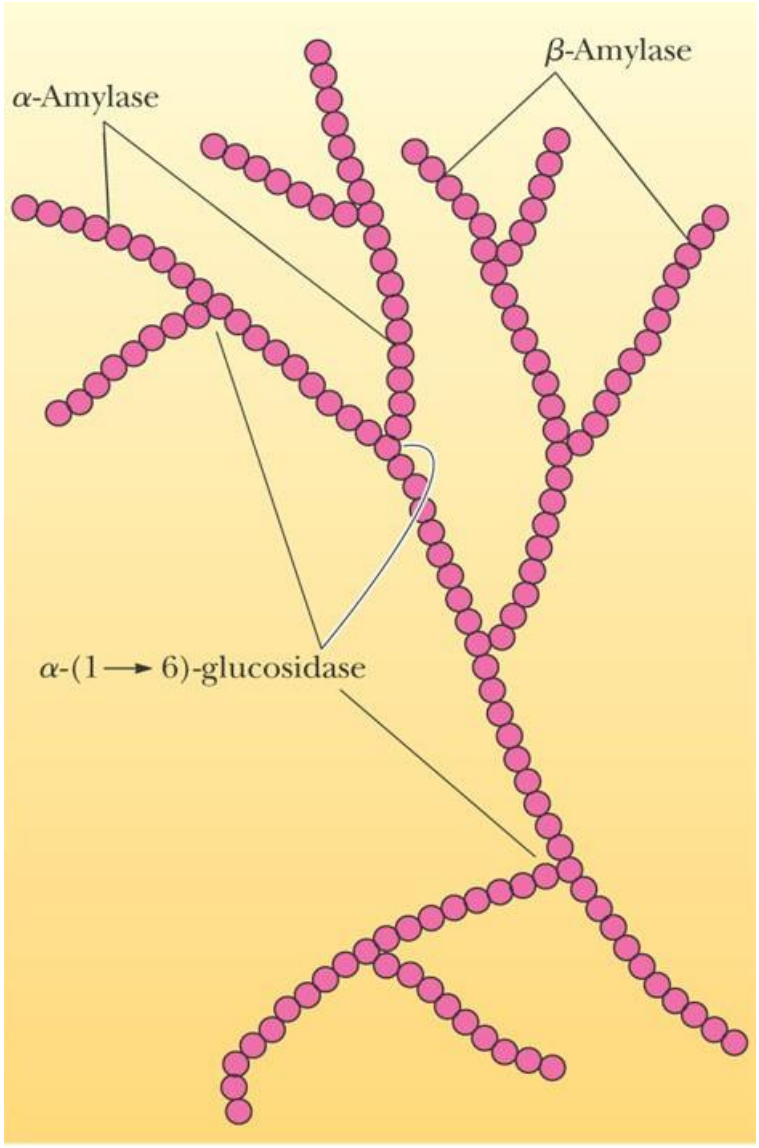
Chapter 22 – Glycogen Metabolism

Reginald Garrett & Charles Grisham • University of Virginia

Starch and Glycogen degradation

Obtaining glucose from storage (or diet)



α-Amylase is an endoglycosidase

Present in saliva and pancreatic secretions hydrolyzes the α1,4 linkage

It cleaves dietary amylopectin or glycogen to maltose (disaccharide), maltotriose (trisaccharide) and other small oligosaccharides

It is active on either side of a branch point, but activity is reduced near the branch points

Debranching enzyme cleaves "limit dextrins"

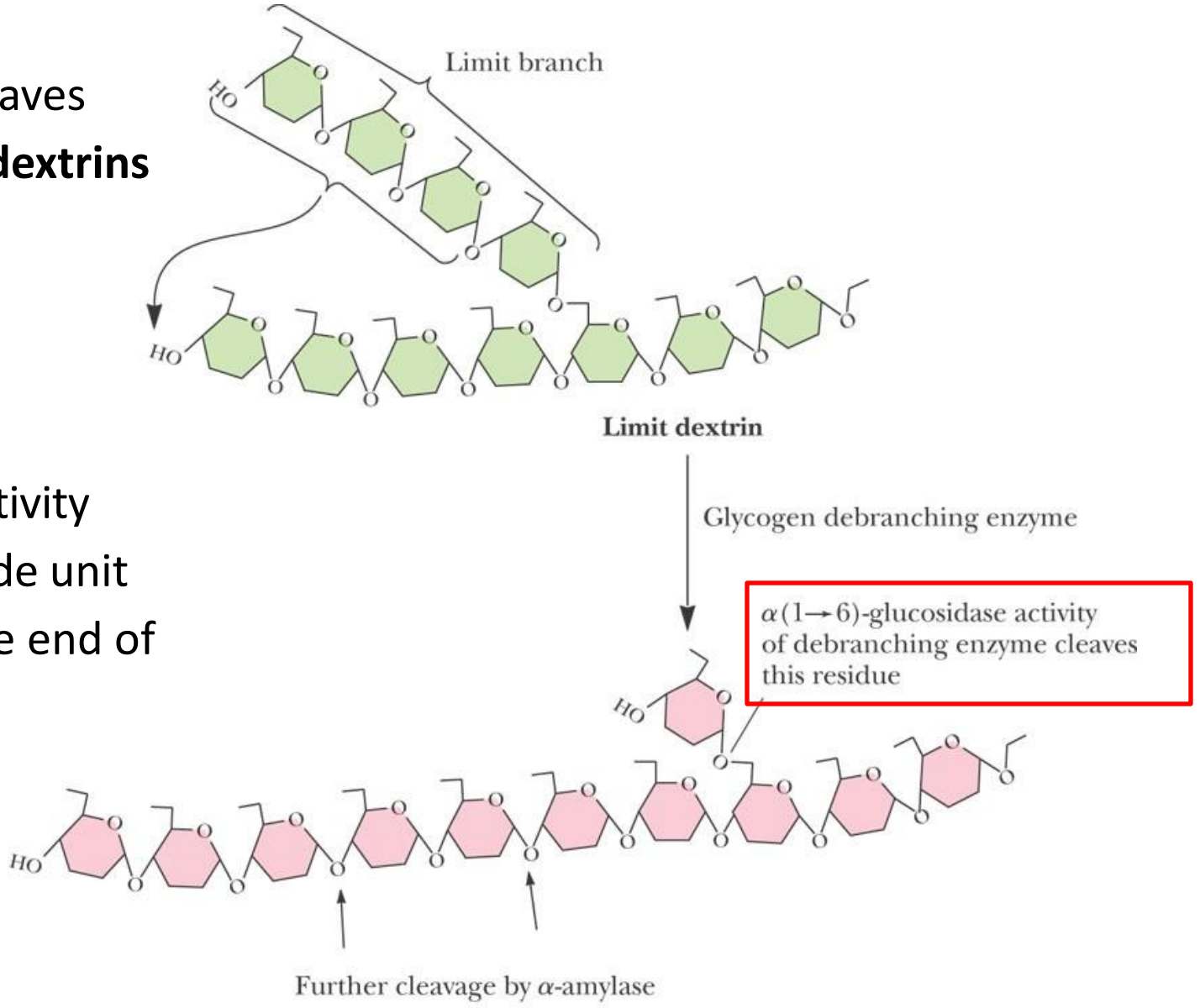
2 activities of the debranching enzyme:

- It transfers trisaccharide groups
- And cleaves the remaining single glucose units from the main chain

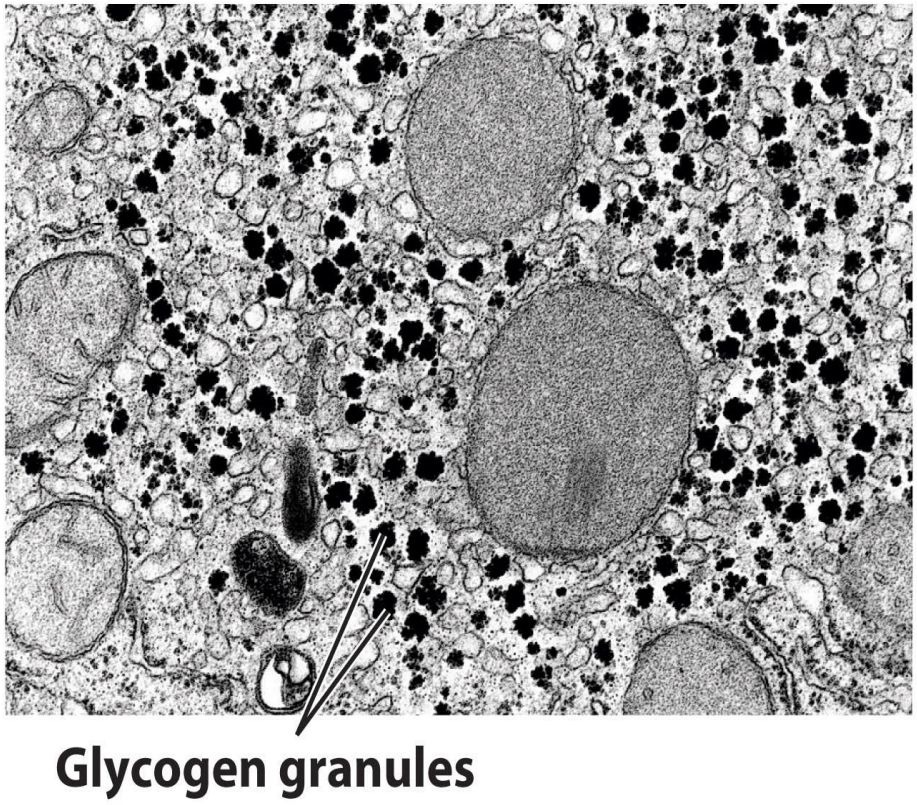
Dietary Starch and Glycogen degradation

α-amylase digestion leaves highly branched **limit dextrins**

Debranching enzyme **glucanotransferase** activity transfers a trisaccharide unit from one branch to the end of another



Storage Glycogen

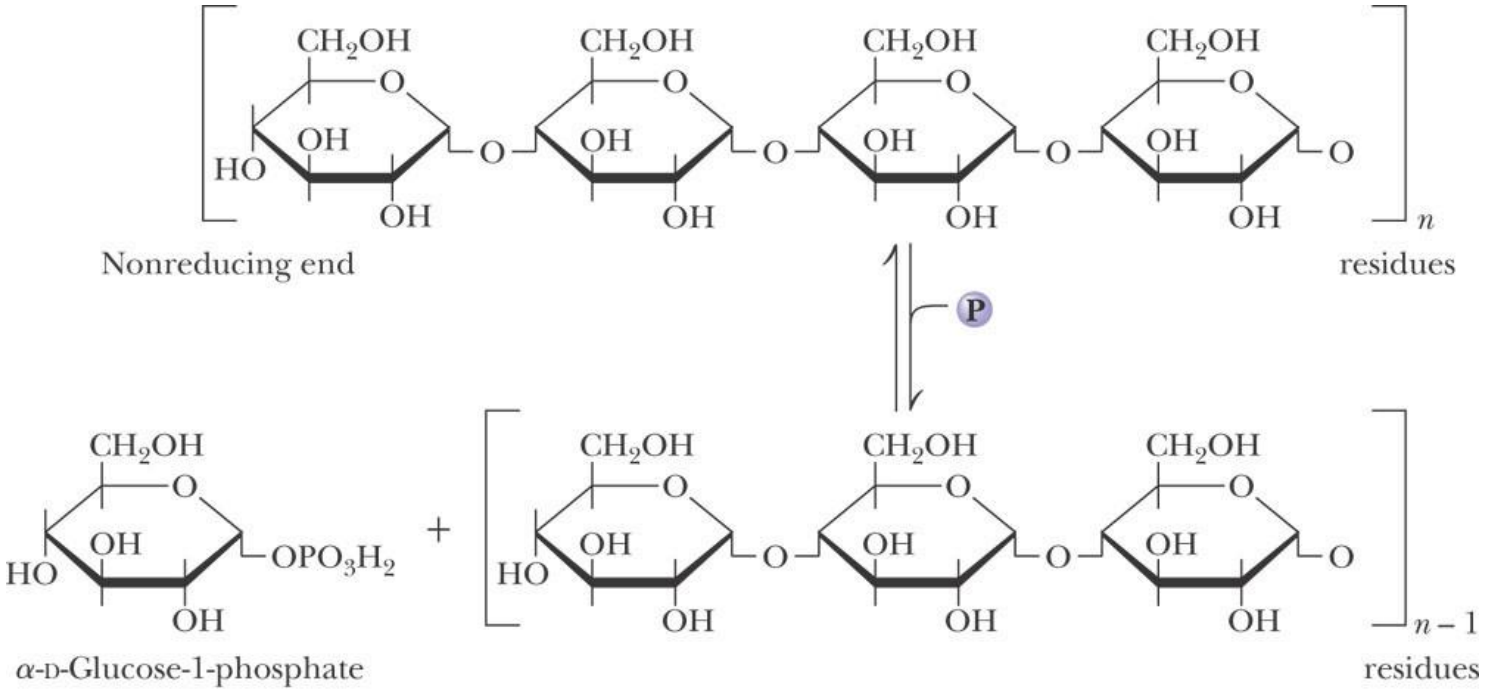


Digestive breakdown of starch (and dietary glycogen) is unregulated - nearly 100% of ingested food is absorbed and metabolized

Tissue glycogen is an important energy reservoir
Synthesis and degradation of storage glycogen is instead tightly regulated
Glycogen consists of "granules" of high MW

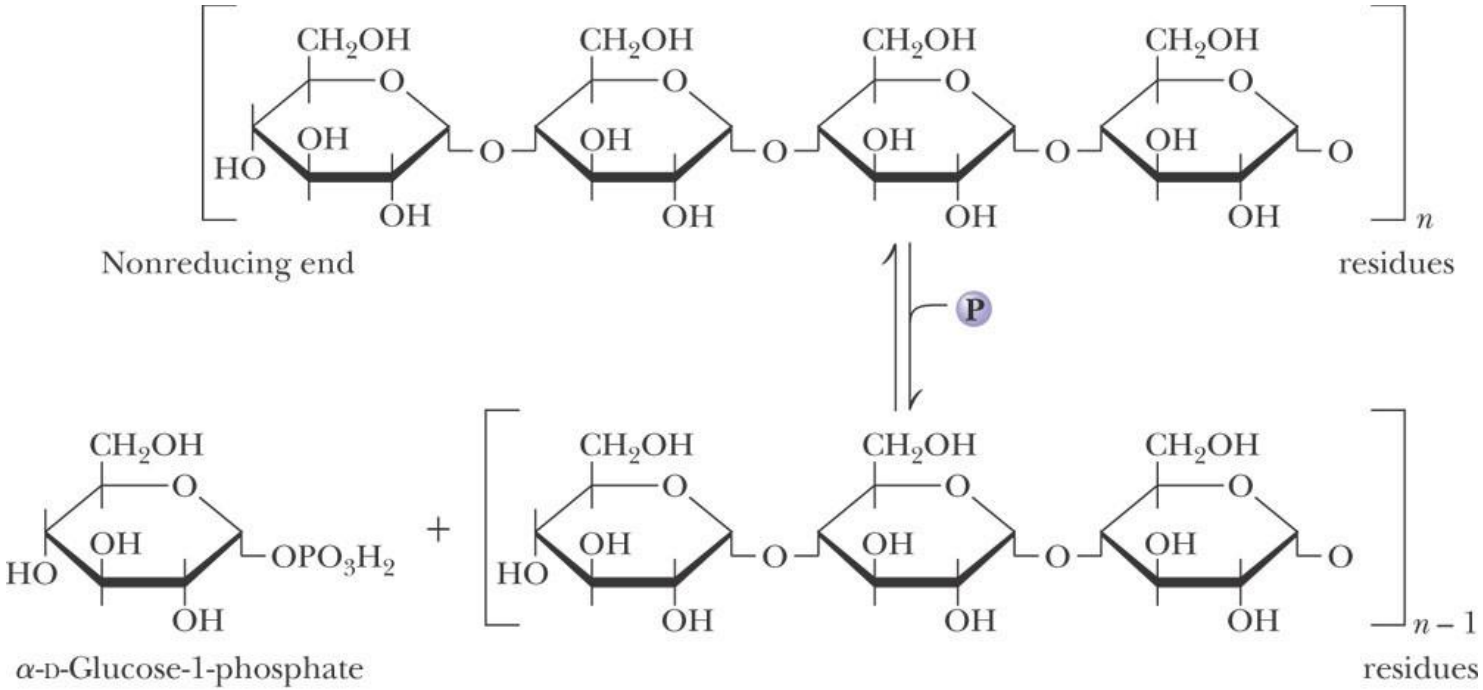
Storage Glycogen degradation

Glycogen phosphorylase reaction



- **Glycogen phosphorylase** cleaves one sugar unit from the end of a glycogen chain, and uses inorganic phosphate to phosphorylate the glucose.
- This avoids use of ATP to phosphorylate glucose.
- Limit dextrins are then degraded by the debranching enzyme. The catabolic and anabolic enzymes are present in glycogen granules
- Glucose-1-phosphate can be converted to glucose-6-phosphate by **phosphoglucomutase**

Storage Glycogen degradation



This reaction is a **phosphorolysis:** the glycosidic bond is split by phosphate and not H_2O

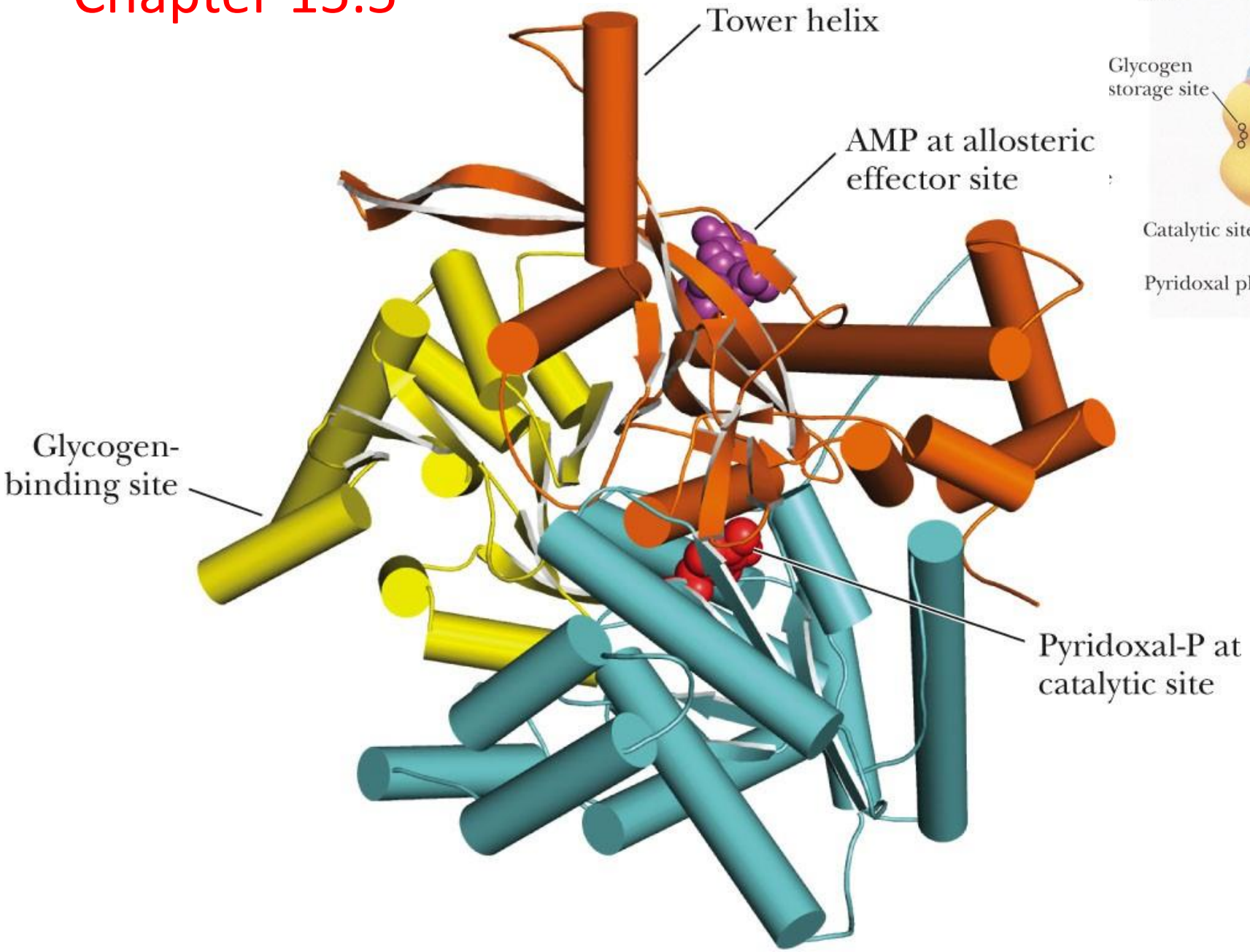
$\Delta G^{o'}$ is close to zero, but ΔG *in vivo* is -6 kJ/mol because of the high ratio of [Pi] to [glucose-1-phosphate].

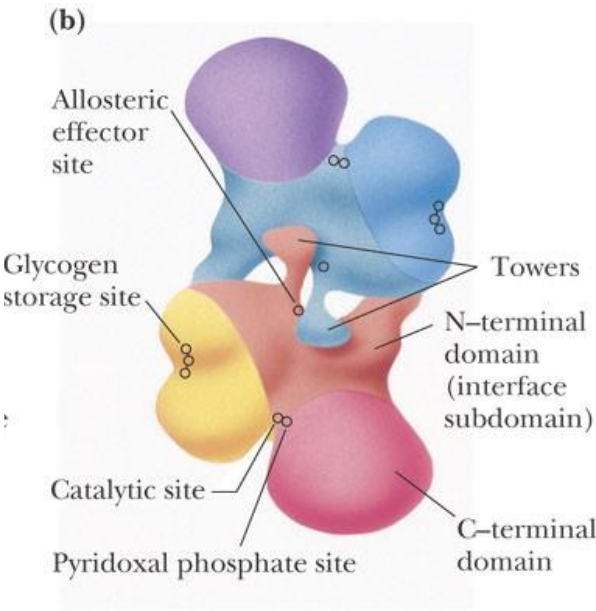
In muscle: enters glycolysis

In liver glucose-6-P is hydrolyzed to glucose for transport to other tissues.

Glycogen Phosphorylase regulation

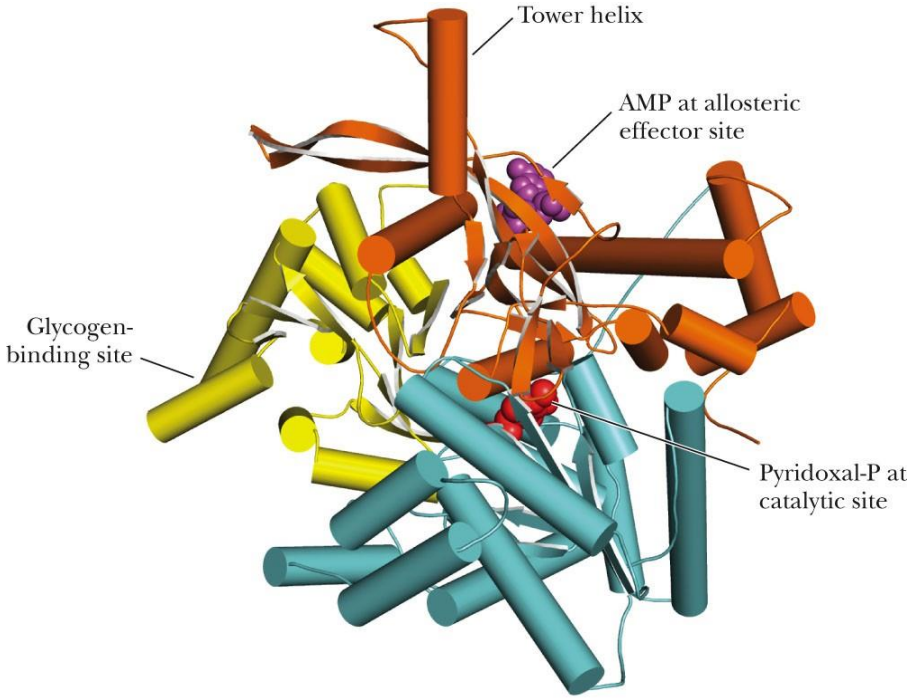
Chapter 15.5



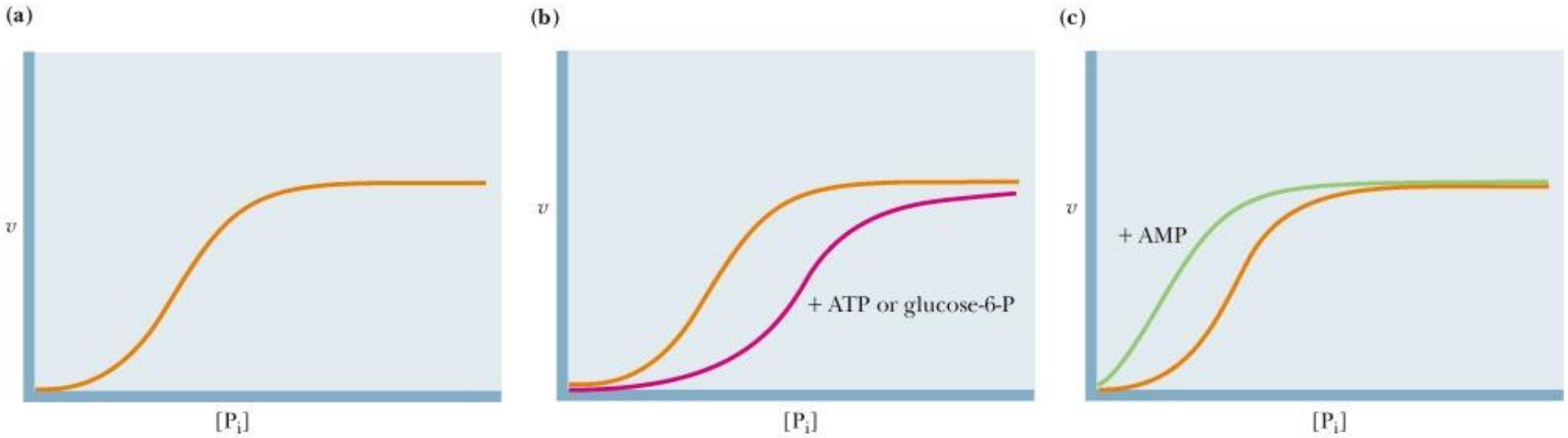


Glycogen Phosphorylase regulation

- Glycogen phosphorylase is a dimer of identical 842 residue subunits
- Each subunit contains an active site (at the center of the subunit) and an allosteric effector site near the subunit interface
- A regulatory phosphorylation site is located at Ser^{14} on each subunit
- A glycogen-binding site exerts regulatory control
- Each subunit contributes a "tower helix" (residues 262 to 278) to the subunit-subunit interface
- In the dimer, the tower helices extend from their respective subunits and pack against each other



Glycogen Phosphorylase regulation



Muscle glycogen phosphorylase shows cooperativity in substrate binding
ATP and glucose-6-P are allosteric inhibitors of glycogen phosphorylase
AMP is an allosteric activator of glycogen phosphorylase
When ATP and glucose-6-P are abundant, glycogen breakdown is inhibited
When cellular energy reserves are low (*i.e.*, high [AMP] and low [ATP] and [G-6-P]) glycogen catabolism is stimulated

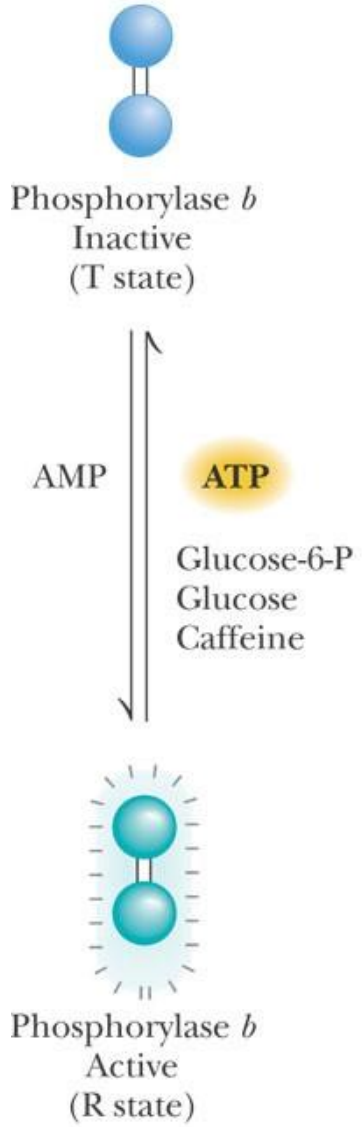
Thus:

high energy status → glycogen breakdown is inhibited

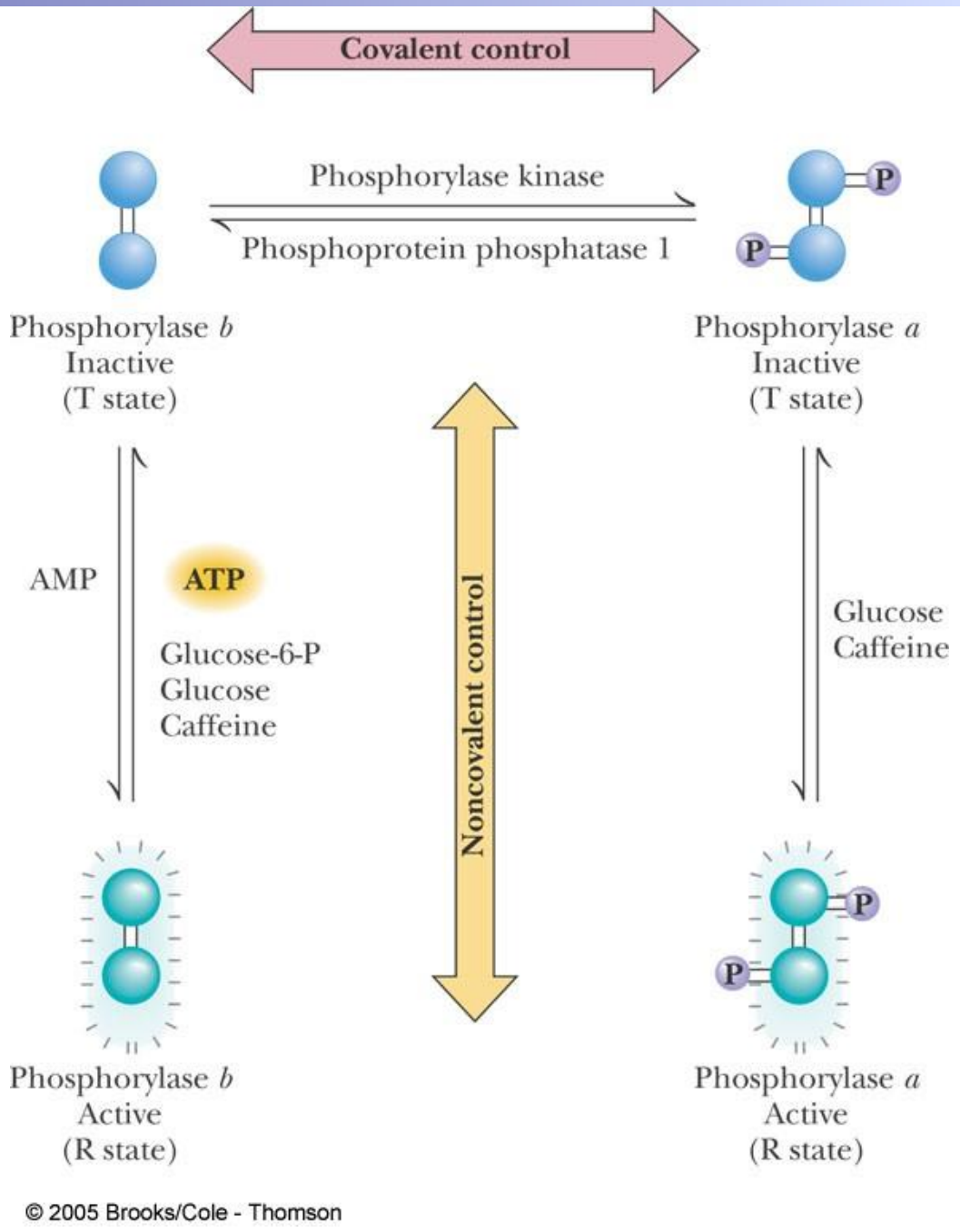
low energy status → glycogen breakdown is stimulated

Glycogen Phosphorylase regulation

- The active form of the enzyme is designated the R state
- The inactive form of the enzyme is denoted the T state
- AMP promotes the conversion to the active state
- ATP, glucose-6-P, and caffeine favor conversion to the inactive T state
- A significant conformation change occurs at the subunit interface between the T and R state
- This conformational change at the interface is linked to a structural change at the active site that affects catalysis



Glycogen Phosphorylase regulation by covalent modification



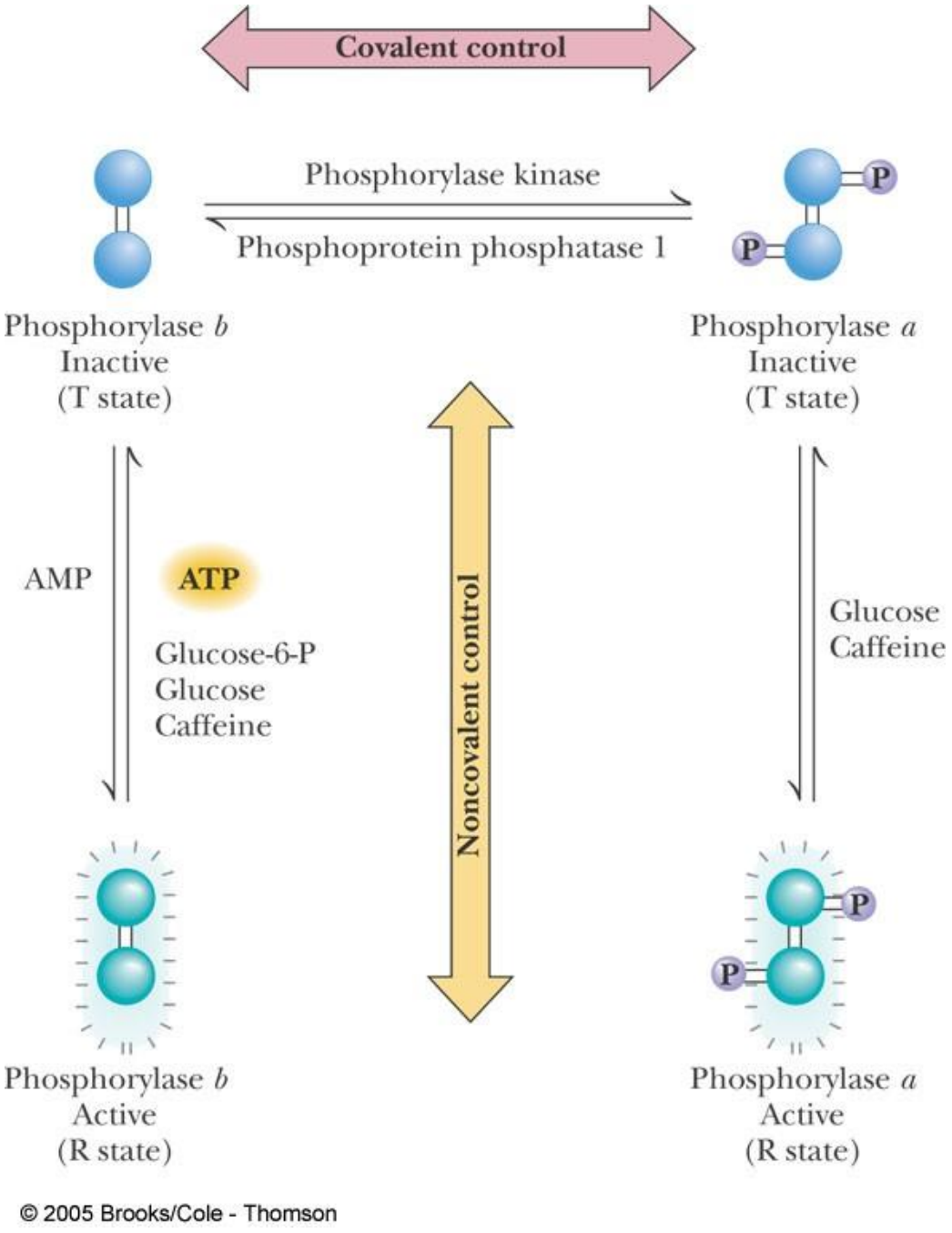
Phosphorylation of serine-14 converts the less active enzyme phosphorylase *b* to the more active phosphorylase *a*

Phosphorylation causes a large conformational change and converts the enzyme to a form in which it is much less sensitive to allosteric regulation

The *a* form is less sensitive to allosteric regulation than the *b* form.

Phosphorylation converts the enzyme from a form that is allosterically regulated, to a form that is persistently active.

Glycogen Phosphorilase regulation by covalent modification

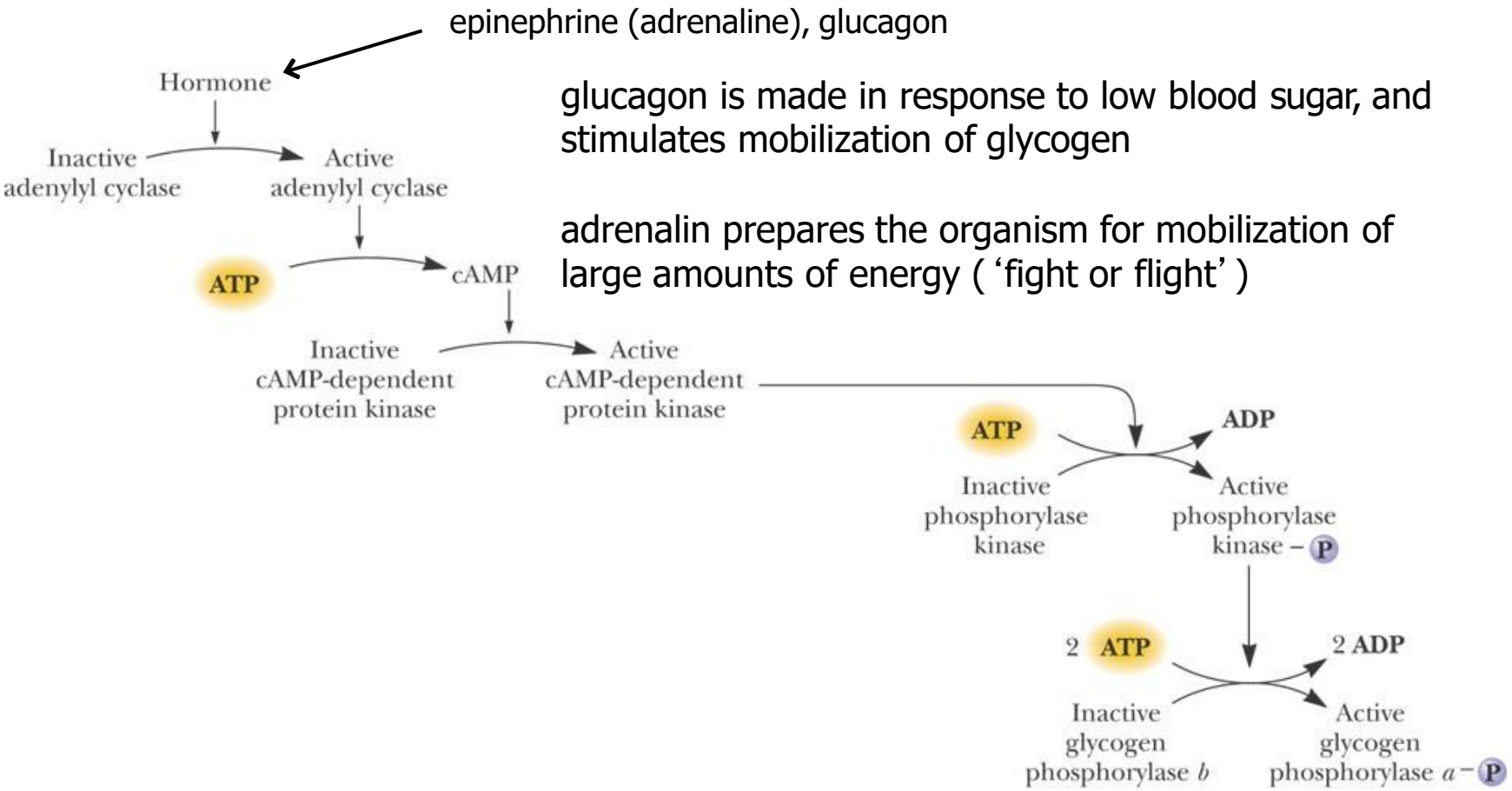


Phosphorylase *a*, the equilibrium is shifted towards the R state. Thus the phosphoryaled enzyme is more active, with no requirement for an allosteric activator

Phosphorylation reduces the value of *L* ($[T_0]/[R_0]$) in the MWC model

Cascade regulation of glycogen phosphorylase

The **phosphorylase kinase** that phosphorylates glycogen phosphorylase is itself regulated by phosphorylation



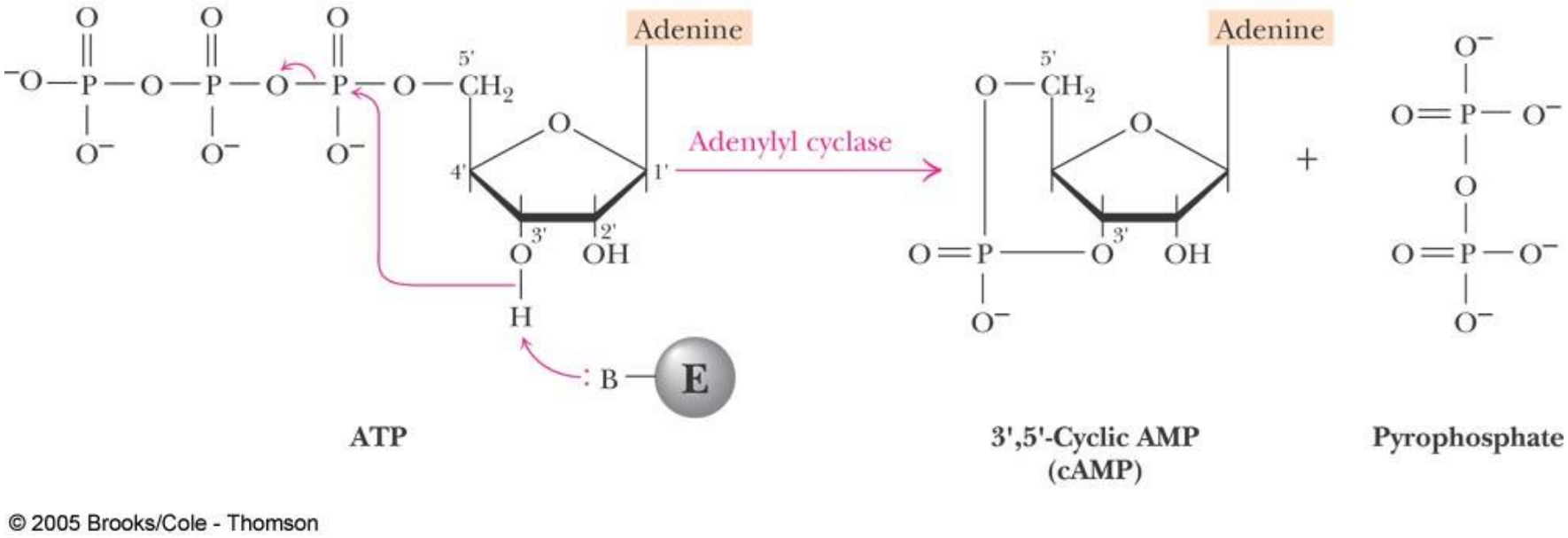
glucagon is made in response to low blood sugar, and stimulates mobilization of glycogen

adrenalin prepares the organism for mobilization of large amounts of energy ('fight or flight')

Glucagon secretion is inhibited by insulin.

In diabetics glycogen is degraded, even when [glucose] is high

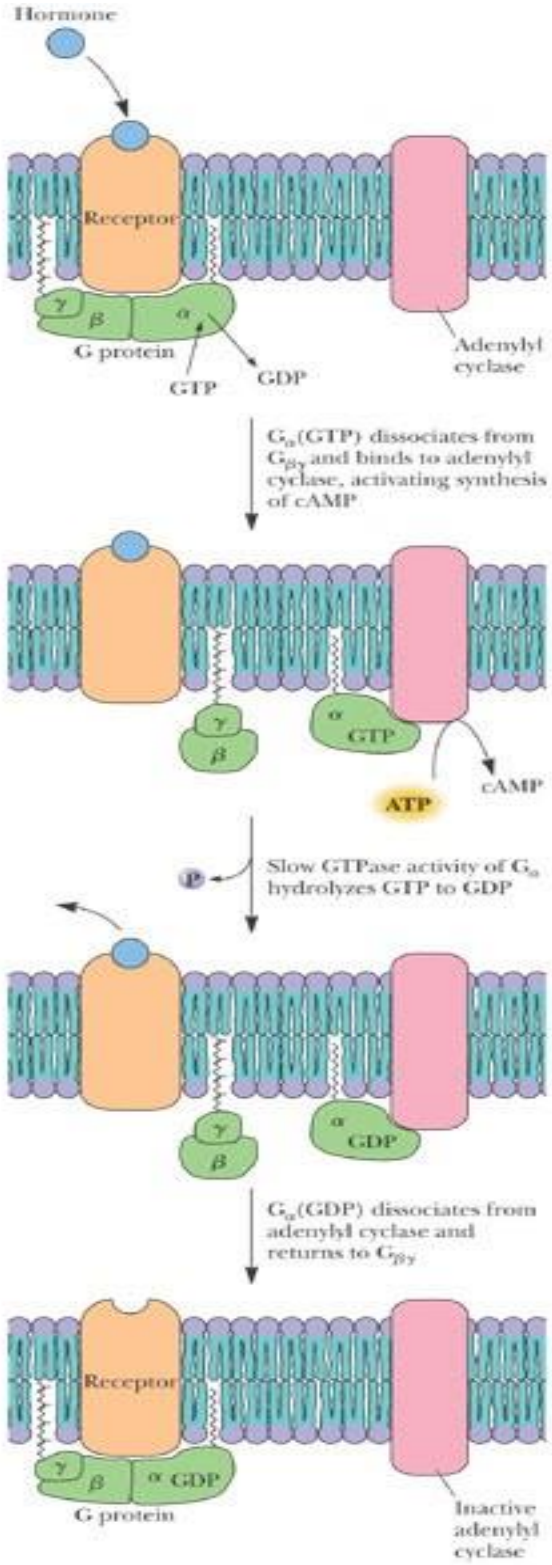
cAMP is a second messenger



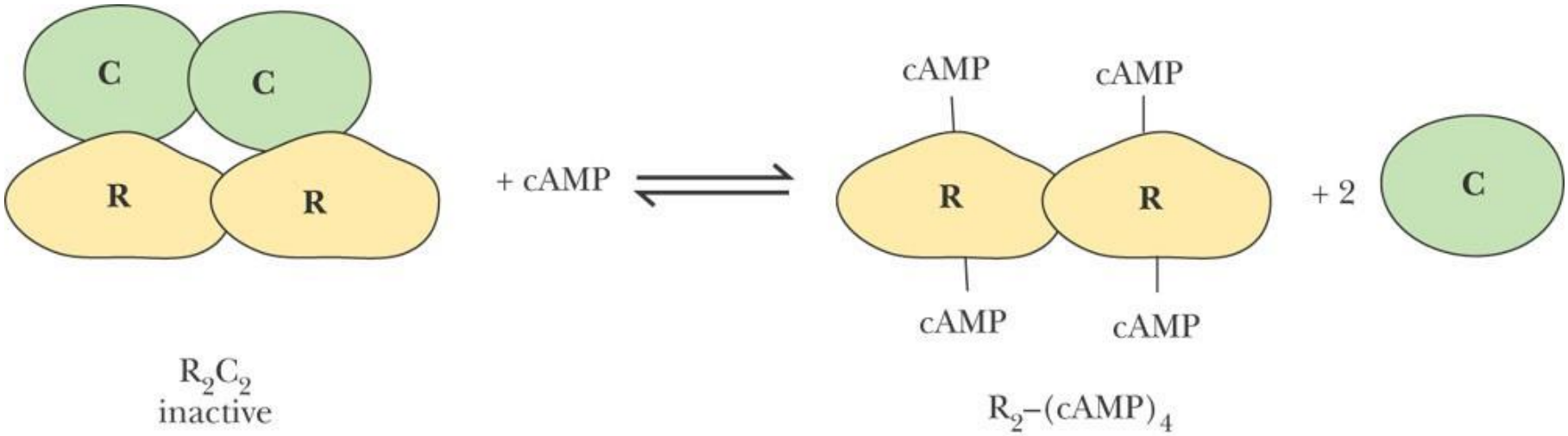
Cyclic AMP is a **second messenger :** transduces the message of the hormone

Adenylyl cyclase is membrane associated

This mechanism **amplifies** the signal, because one hormone-receptor complex can activate many G proteins, and many cAMP molecules can be synthesized before the G protein dissociates



cAMP- dependent protein kinase



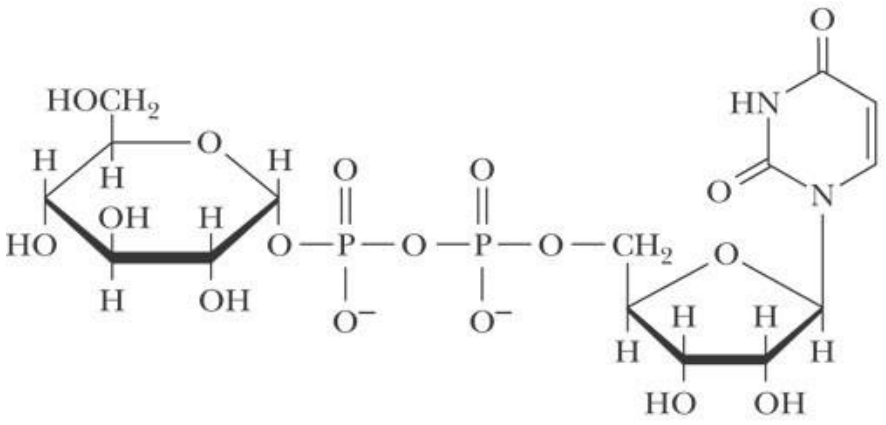
cAMP activates **cAMP-dependent protein kinase**.
cAMP binding causes dissociation of the C subunit, which is the active kinase, which phosphorylates phosphorylase kinase
This is an example of enzyme regulation by binding to a regulatory protein

Glycogen Synthesis

Glycogen synthesis pathway is different than degradation.

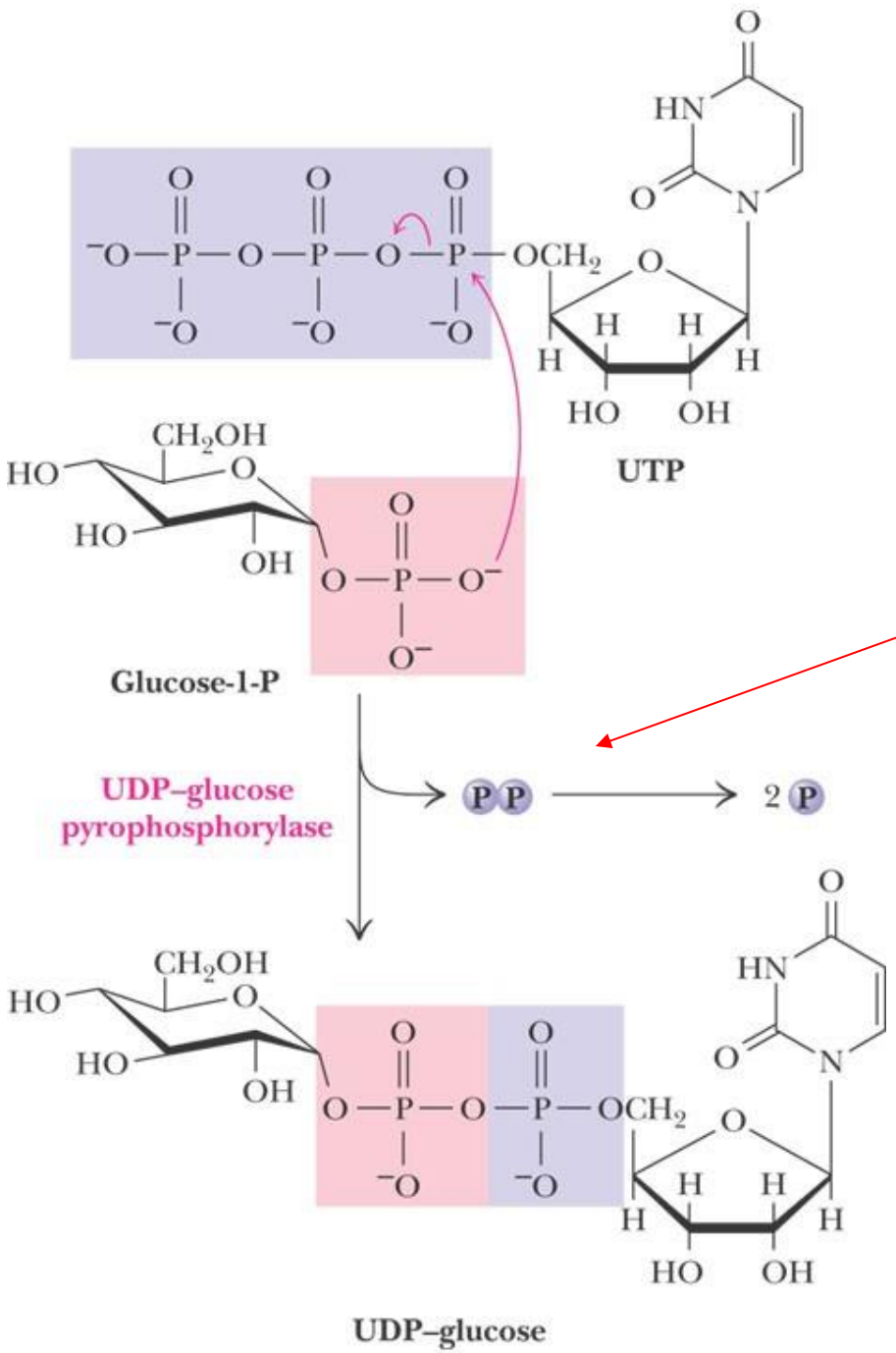
Glucose is activated for glycogen synthesis by attachment to **uridine diphosphate**, to form the **sugar nucleotide UDP-glucose**.

formation of UDP-glucose from glucose-1-phosphate and UTP is catalyzed by **UDP-glucose pyrophosphorylase**



Uridine diphosphate glucose
(UDPG)

UDP-glucose pyrophosphorylase reaction

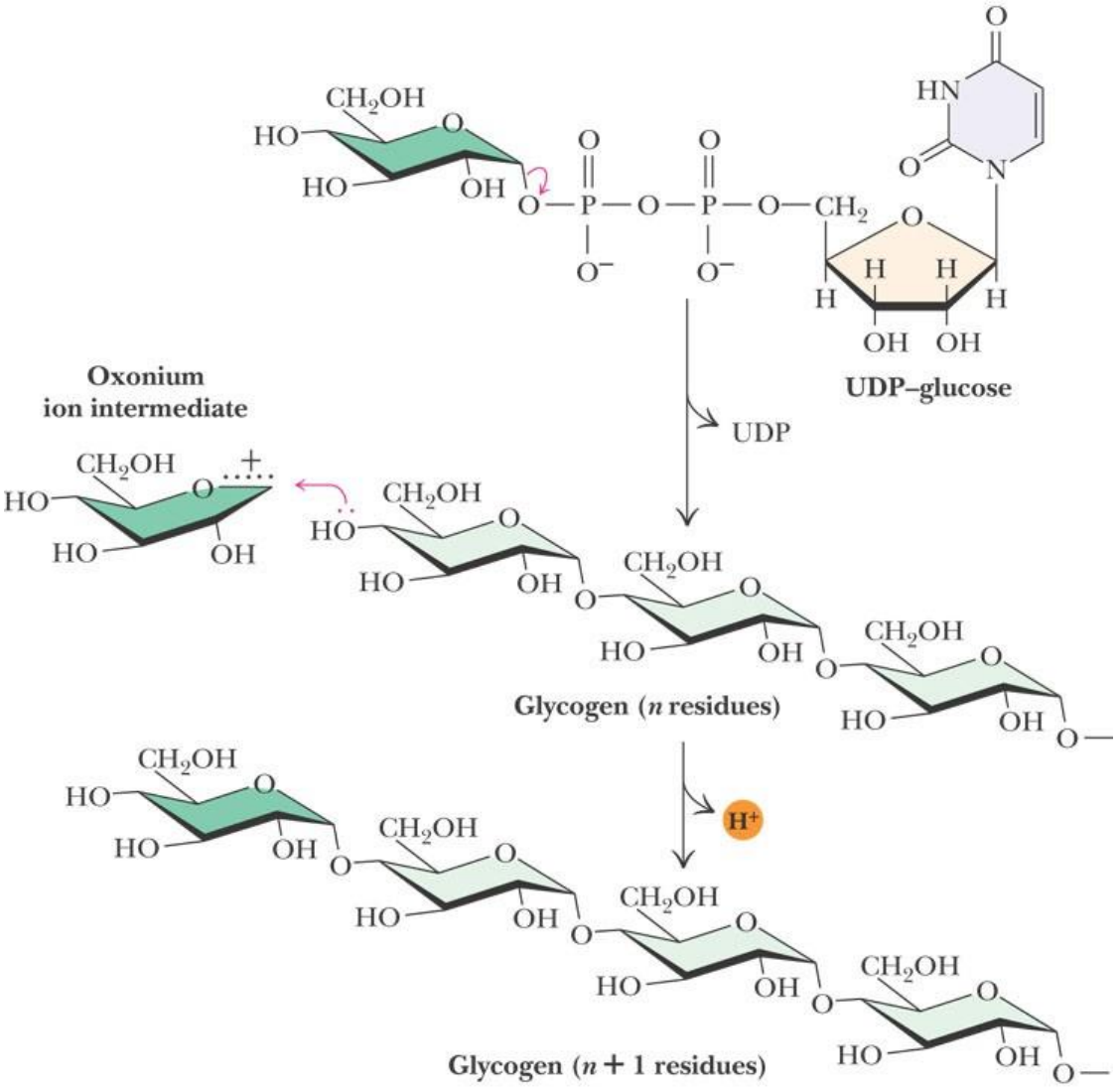


The mechanism of the UDP-glucose pyrophosphorylase reaction involves the attack by a phosphate oxygen of glucose-1-P on the α-phosphorus of UTP, followed by release of the pyrophosphate anion.

Hydrolysis of PP_i provides the driving force for the reaction

Next step - Glycogen Synthase

- Glycogen Synthase catalyzes Formation of α(1→4) glycosidic bonds in Glycogen
- The large glycogen particle is built around a single protein, **glycogenin**, at the core
- The first glucose is linked to a tyrosine -OH on the protein
- Sugar units are then added by the action of glycogen synthase



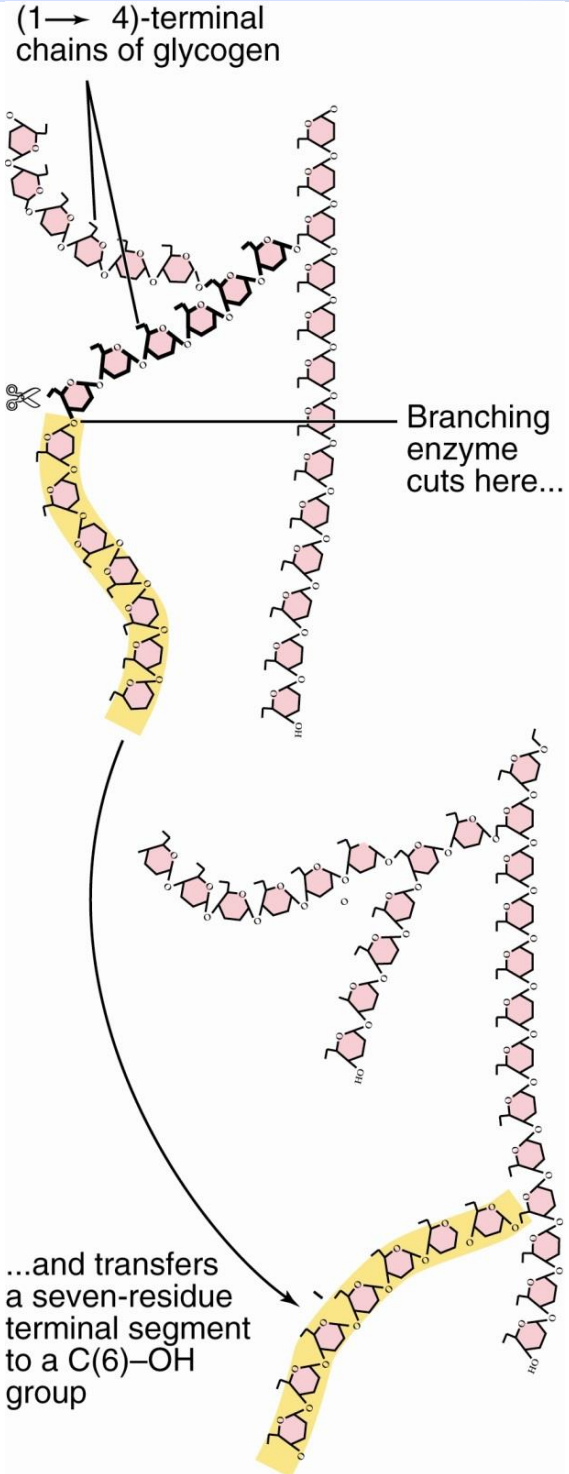
Glycogen synthase transfers glucosyl units from UDP-glucose to C-4 hydroxyl at a nonreducing end of a glycogen strand

An oxonium ion intermediate is formed

Glycogen Branching Enzyme

Formation of glycogen branches is catalyzed by the branching enzyme.

Six- or seven-residue segments of a growing glycogen chain are transferred to the C-6 hydroxyl group of a glucose residue on the same or a nearby chain.



Glycogen Metabolism Control

- ***Glycogen metabolism is a highly regulated process, involving reciprocal control of glycogen phosphorylase and glycogen synthase***
- GP allosterically activated by AMP and inhibited by ATP, glucose-6-P and caffeine
- GS is stimulated by glucose-6-P
- Both enzymes are regulated by covalent modification - **phosphorylation**

Glycogen Synthase regulation

Glycogen synthase is phosphorylated at multiple sites by protein kinases (including cAMP dependent protein kinase)

Phosphorylated glycogen synthase has a lower activity and is allosterically activated by high concentrations of glucose-6-phosphate.

At least 9 serine residues are phosphorylated and 4 different **protein kinases** are involved

Dephosphorylation is carried out by **phosphoprotein phosphatase-1 (PP1)**

PP1 inactivates glycogen phosphorylase and activates glycogen synthase

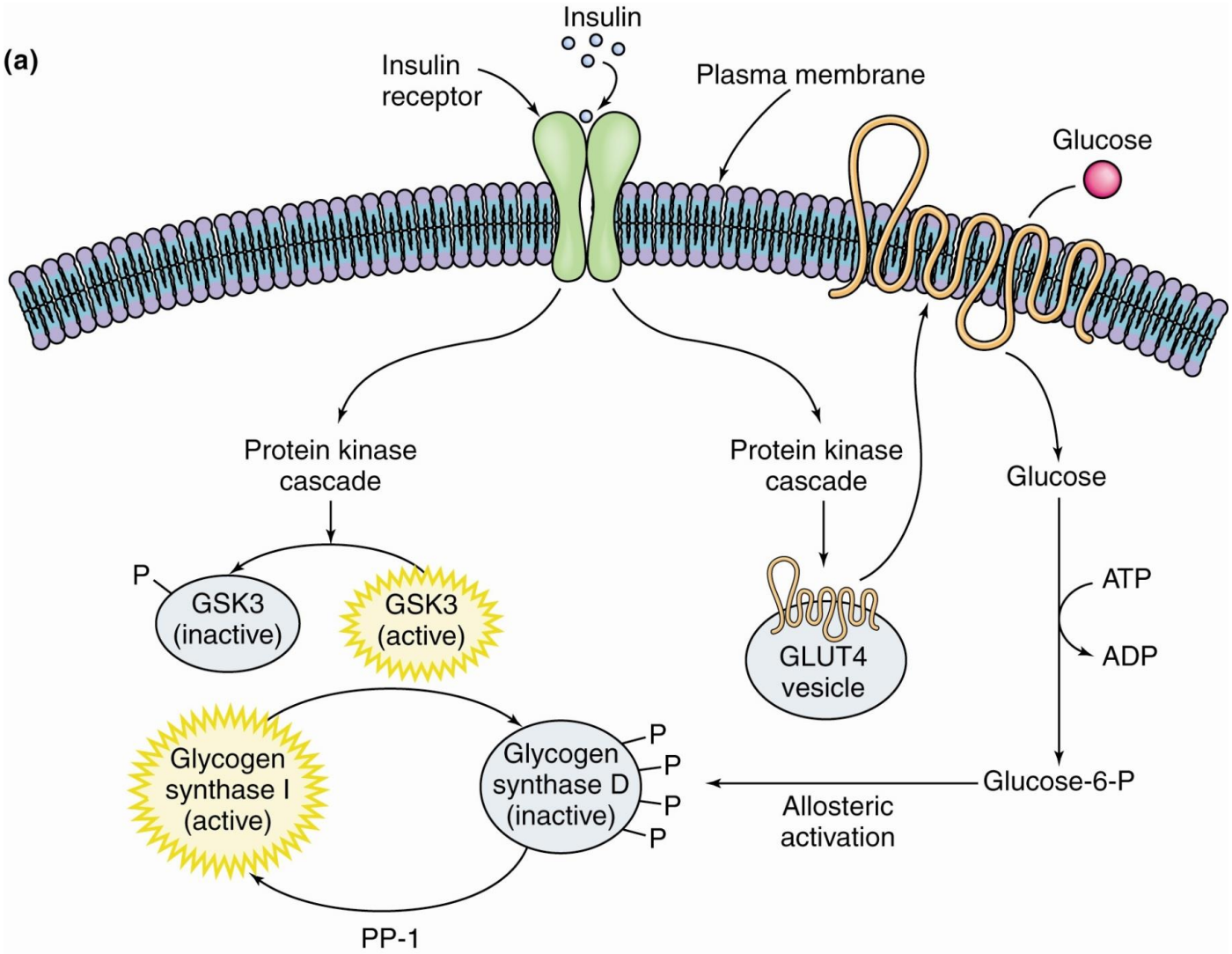
Dephosphorylated enzyme has a high activity and does not require glucose-6-phosphate for activity.

Phosphorylation has **opposite** effects on glycogen phosphorylase (the catabolic enzyme) and glycogen synthase (the anabolic enzyme).

Hormones Regulate Glycogen Synthesis and Degradation

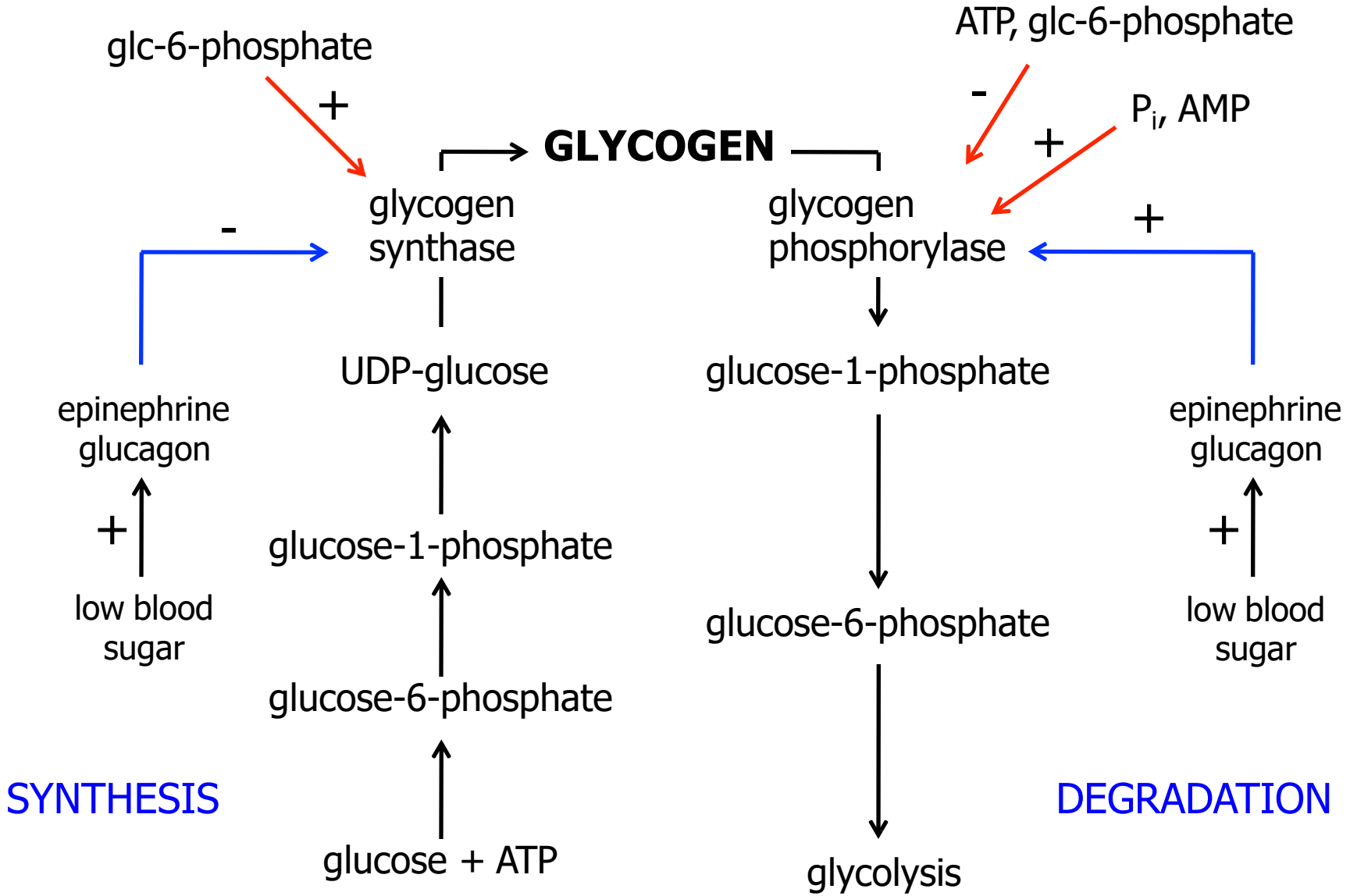
- Storage and utilization of tissue glycogen and other aspects of metabolism are regulated by hormones, including glucagon, epinephrine, and the glucocorticoids
- Insulin is released in response to increased blood glucose
- Insulin triggers glycogen synthesis when blood glucose rises
  - Between meals, blood glucose is 70-90 mg/dL
  - Glucose rises to 150 m/dL after a meal and then returns to normal within 2-3 hours
- Insulin is secreted from the pancreas (to liver) in response to an increase in blood glucose
- Insulin acts to lower blood glucose rapidly in several ways, including stimulating glycogen synthesis and inhibiting glycogen breakdown
- Glucagon and epinephrine stimulate glycogen breakdown

Insulin Modulates the Action of Glycogen Synthase



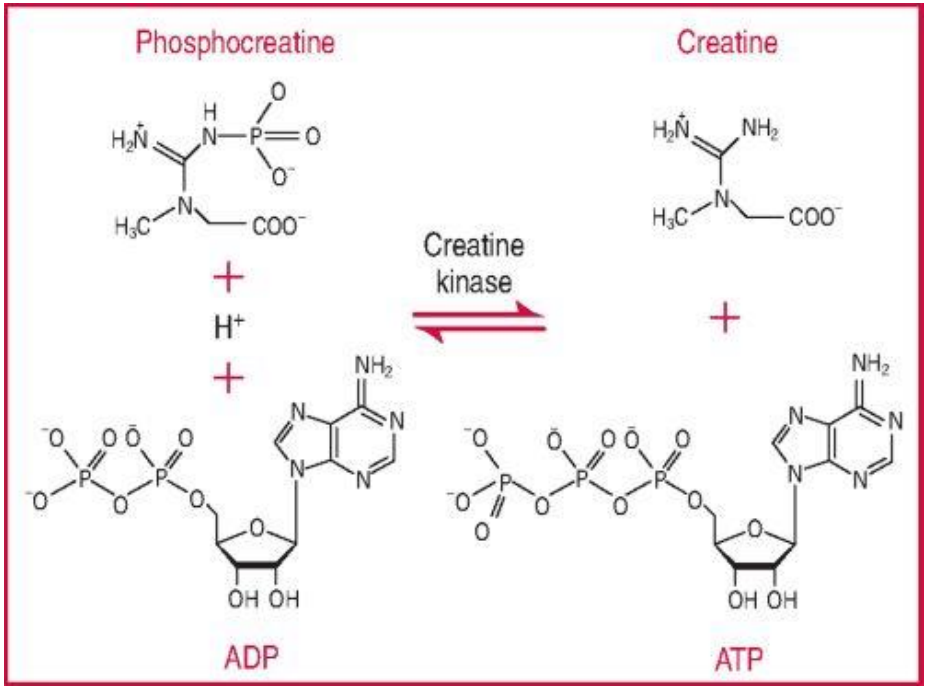
- Binding of insulin to plasma membrane receptors in the liver and muscles triggers protein kinase cascades that stimulate glycogen synthesis
- Insulin's effect include stimulation of lipid synthesis, glycogen synthesis, protein synthesis, glycolysis, and active transport, and inhibition of gluconeogenesis and lipid breakdown
- Glucose uptake provides substrate for glycogen synthesis and glucose-6-P, which allosterically activates the otherwise inactive form of glycogen synthase

Glucagon and Epinephrine



red arrows: allosteric regulation;
blue arrows: covalent control via cAMP dependent protein kinase (also called protein kinase A)

Phosphocreatine

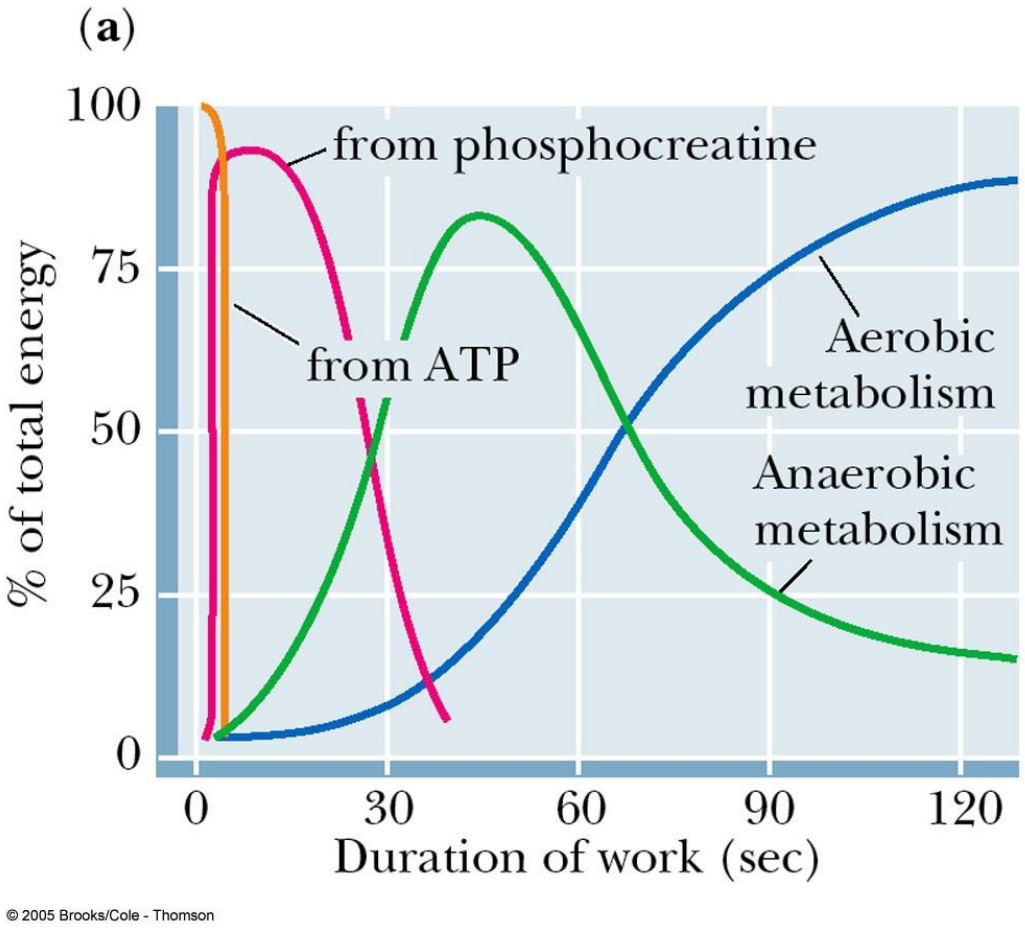


Phosphocreatine is a phosphorylated creatine molecule that serves as a rapidly mobilizable reserve of high-energy phosphates. It provides a short-term source of ATP in muscle (and brain), because it can phosphorylate ADP to make ATP

Dietary supplementation with creatine increases muscle store of phosphocreatine and improves performance during brief intense exercise (but FDA recommends doctor's approval)

During intense exercise, free ATP is depleted within seconds, phosphocreatine prolongs ATP availability for a few more seconds

Sources of energy during exercise

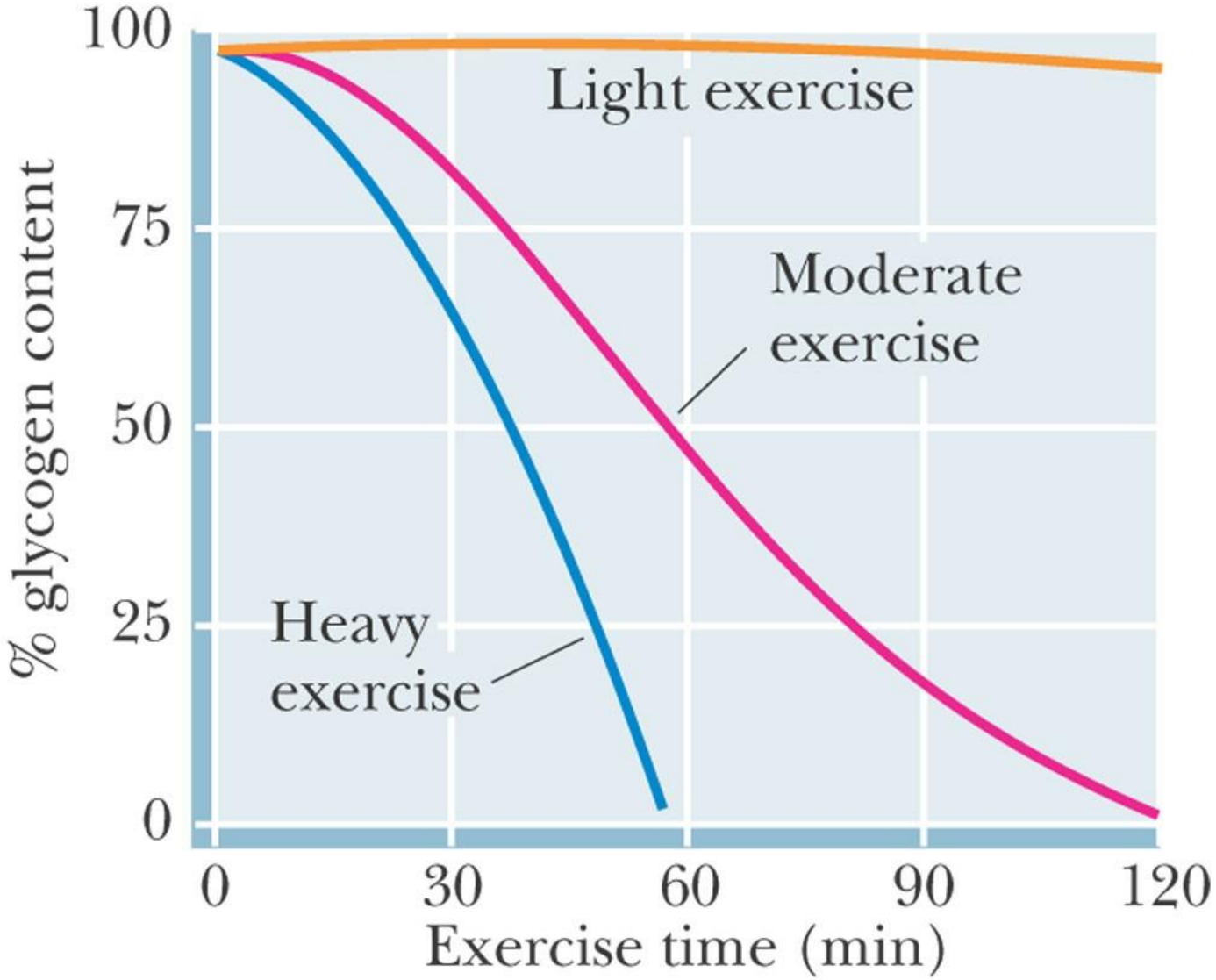


During brief intense exercise (100m sprint) energy sources are free ATP, phosphocreatine and anaerobic glycolysis

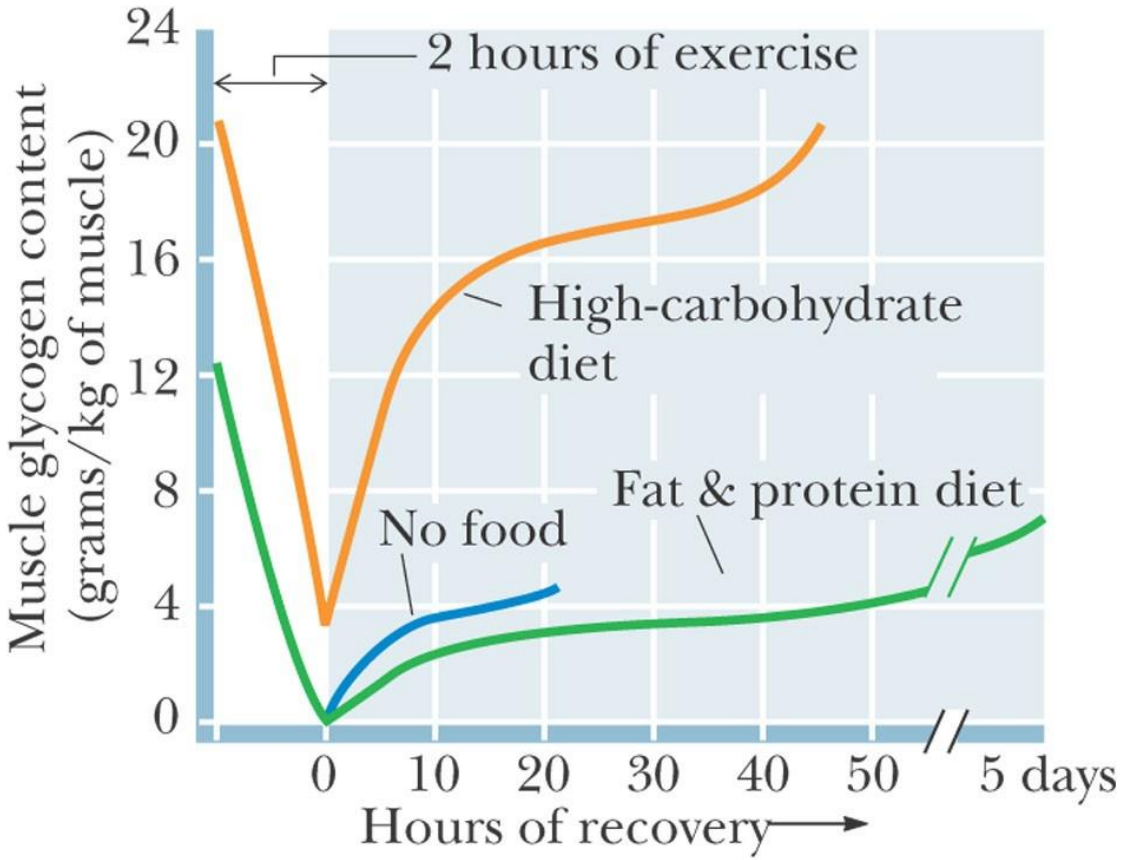
This cannot persist for long, because ATP and phosphocreatine are quickly used up, and anaerobic glycolysis would cause acidosis

In longer term exercise (1000m) glycogen breakdown and aerobic metabolism become important

Degradation of glycogen stores in exercise



Replenishment of glycogen stores after exercise



Glycogen storage diseases

von Gierke's disease (glucose-6-phosphatase).
Glycogen is normal in structure but present in excess. Glucose-6-phosphate accumulates in liver (cannot be converted to glucose), stimulates glycolysis causing lactate acidosis

Cori disease (debranching enzyme), only outermost branches of glycogen can be degraded.
Symptoms similar to von Gierke.

McArdle disease (muscle glycogen phosphorylase). Limited ability to perform strenuous exercise, but gentle exercise is possible