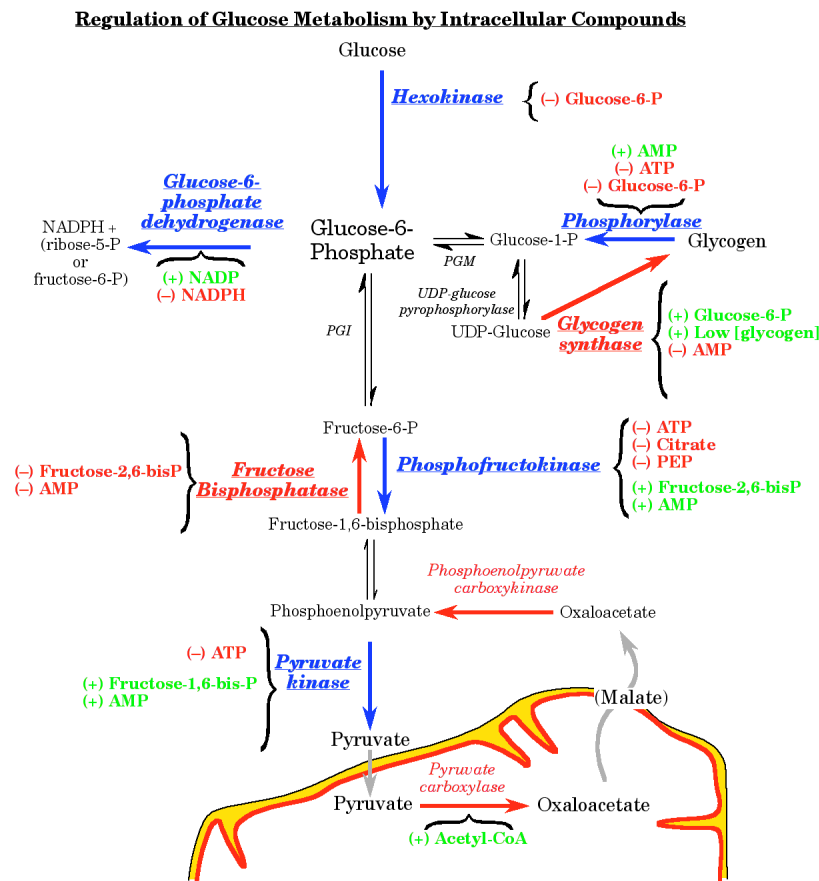


Regulation of carbohydrate metabolism

Intracellular metabolic regulators

Each of the control point steps in the carbohydrate metabolic pathways in effect regulates itself by responding to molecules that reflect the state of the cell. To examine this, consider a “normal cell” (this “normal cell” is not a liver cell or a muscle cell; we will consider these in more detail later).

The diagram below summarizes the effects of the compounds that cells use to regulate their own metabolism.

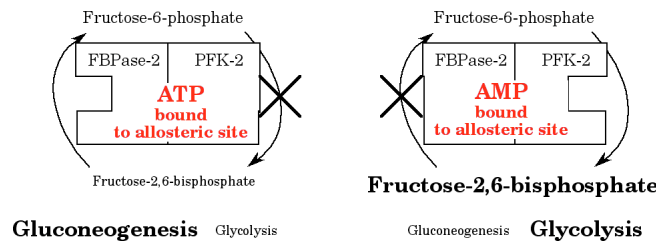


Glucose uptake is regulated by the amount of glucose-6-phosphate available, because **glucose-6-phosphate inhibits hexokinase**. In “normal cells” glucose entry into the cell is not regulated except by the conversion of glucose to glucose-6-phosphate; the rate of glucose transport usually exceeds the rate of conversion to glucose-6-phosphate. (Note that skeletal muscle and adipose tissues are exceptions; in these tissues, uptake of glucose is usually limited by the rate of transport, which is a function of the number of transporters in the plasma membrane. The liver is also an exception, because the liver glucose transporter has a low affinity for glucose, and the rate of glucose influx increases as a function of concentration.)

The glycolytic pathway is controlled by the energy state of the cell. If the **cell has enough energy**, high levels of ATP inhibit phosphofructokinase and pyruvate

kinase. In addition, high levels of NADH inhibit isocitrate dehydrogenase, allowing an increase in citrate levels, which also inhibits phosphofructokinase (note that NADH inhibits both isocitrate dehydrogenase and citrate synthase, but isocitrate dehydrogenase is more sensitive to NADH, and is inhibited first). Finally, phosphoenolpyruvate is also an inhibitor of phosphofructokinase. The **levels of fructose-2,6-bisphosphate are controlled by the same compounds that control phosphofructokinase** (e.g., high levels of ATP decrease fructose-2,6-bisphosphate concentration, while high levels of AMP increase its concentration).

The enzyme that produces and hydrolyzes fructose-2,6-bisphosphate acts to control the levels of this regulatory compound. The protein has two active sites, of which only one is normally active at any given time. High levels of ATP result in a decrease in fructose-2,6-bisphosphate concentration, and therefore in a decrease in phosphofructokinase activity.



If the cellular energy level decreases, AMP levels rise. AMP stimulates phosphofructokinase and pyruvate kinase. It also stimulates production of fructose-2,6-bisphosphate, and therefore increases phosphofructokinase activity. In addition, fructose-1,6-bisphosphate stimulates pyruvate kinase; if phosphofructokinase is active, its product activates pyruvate kinase.

Gluconeogenesis is unimportant in most normal cells. The levels of pyruvate carboxylase and phosphoenolpyruvate carboxykinase are generally quite low in most non-liver cells.

Flow of glucose through the hexose monophosphate pathway is controlled by the relative amounts of NADPH and NADP, because these compounds regulate the control enzyme, glucose-6-phosphate dehydrogenase.

Finally, glycogen is relatively unimportant in most “normal cells”. In those cells that do produce glycogen, net synthesis occurs if the cellular energy levels are high (as indicated by high levels of ATP and glucose-6-phosphate), while net glycogen breakdown occurs if the AMP/ATP ratio rises.

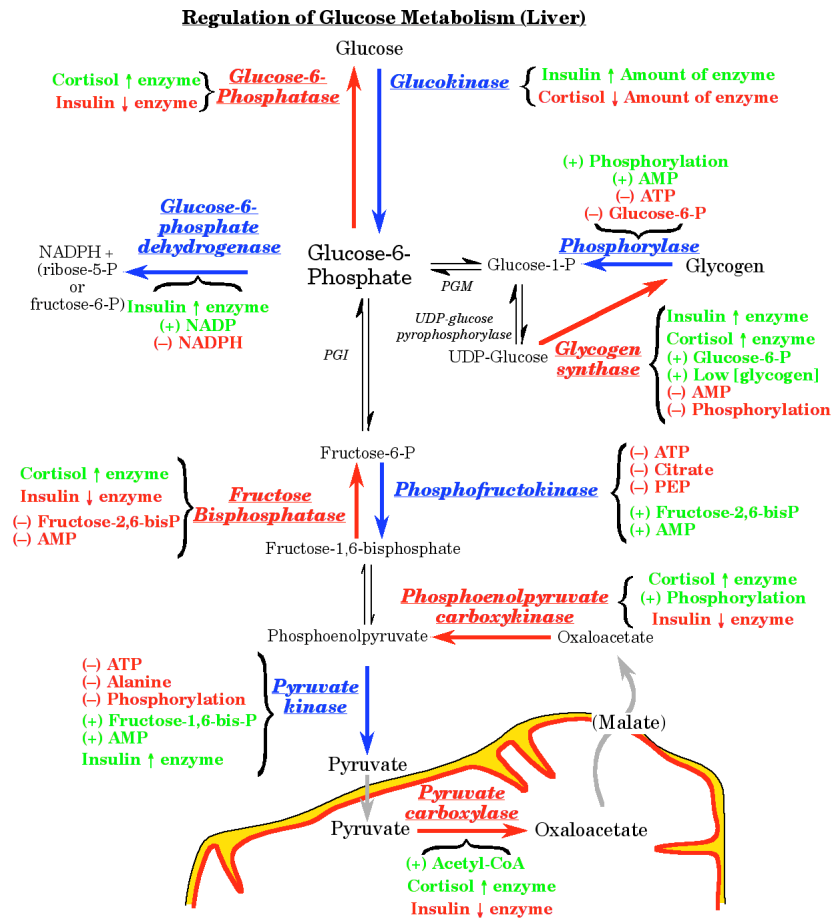
External metabolic regulators

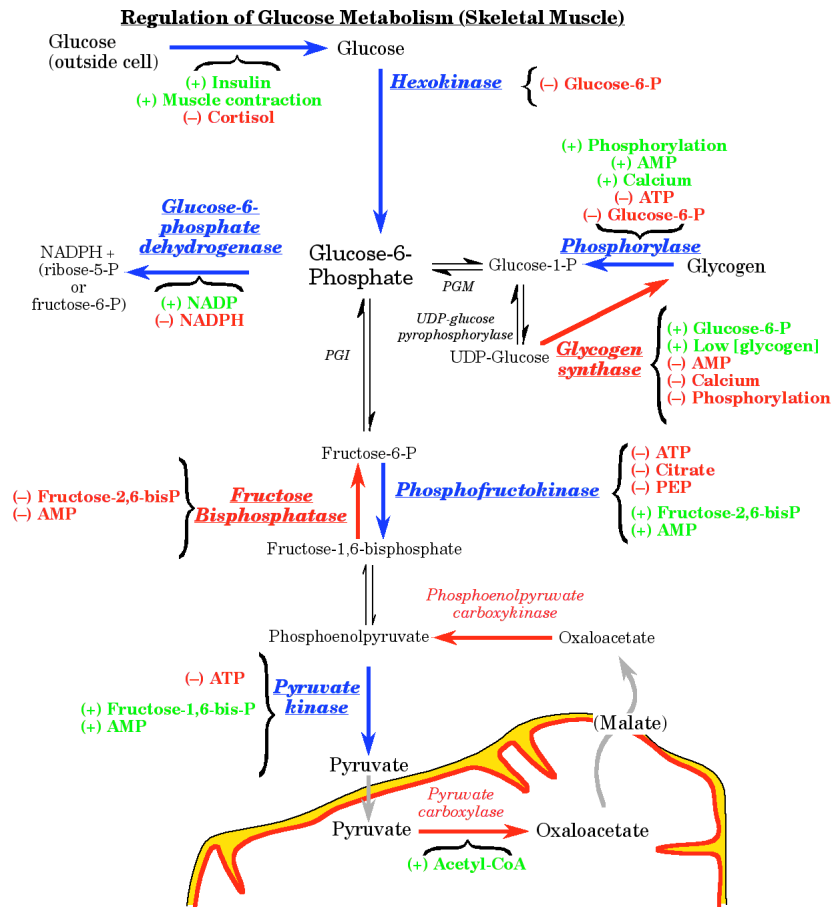
The liver and skeletal muscle self-regulate carbohydrate metabolism in basically the same way as do other cells. However, these cell types are also required to respond to external signals by altering their carbohydrate metabolism. These two tissues, along with adipose tissue (which is primarily involved in lipid metabolism), act as the major regulators of nutrient levels in circulation during most metabolic conditions. The regulation has two goals: 1) maintenance of normal circulating

glucose levels in the face of changing conditions, and (when necessary) 2) support of physical activity.

These tissues are tightly controlled by **external signals**: the levels of the **pancreatic hormones** insulin and glucagon, the **adrenal hormones** epinephrine and cortisol, and, in the case of skeletal muscle, the **neuronal signals** that govern muscle contraction. The following description of events simplifies some rather complex processes. In general, glucagon and epinephrine result in phosphorylation of regulatory enzymes, while insulin results in removal of the phosphate; calcium usually increases phosphorylation (one major exception is the mitochondrial enzyme pyruvate dehydrogenase, in which calcium stimulates phosphate removal). Some of the hormones, especially cortisol and insulin, and to a lesser extent glucagon, alter the amounts of the enzymes present in the cell. The phosphorylation and dephosphorylation events occur rapidly, while effects on enzyme concentration are relatively slow processes.

The cells of the liver and muscle must also use the same feedback regulatory metabolites as do “normal cells”; these effects interact with the hormonal signals to result in the overall metabolic changes that occur within these cells. The two diagrams below summarize the control of the various pathways by metabolic and hormonal effects in liver and in skeletal muscle. (Note that “hormone ↑ enzyme” refers to changes in enzyme concentration induced by that hormone.)





A full understanding of the regulation of carbohydrate metabolism in skeletal muscle and liver requires looking at several different metabolic states.

Fed state

During absorption of nutrients from the digestive tract, circulating glucose levels typically become slightly elevated. This results in increased insulin and decreased glucagon levels. **High insulin levels result in increased glucose uptake in skeletal muscle** and adipose tissue (as a direct result of increased glucose transport due to the movement of the transporters to the membrane). The muscle is capable of dramatic increases in glucose uptake, a specialization that is related to its increased glucose requirements during muscle contraction; the organism uses this ability to rapidly deal with sudden increases in plasma glucose.

Insulin induces glycogen storage in liver and muscle. Insulin also increases glycolysis in liver. The increase in liver glycolysis has two purposes: 1) it decreases glucose availability, and 2) it increases the amount of intermediates usable for biosynthetic reactions. Insulin also increases hexose monophosphate pathway activity by increasing the concentration of glucose-6-phosphate dehydrogenase; this also increases both glucose breakdown and the cellular capacity for biosynthetic processes.

The net effect of these processes is the removal of glucose from circulation to be either stored, used for energy, or used to produce other biologically relevant compounds.

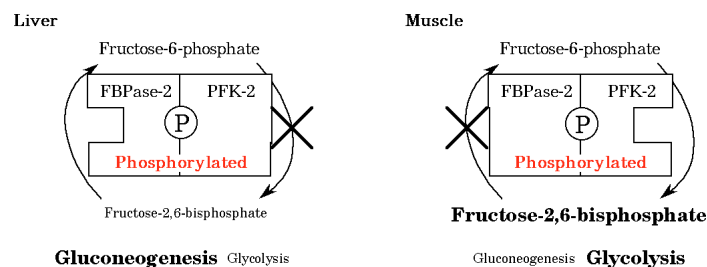
Exercise

During exercise, the liver and muscle must respond somewhat differently to the same external signals. The responses are mediated by three physiological signals: 1) increased epinephrine, 2) increased calcium in muscle, and 3) decreased insulin levels.

Both muscle and liver increase glycogen breakdown. This is the result of phosphorylation of both glycogen synthase and glycogen phosphorylase in both tissues; phosphorylase is stimulated by phosphorylation, while glycogen synthase is inhibited. The glucose is released into the circulation by the liver; the muscle takes up glucose from circulation, and also uses the glucose released from its own glycogen stores.

One method of simultaneously altering both gluconeogenesis and glycolysis is to alter **fructose-2,6-bisphosphate** levels. Fructose-2,6-bisphosphate stimulates phosphofructokinase and inhibits fructose-bisphosphatase; fructose-2,6-bisphosphate therefore simultaneously stimulates glycolysis and inhibits gluconeogenesis. **Exercising muscle must be able to perform glycolysis;** in contrast, during exercise, **the liver must turn off glycolysis** and turn on gluconeogenesis. These contrasting events are mediated by different isoforms of the PFK-2/FBPase-2 protein.

Phosphorylation of **liver** PFK-2/FBPase-2 results in decreased fructose-2,6-bisphosphate levels (because it alters the enzyme conformation to favor the phosphatase activity). In contrast, phosphorylation of the **muscle** PFK-2/FBPase-2 isoform results in an increase in the fructose-2,6-bisphosphate levels, and therefore in an increase in the muscle capacity for glycolysis.



The liver also contains an isoform of pyruvate kinase that is inhibited by phosphorylation. The muscle pyruvate kinase is not affected by phosphorylation.

Exercising muscle tends to release some lactate into circulation; the liver uses this as substrate for gluconeogenesis. This exchange of materials between the liver and the muscle is known as the Cori cycle (this was already mentioned in the Lecture Notes on Gluconeogenesis).

The net effect of these metabolic changes is increased glucose release by the liver and uptake and utilization by the muscle to support generation of mechanical energy by the muscle.

Starvation

During starvation, insulin levels decrease, and glucagon and cortisol levels increase resulting in a variety of metabolic changes. One major effect is the breakdown of muscle protein to provide amino acids for gluconeogenesis. The liver responds by increasing glycogen breakdown and by increasing glucose release. It also responds by greatly increasing gluconeogenesis, using amino acids released by the muscle as substrates. The alanine cycle (mentioned in the section on gluconeogenesis) is an important part of this process.

The net effect is the release of glucose from the liver for the use by other tissues, with breakdown of muscle and fat to supply the requisite energy and intermediates.

Insulin deprivation

Diabetes mellitus is a relatively common disorder resulting either from destruction of the cells that release insulin or from lack of response to insulin by the tissues. The absence of insulin action results in a condition that is similar to starvation; tissues are broken down to provide substrates for liver gluconeogenesis. The liver then works very hard to produce glucose to release into circulation, raising plasma glucose levels to concentrations that have deleterious effects. This effect is exacerbated by the fact that the individual typically continues to eat, and therefore absorb nutrients, and by the fact that the skeletal muscle and adipose tissue require insulin for uptake of glucose.

The net effect is a dramatic increase in plasma glucose concentration, because the liver is releasing glucose while the other tissues are not taking up glucose and are performing reduced levels of glycolysis.

More information regarding the control of glucose homeostasis and the etiology and effects of insulin deprivation may be found in the “Endocrine Notes” section on the course website.

Summary

Most cells are capable of regulating their carbohydrate metabolism based on their current energy requirements. This is achieved by feedback inhibition or stimulation of regulatory enzymes by various metabolites. The important metabolites involved in regulation of carbohydrate metabolism include ATP, NADH, glucose-6-phosphate, citrate, and fructose-2,6-bisphosphate.

Many cell types respond to hormonal and neuronal signals that allow the coordination of metabolism at the level of the entire organism. For carbohydrate metabolism, the liver and skeletal muscle have the most important roles. The liver either takes up glucose for storage in the form of glycogen, or releases glucose for use by other tissues. The muscle takes up glucose for storage or for conversion to mechanical energy; it can release free amino acids derived from protein breakdown to act as substrates for liver gluconeogenesis.