

Bryan Krantz: University of California, Berkeley  
MCB 102, Spring 2008, Metabolism Lecture 6

Reading: Ch. 15 of *Principles of Biochemistry*, “Principles of Metabolic Regulation, Illustrated with Glucose and Glycogen Metabolism.”

## PRINCIPLES OF METABOLISM

**Pathways** are not simple linear trajectories, but rather pathways are interconnected, complex, yet organized. Metabolites are produced and fed in a variety of directions at once.

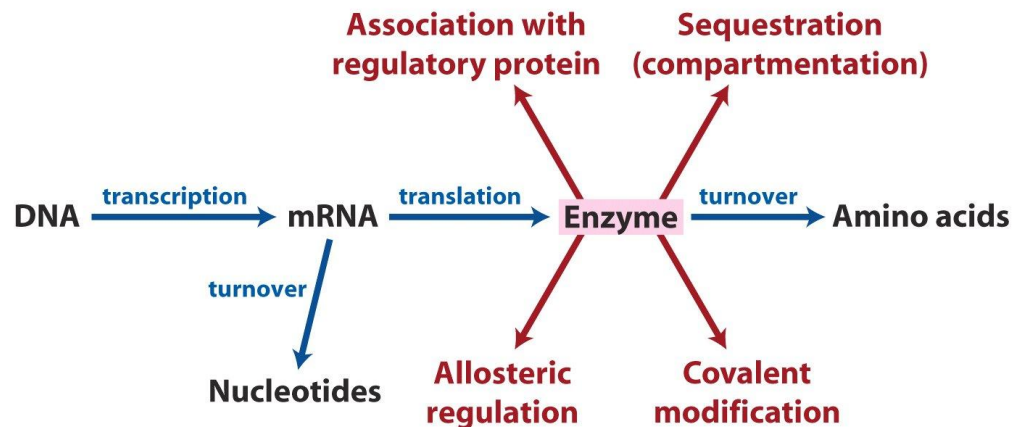
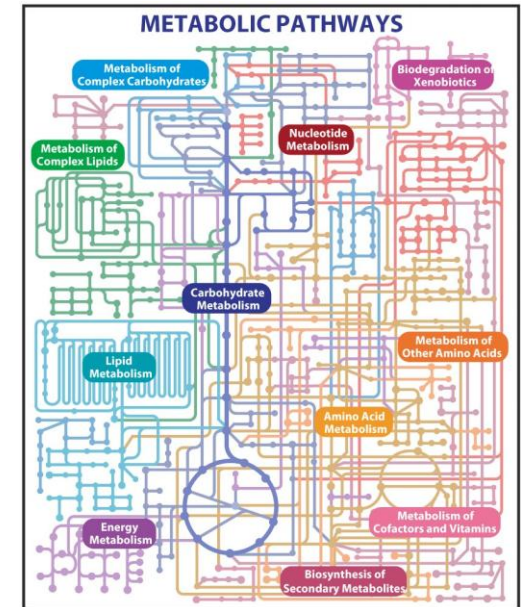
**Regulation** organizes the flow of energy and metabolites.

[1] **Allosteric regulation**—the regulation of an enzyme by binding an effector molecule at the protein's allosteric site (that is, a site *other* than the protein's active site).

[2] [Product] & [Reactant], or thermodynamic control:

$$\Delta G = \Delta G^{\circ} + RT \ln Q.$$

[3] Covalent modification of the enzyme by **phosphorylation**.



## GLYCOGEN

Glycolysis starts from **glycogen**, which is a polymer of glucose that is linked together by  $(\alpha 1 \rightarrow 4)$  bonds.

**Starch** can be **amylose** or **amylopectin**. Amylose has little branching—a long chain of  $(\alpha 1 \rightarrow 4)$  linked glucose. Amylopectin is  $(\alpha 1 \rightarrow 4)$  but has more branching. **Glycogen** is also  $(\alpha 1 \rightarrow 4)$ -linked.

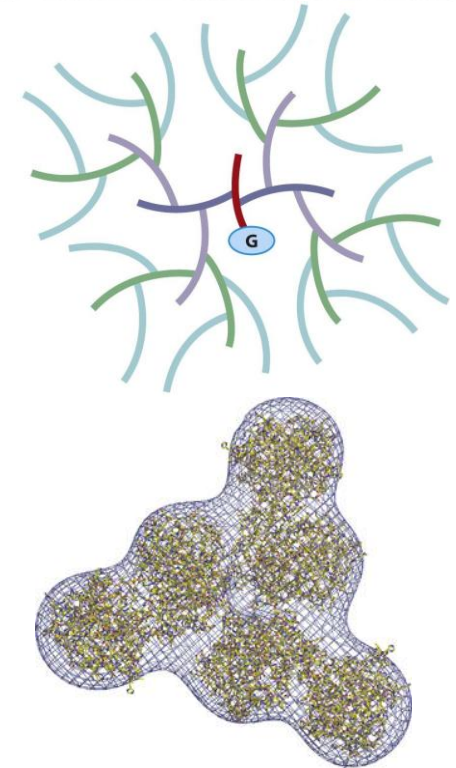
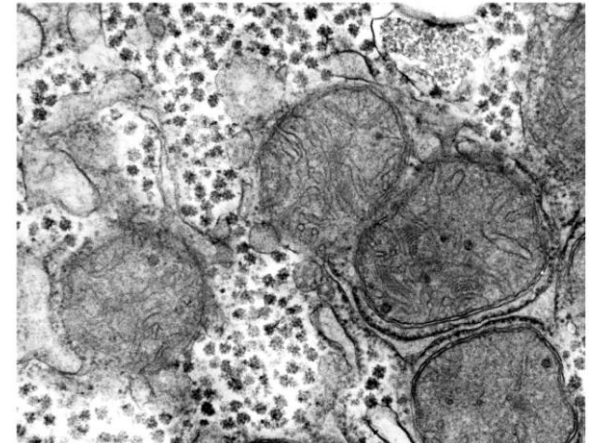
Glycogen, however, has extensive **branching**.

Humans store glucose as glycogen in primarily muscle & liver cells. One **glycogen  $\beta$  partical** can hold 55,000 glucose molecules. 10% of the liver's mass is glycogen under well-fed conditions.

### Glucose storage as glycogen minimizes osmotic stress.

To store glucose at sufficient concentrations as that contained in typical glycogen stores would make the cell 0.4 M in glucose. This would create osmotic pressure; and glucose would leak out of the cell.

Storing glucose as glycogen reduces osmotic pressure and is energetically less costly for the cell.

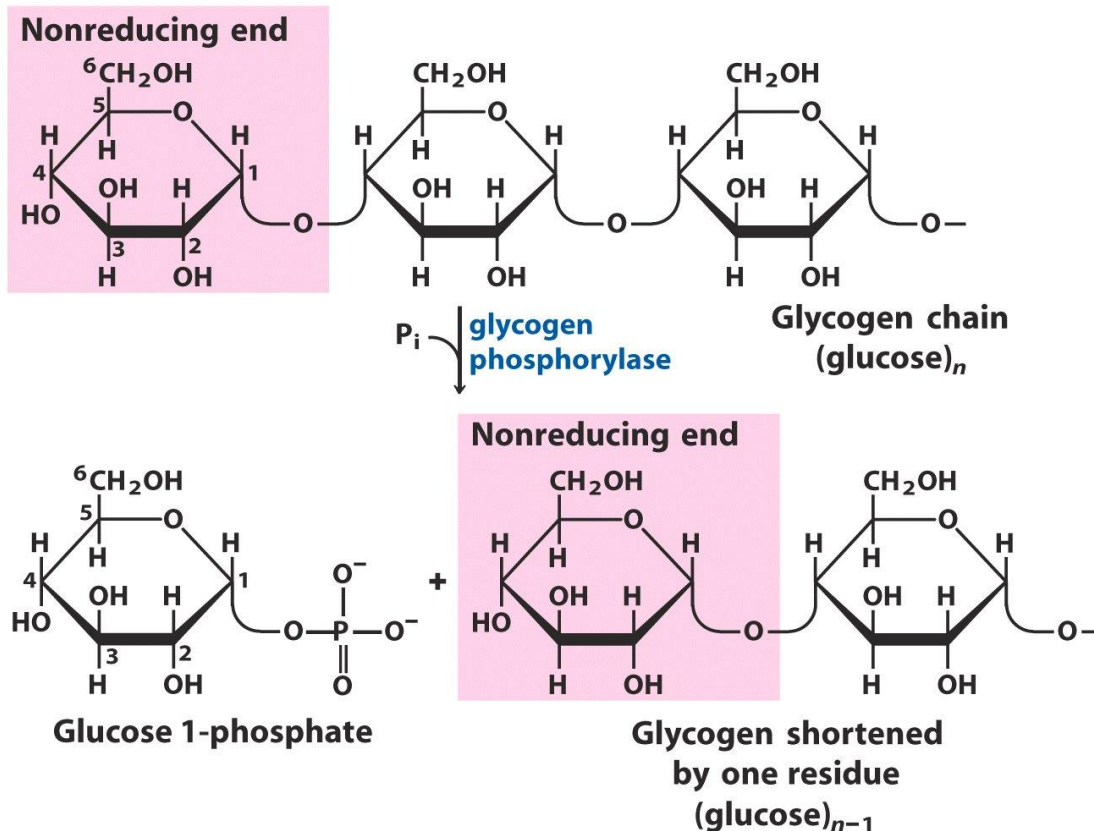


## Glycogen Breakdown.

**Glycogen Phosphorylase.** Glycolysis in muscle begins by the degradation of glycogen by **glycogen phosphorylase**. It is a famous enzyme discovered by Nobel Laureates, Gerty Cori and Carl, Cori, at Washington University in the 1920s-1940s.



**Mechanism.** Glycogen phosphorylase catalyzes a **phosphorolysis** reaction. Instead of water, an inorganic phosphate attacks C1, liberating glucose 1-phosphate.



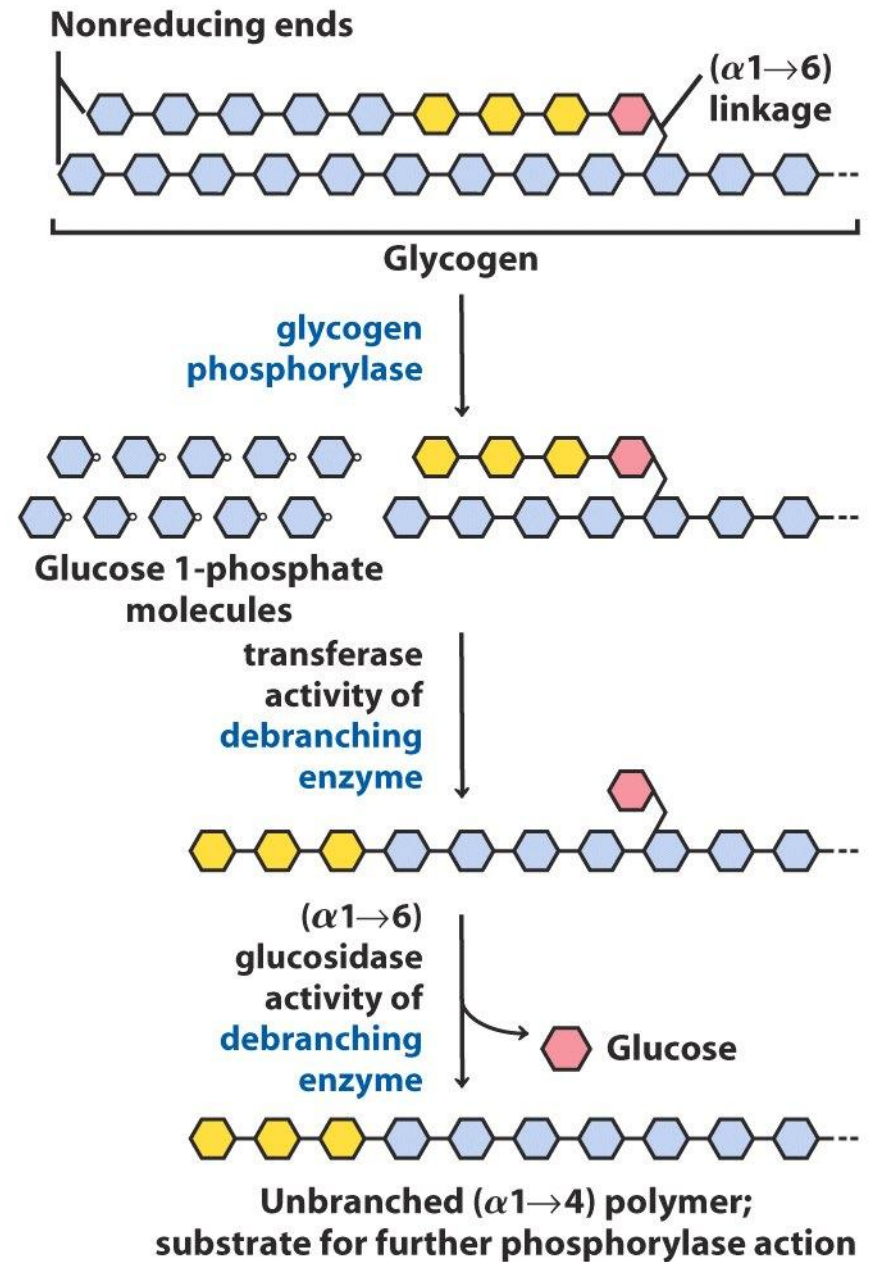


## Glycogen degradation

Breakdown thus occurs at one end of the long chain of the molecule and not in the middle. The degradation has to start at the **non-reducing end**, *i.e.*, where the glycosidic linkage is made between the **reducing end** of one sugar (C1, the aldehyde) and another position (an alcohol, C4). The reducing end is in the center of the branched glycogen. Only the non-reducing ends are available.

**Glycogen is branched.** So instead of a slow phospholysis as would be expected for a linear chain, like amylose, glycogen breakdown is quick as it is branched. Animals are mobile and require this speed. Plants, however, metabolize slowly, which may explain why they use amylose.

- Dealing with branching requires **debranching enzyme**.



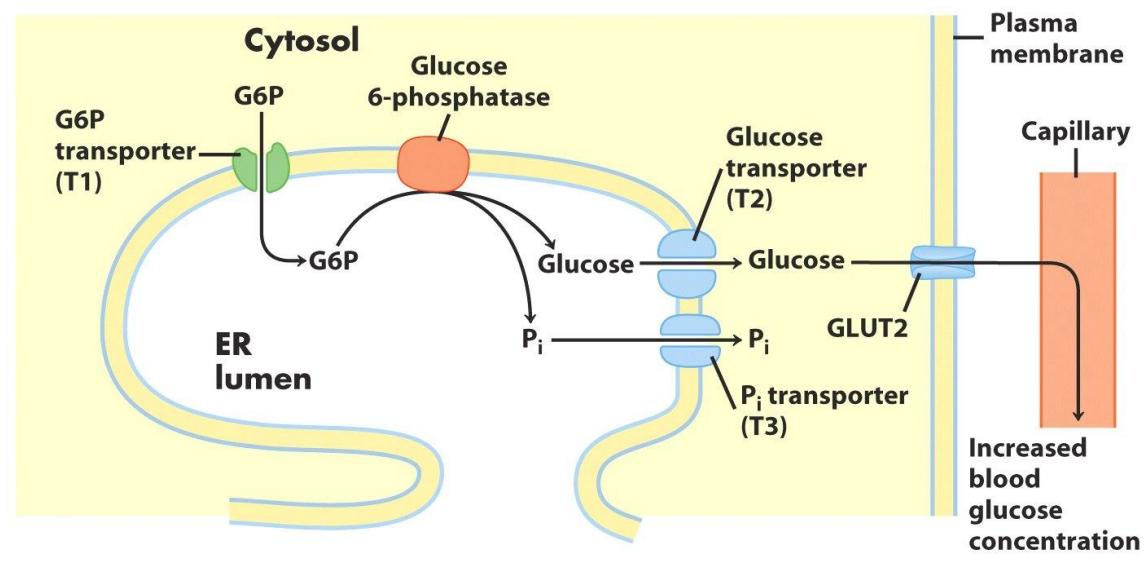
**Phosphoglucomutase.** We need glucose 6-phosphate for various pathways, *i.e.*, glycolysis , but glycogen phosphorylase makes glucose 1-phosphate.

### Glucose 1-P → Glucose 6-P

**Mechanism.** The enzyme is phosphorylated at a serine residue to make a E-Pi intermediate. The sugar at some point is made into glucose 1,6-bisphosphate. Mechanism is conceptually identical to that for the mutase encountered in glycolysis.

### **Cori Cycle.**

In the muscle under hypoxia, glycogen→glucose→lactate. Lactate goes into the bloodstream to the liver. In the liver, lactate→glucose. Glucose goes back into the blood, and in the muscle, glucose is converted back to glycogen. The **Cori Cycle** is, of course, named after Carl and Gerty Cori.



**Glycogen Synthesis.** Following gluconeogenesis, the glucose goes back to the muscle cell. In the muscle, you have to regenerate glycogen. For years, it was thought glycogen was made by the reverse reaction of glycogen phosphorylase; this is not true. Examining degradation, the key steps are always done by different enzymes, which may be regulated differently.

**Muscle hexokinase.** When glucose enters into the muscle cell, it gets phosphorylated by hexokinase, producing glucose-6-phosphate.

The function of **muscle hexokinase** is not to start glycolysis, but to fate the glucose for glycogen synthesis.

**Regulation.** Hexokinase in muscle is a biosynthetic enzyme for making glycogen. Thus hexokinase in muscle is inhibited by excess glucose 6-phosphate. When glucose 6-phosphate accumulates, it means glycogen biosynthesis is low so glucose 6-phosphate is not needed.

**Phosphoglucomutase.** Glucose 6-phosphate gets converted by the backward reaction of phosphoglucomutase into glucose 1-phosphate, which goes to glycogen.

**Glucose 6-phosphate  $\leftrightarrow$  Glucose 1-phosphate**

## UDP-glucose pyrophosphorylase.



**Mechanism.** Glucose 1-phosphate can attack the  $\alpha$  phosphorus of a compound called UTP, like ATP, but the base is uridine. The final compound **UDP-glucose** is glucose-P-P-UDP, and it is a precursor for the biosynthesis of glycogen.

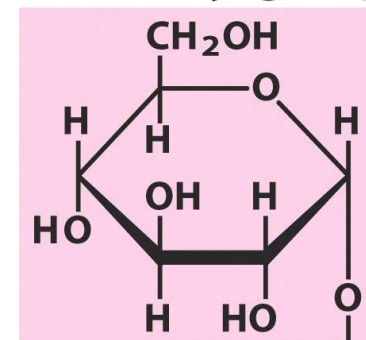
**Energetics.** For this reaction alone, starting with UTP and glucose 1-phosphate and ending up by generating one molecule of UDP-glucose and inorganic pyrophosphate, the  $\Delta G^{0'}$   $\sim 0$  kJ/mol. Physiologically, however, the reaction proceeds toward the biosynthesis of UDP-glucose.

This reaction does not go backwards because one of the products, inorganic pyrophosphate ( $\text{PP}_i$ ), has a high hydrolysis free energy.

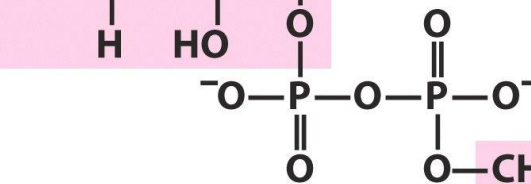
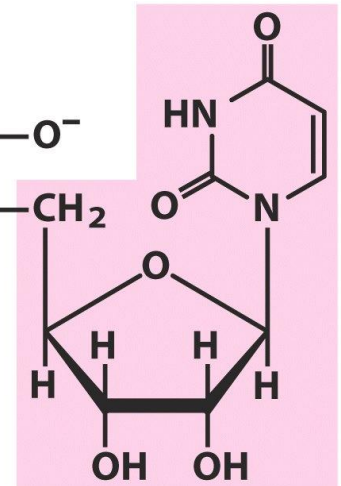


When it gets hydrolyzed by **pyrophosphatase** into two molecules of inorganic pyrophosphate, it has a large negative free energy change of  $-19$  kJ/mol.

**D-Glucosyl group**



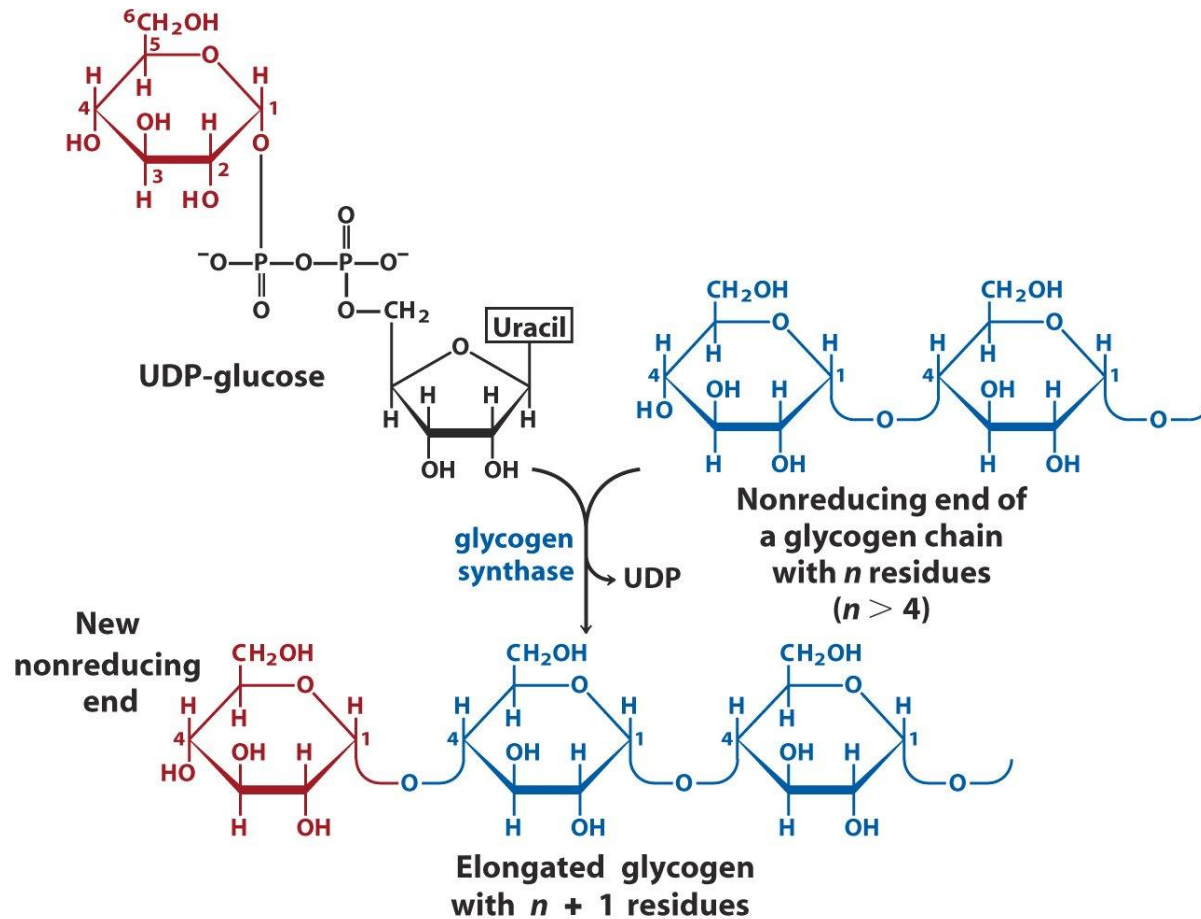
**Uridine**



**UDP-glucose**  
(a sugar nucleotide)

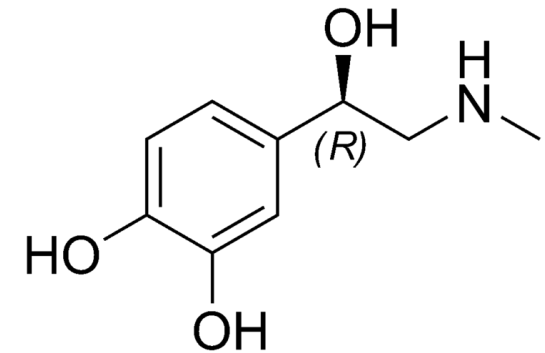
## Glycogen Synthase.

Using UDP-glucose, glucose can then be added to the non-reducing end of the glycogen to elongate the chain one-by-one. The enzyme responsible is called **glycogen synthase**.

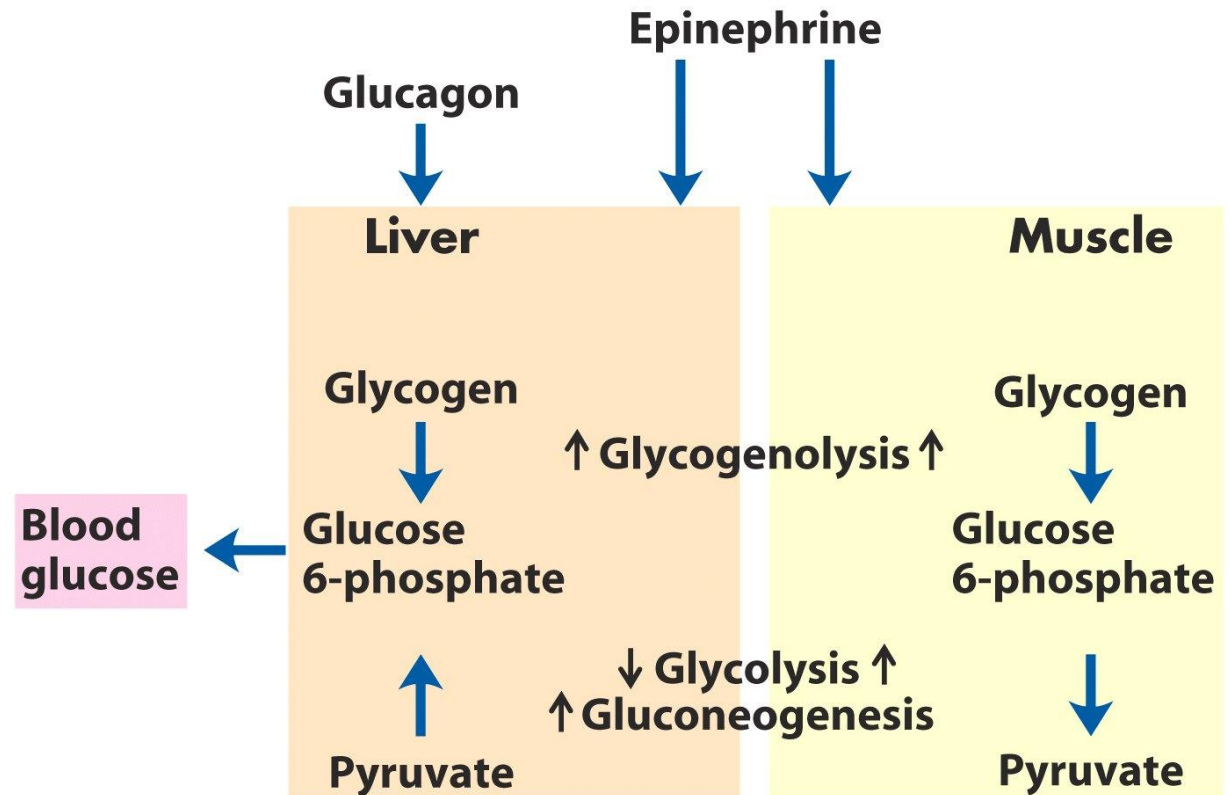




**Hormonal Regulation.** Allosteric regulation allows cells to respond to the local conditions. Allosteric regulation cannot control metabolism in different organs. Recall the Cori Cycle, the muscle degrades glycogen into lactate. The liver regenerates glucose from lactate. Muscle and liver have to be regulated oppositely. Whenever you want to regulate metabolism, one organ responds to what is happening elsewhere in your body, requiring hormones.

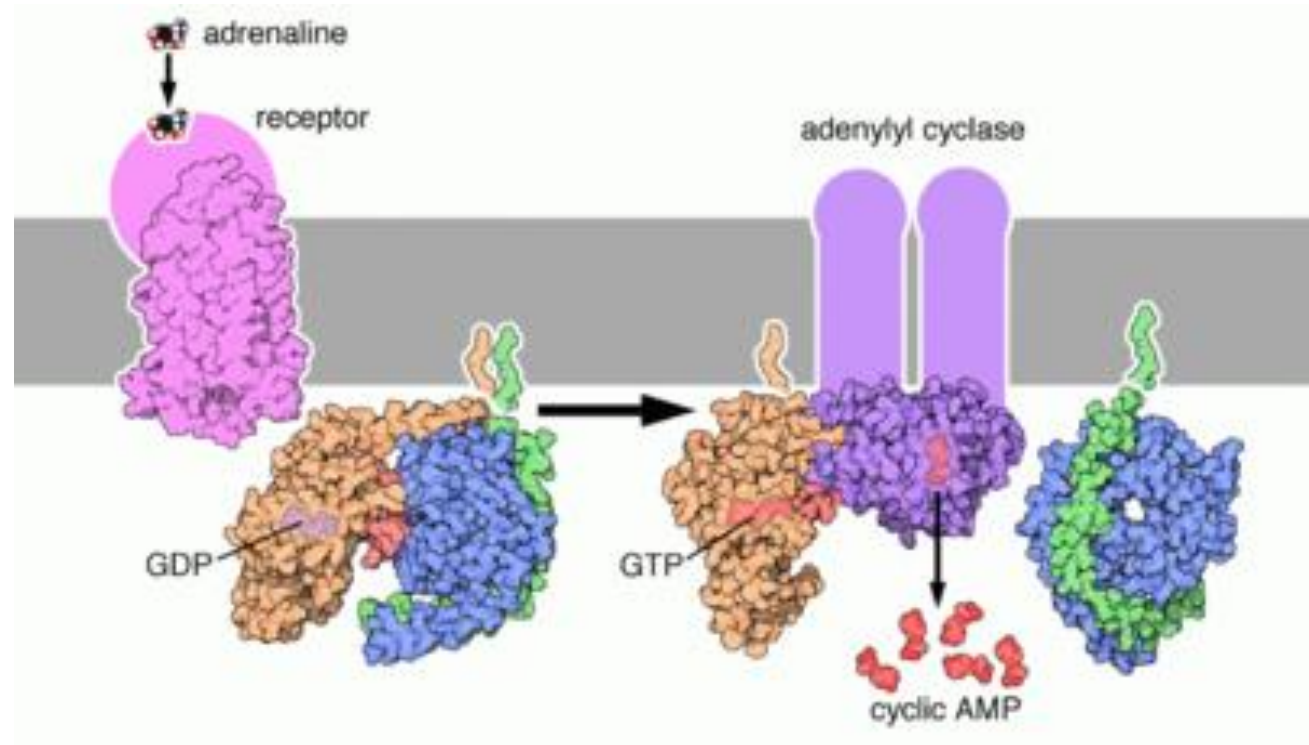


**Epinephrine.** A classic example of a regulatory hormone is **epinephrine**. Among other things, epinephrine regulates glycolysis in muscle. Upon sensing danger, epinephrine is secreted by the adrenal glands and enters the bloodstream. Muscle cells are full of epinephrine receptors. Most hormones cannot cross the plasma membrane and have to stay outside, so the cells have receptors. You need a receptor in the membrane for epinephrine. The epinephrine receptor is on the surface of the muscle cell, and epinephrine binds to the receptor.

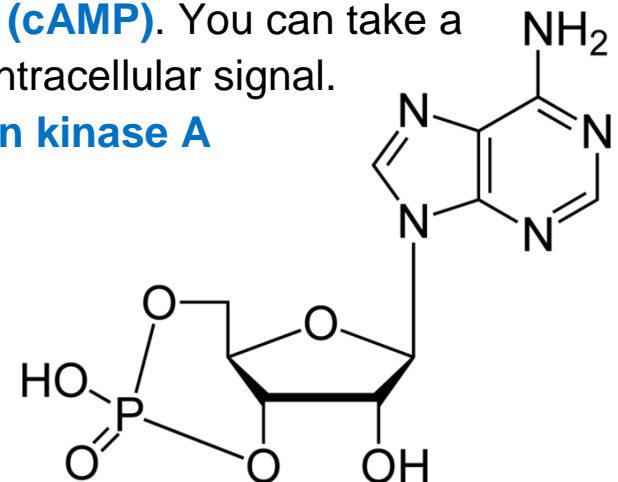


**G-protein coupled receptor.**

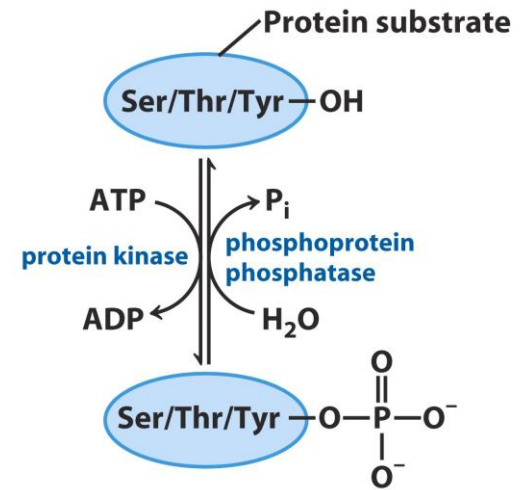
First, there is a protein called **G-protein**. G-protein is normally associated with GDP. When epinephrine binds to the receptor, GTP replaces the GDP. It is called a G-protein because it binds to GDP and GTP. With GTP bound, the G-protein goes to another place on the membrane and activates another membrane-associated enzyme called **adenylyl cyclase**.



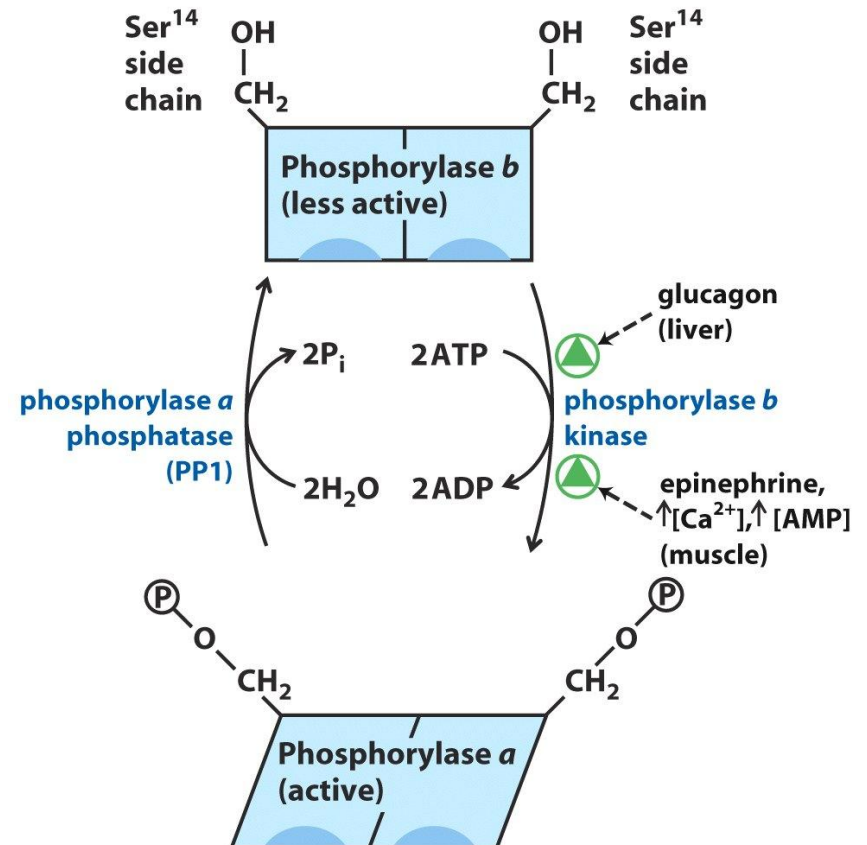
**cAMP.** Adenylyl cyclase takes ATP and converts it into **cyclic AMP (cAMP)**. You can take a look at its structure in the textbook or the reader. Cyclic-AMP is an intracellular signal. Cyclic-AMP then activates an enzyme that is called **phosphoprotein kinase A (PKA)**.



**PKA phosphorylation.** Then, there is a succession of phosphorylations of various enzymes. PKA phosphorylates an enzyme called **phosphorylase kinase** and activates it, leading ultimately to the phosphorylation of glycogen phosphorylase (also called **phosphorylase**). The activity of phosphorylase is much higher when it is phosphorylated and is called **phosphorylase-a**. The unphosphorylated form of glycogen phosphorylase is **phosphorylase-b**.



**Reciprocal regulation.** The same thing happens with glycogen synthase. Glycogen synthase also becomes phosphorylated. In the case of glycogen synthase, the unphosphorylated form is active. **Glycogen synthase-a** is the unphosphorylated active form of the enzyme. The phosphorylated form is **synthase-b**, which is inactive. The phosphorylase will become activated and glycolysis will start going on. At the same time, glycogen synthesis will become inhibited. This is **reciprocal regulation**.



## Overview of the Epinephrine Activation Pathway.

