

CHAPTER 21 Mammalian Fuel Metabolism: Integration and Regulation

Introduction

We must view the metabolic pathways we've been studying in the context of the whole organism in order to fully appreciate their significance, as well as their regulation.

Since division of labor is an important feature of multicellular organisms, different tissues carry out different pathways, and the same pathways will be carried out at different rates in different tissues. The liver plays a central processing and distributing role in metabolism, hence is one of only a few organs which carry out all the pathways we've studied this semester (summarized in Figure 21-1).

Coordination of metabolism in various organs of mammals is achieved at the molecular level by hormonal and neuronal signaling, mediated by the neuroendocrine system.

Organ Specialization

Recall that acetyl CoA, and also pyruvate, occur at the crossroads of the major metabolic pathways. Acetyl CoA is produced by degradation of glucose, fatty acids and ketogenic amino acids. Acetyl CoA can enter the citric acid cycle where it is stripped of electrons as it is catabolized to CO₂, the electrons enter the electron transport chain via NADH and FADH₂, providing the energy to produce ATP via oxidative phosphorylation. Alternatively, acetyl CoA can be used to form ketone bodies by the liver as an exportable fuel (Figure 21-1).

As mentioned, most non-hepatic tissues carry out only a small portion of the pathways depicted in 21-1 at a significant rate. Some examples follow.

Brain:

The brain normally uses only glucose as fuel, but it can use ketone bodies when necessary (extended fasting). Since the brain stores very little glycogen, brain cells require a steady stream of glucose from the blood, the level of which is maintained by the liver.

The brain has a very active respiratory metabolism, using almost 20% of the total O₂ consumed by a resting adult. Most of the ATP produced by the brain maintains Na⁺ and K⁺ gradients generated by the plasma membrane (Na⁺K⁺)-ATPase to maintain membrane potential required for nerve impulse transmission.

Muscle: Skeletal and heart muscle must be considered separately because the heart operates continuously, whereas skeletal muscle operates intermittently.

skeletal muscle accounts for over 30% (this figure varies) of the total O₂ consumption in a resting person and up to 90% during very active muscular work. Skeletal muscle is adapted to do mechanical work in an intermittent fashion, on demand.

The major fuels of muscle cells are glucose from stored glycogen (as well as serum glucose), fatty acids (from stored triglycerides in adipose tissue), and ketone bodies (exported by the liver). Glycogen can be mobilized more rapidly than stored triglycerides, so are a more efficient form of energy storage for muscle cells, which must be able to produce ATP rapidly. Furthermore, glucose can be catabolized anaerobically, whereas fatty acids, which require the citric acid cycle, cannot.

Phosphocreatine (p. 411) acts as an energy reserve, capable of transferring its high-energy phosphate group to ADP:



However, under conditions of maximal exertion, muscle has only about a 4 second supply of phosphocreatine. It must then shift to glycolysis (anaerobic), whose maximum rate exceeds those of the citric acid cycle and oxidative phosphorylation. Muscle fatigue (occurs about 20 seconds into maximal exertion) results from a decrease in pH due to lactate production. Recall that in the Cori cycle, lactate is transported to the liver where it is converted back to glucose via gluconeogenesis. The relatively small amount of glycogen stored in skeletal muscle (about 2%) also limits the amount of glycolytic activity during strenuous activity. Oxygen debt refers to the increased rate of respiration to provide the ATP to power this energy-requiring cycle (and to replenish resting levels of phosphocreatine by a reversal of the above reaction. Note that since the Cori cycle requires energy with no net overall change in [glucose], it would be a futile cycle were it not for the fact that it cycles between muscle and liver. Thus, NAD⁺ is regenerated in muscle (and consumed in the liver), and the liver provides muscle with glucose for rapid ATP production.

Since the **heart** operates continuously, it must rely entirely on aerobic catabolism. This explains the fact that heart muscle cells contain many more mitochondria than skeletal muscle cells. Note that the fact that the heart is critically dependent on O₂ delivery, artery blockage which characterizes atherosclerosis can lead to a heart attack.

The heart imports most of its fuel as fatty acids, ketone bodies, and glucose. Note that the text states that pyruvate and lactate can also be used by the brain. Both of these metabolites will be found in the blood during operation of the Cori cycle. The resting heart prefers fatty acids as the fuel of choice, but during heavy work the heart greatly increases its consumption of glucose, which is derived mostly from its relatively limited glycogen stores.

Adipose Tissue:

Because of the lipophilic nature of triglycerides, and the highly reduced state of the fatty acyl chains, triglycerides are a more efficient form of energy storage than glycogen (complete catabolism yields almost twice the free energy than an equivalent mass of anhydrous glycogen about 9 kcal/g as compared to 4 kcal/g). Since glycogen is highly hydrated, its effective mass is greater, and a gram of anhydrous fat yields more than six times as much energy as a gram of hydrated glycogen. Thus a typical 70-kg man has fuel reserves of about 100,000 kcal in fat, 25,000 cal in protein, 600 kcal in glycogen and 40 kcal in glucose. This fellow is a little more trim than the “typical” 70-kg man in the text, with about 11 kg of his total body weight as opposed to 15 kg.

Adipose tissue obtains most of its fatty acids from circulating chylomicrons and VLDL. These are esterified via glycerol 3-phosphate to form triglycerides, the storage form. Note that glycerol 3-phosphate is a product of glycolysis, and if it is not available, the fatty acids must enter the bloodstream. Thus, fatty acid mobilization depends in part on the rate of glucose uptake by adipocytes.

Fatty acid mobilization is initiated by hormone-sensitive lipase, which hydrolyzes stored triglycerides. Note that a decrease in [glucose] will also lead to increased levels of fatty acids, the exportable fuel.

Liver: As mentioned above the liver plays a central role in metabolism, maintaining proper levels of serum fuels for use by the brain, muscles and other tissues.

Not only does the liver export glucose in times of need, it also takes up excess glucose after a carbohydrate-containing meal. We already know that insulin signals uptake of glucose. Glucokinase, an isozyme of hexokinase, converts glucose into glucose 6-phosphate, thereby preventing glucose levels from building up in the cell.

Hexokinase binds glucose with high affinity (small K_m see Michaelis-Menten equation, p.364). A K_m for glucose of less than 0.1mM means that it achieves half-maximal velocity at 0.1mM, which means that hexokinase is saturated after a meal when blood [glucose] reaches about 6mM. Since K_m for glucokinase is about 5mM, it is capable of rapidly increasing its activity after a meal (glucokinase is an allosteric enzyme, somewhat puzzling in light of the fact that it is monomeric), whereas hexokinase cannot. See Figure 21-4 for a graphical illustration. Thus, glucokinase is responsible for the liver's being capable of increasing cellular uptake of excess glucose. This, in combination with the liver's ability to rapidly breakdown glycogen and export glucose in times of need, explains the liver's functioning as a glucose "buffer."

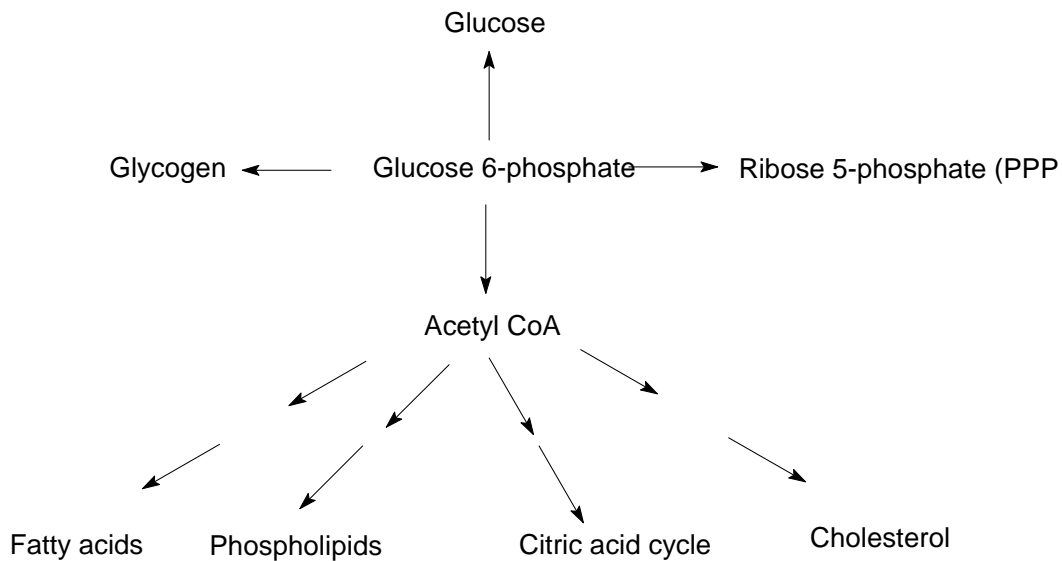
The regulatory mechanism of glucokinase is unique. It is inhibited by a protein (glucokinase regulatory protein), which binds to and inhibits glucokinase in the presence of fructose 6-phosphate, a glycolytic intermediate. Note that this, in effect, is product inhibition since fructose 6-phosphate is in equilibrium with the product of the glucokinase reaction, namely glucose 6-phosphate via the action of phosphoglucoisomerase.

In other tissues, fructose enters glycolysis as glucose 6-phosphate via the action of hexokinase, which phosphorylates fructose as well as glucose at the 6 position. In the liver fructose is phosphorylated to fructose 1-phosphate which enters glycolysis as dihydroxyacetone phosphate and glyceraldehyde 3-phosphate (beyond the main regulatory point in glycolysis). Fructose 1-phosphate competes with fructose 6-phosphate for the binding site on the glucokinase regulatory protein. Thus, since fructose 6-phosphate is displaced by fructose 1-phosphate, which results in the release of the glucokinase regulatory protein from glucokinase, thereby relieving the inhibition of glucokinase, fructose acts to **increase** the rate of glucose uptake.

Although fructose can act, in a sense, as a signal to increase uptake of dietary glucose by the liver, recall that fructose is also a bad guy because its conversion to pyruvate is controlled only by glucokinase since the phosphofructokinase-catalyzed reaction is bypassed. This means

that acetyl CoA (precursor of cholesterol) production is increased directly by fructose, and also indirectly via alleviating the inhibitory effect of glucokinase regulatory protein on the activity of glucokinase. (In other words, fructose can be a double whammy as far as jacking up levels of serum cholesterol avoid “high-fructose corn syrup” soft drinks).

Recall that glucose 6-phosphate is at an crossroad in carbohydrate metabolism:



Thus, glucose 6-phosphate can be converted to glucose via the action of glucose 6-phosphatase for export (resulting from the hormonal (glucagon), c-AMP mediated, breakdown of glycogen, converted to glycogen, converted to ribose 5-phosphate via the pentose phosphate pathway if reducing power (NADPH) or ribose is needed, or catabolized to acetyl CoA and CO₂. Acetyl CoA also has a variety of biosynthetic fates, including cholesterol biosynthesis.

Although the liver supplies other organs with ketone bodies, it is itself incapable of catabolizing ketone bodies because it lacks an enzyme necessary to convert ketone bodies to acetyl CoA. Fatty acids are transported to the liver either via serum albumin (during hormonal-mediated triglyceride breakdown) or chylomicron remnants. These provide the liver’s primary source of fuel under conditions of high metabolic demand.

The liver exports fatty acids by esterifying them to triglycerides, then packaging the triglycerides into VLDL for export.

Immediately after a meal containing protein, amino acids are present in relatively high concentrations in the blood and provide a significant fraction of metabolic energy. Additionally, glucogenic amino acids can be converted to glucose in times of need. Thus, proteins are

important fuel reserves as well as important structural components. Recall that amino acids are stripped of their amino groups via transaminations in which the amino groups are attached to the amino group acceptor, alpha-keto glutarate. In muscle cells pyruvate can act as the acceptor, thereby producing alanine. The alanine travels through the blood to the liver, where it is stripped of its amino group to produce pyruvate, which undergoes gluconeogenesis. The resulting glucose is cycled back to the muscle to complete the glucose-alanine cycle (Figure 21-7), a variation of the Cori cycle, which we studied earlier in the semester (Figure 21-6).

Hormonal Control of Fuel Metabolism

We studied hormones and their involvement in regulating metabolism when we studied glycogen metabolism and, to a lesser extent, glycolysis/gluconeogenesis and fat mobilization. Hormones are chemical messengers synthesized, stored in and released from endocrine glands. They include steroid hormones, such as those of the adrenal cortex (glucocorticoids and mineralocorticoids), which we studied briefly last semester, the catecholamines derived from tyrosine (adrenal medulla) and the polypeptide hormones glucagon and insulin (pancreas). The majority of the pancreas is involved with producing digestive enzymes such as chymotrypsin, trypsin, etc. Approximately 1 - 2 % consists of the islets of Langerhans, which secrete glucagon (" cells) and insulin (\$ cells). It is of interest to note that there appear to be no cell surface glucose receptors on \$ cells by which serum glucose concentrations could be communicated to these cells. In these cells, pathways that initiate from branch points in glycolysis such as glucose-6-phosphate (glycogen metabolism) and pyruvate (lactate formation) are minimized, thus creating a linear pathway from glucose through oxidative phosphorylation. Insulin production and secretion from \$ cells appears to be linked to activity of oxidative phosphorylation.

Insulin promotes glucose uptake in muscles and adipose tissue, and also by inhibiting glycogen breakdown, promoting glycogen synthesis and inhibiting gluconeogenesis in the liver. Inhibition of gluconeogenesis is achieved by inhibiting the transcription of genes encoding enzymes involved only in gluconeogenesis (PEP carboxykinase, fructose 1,6 and glucose 6-phosphatase), and stimulates glycolysis in the liver by stimulating the transcription of glycolytic enzymes (glucokinase and pyruvate kinase). Fatty acid biosynthesis in the liver is stimulated by stimulating the expression of lipogenic enzymes.

As you know, glucagon and epinephrine counter the effects of insulin. Although muscle

cells lack a glucagon receptor, they benefit indirectly from the effects of glucagon because glucagon increases the concentration of serum glucose which is free to enter muscle cells. See Table 21-1 for a summary of the effects of insulin, glucagon and epinephrine.

Finally, note that epinephrine binds to liver cells as well as to muscle cells. This hormone binds to either α - or β -adrenergic receptors; the liver possesses both types, whereas muscle cells contain only β -receptors. α -receptors are associated with the secondary messenger Ca^{++} , whereas c-AMP is associated with β -receptors. Ca^{++} reinforces the liver's response to c-AMP by increasing the rate of glycogen breakdown. It does so by binding to the γ -subunit (calmodulin) of phosphorylase kinase, which then relieves inhibition of the catalytic subunit.

Signal Transduction

Cells are capable of responding to hormones such as epinephrine and insulin by displaying receptors for these hormones. A common class of receptors are known as G-protein coupled receptors (GPCRs). G proteins are heterotrimers named for their ability to bind GDP and GTP, and also to hydrolyze GTP to GDP. G proteins are capable of activating other proteins, including adenylate cyclase, a secondary messenger. The mechanism of action of the adenylate cyclase activating system is depicted in Figure 21-15, p 762.

Problems: 1, 2, 4, 5, 6