Metabolism in the Mammalian Body: Division of Labor

The major metabolic pathways that sustain life in multicellular organisms are covered in Chapter 16. Any true understanding of metabolism, however, requires a more integrated approach. The feeding-fasting cycle, the self-regulating mechanism by which the mammalian body extracts energy and nutrients from food, is a well-understood process. A brief review of its operation in Chapter 16 provides an opportunity to observe biochemical reactions as they actually occur. Although the feeding-fasting cycle is a complex process, it is made more accessible with a brief overview of the roles of each body organ.

Each organ in the mammalian body contributes to the individual's function in several ways. For example, some organs are consumers of energy so that they may perform certain energy-driven tasks (e.g., muscle contraction). Other organs, such as those in the digestive tract, are responsible for efficiently supplying energy-rich nutrient molecules for use elsewhere. Information in the form of signal molecules (e.g., hormones and neurotransmitters) is used to regulate the balance between energy generation and energy expenditure. Nutrient transport across cell plasma membranes is also an important feature of organ function. Glucose transport is a well-researched example. Active transport of glucose by the Na^+/glucose transporter is linked to a Na^+ gradient established by the ATP-driven Na^+–K^+ pump. The facilitated diffusion of glucose across cell membranes occurs by glucose carriers called GLUTs: GLUT 1 (most cells), GLUT2 (liver, β-pancreatic cells, and intestinal enterocytes), GLUT3 (neurons), and GLUT4 (insulin-sensitive muscle and adipose tissue cells). GLUT5, principally found in intestinal enterocyte and liver cell plasma membranes, transports fructose.

Gastrointestinal Tract

The most obvious role of the organs of the gastrointestinal (GI) tract is the digestion of nutrients such as carbohydrates, lipids, and proteins into molecules that are small enough to be absorbed (sugars, fatty acids, glycerol, and amino acids) by the enterocytes of the small intestine. Enterocytes then transport these molecules (and water, minerals, vitamins, and other substances) into the blood and lymph, which carry them throughout the body.

The enterocytes require enormous amounts of energy to support active transport and lipoprotein synthesis. Although some glucose is partially oxidized (leaving the enterocytes as lactate or alanine), most of the energy is supplied by glutamine. During the digestive process, enterocytes obtain glutamine from degraded dietary protein. Under fasting conditions, glutamine is acquired from arterial blood. Enterocytes also use some glutamine to form Δ^1-pyrroline-5-carboxylate, which is ultimately converted to proline. Other products of glutamine metabolism include lactate, citrate, ornithine, and citrulline.

The GI tract also produces a wide variety of protein hormones that provide the body with information concerning nutrient levels. Insulin, the hormone that regulates carbohydrate and fat metabolism, is synthesized by pancreatic β-cells. Insulin secretion is controlled by a glucose sensor mechanism in which the transport of glucose by the low-affinity transporter protein GLUT2 and its subsequent phosphorylation by glucokinase triggers insulin release. In addition to insulin, prominent examples include ghrelin (Ghr), peptide YY (PYY), cholecystokinin (CCK), and glucagon-like peptide 1 (GLP-1). **Ghrelin**, produced by cells in the stomach and small intestine, stimulates appetite (food intake), whereas insulin, PYY, CCK, and GLP-1 promote satiety (i.e., inhibit food intake).

ghrelin A protein that stimulates appetite, produced by the cells of the stomach and small intestine.

Liver

The liver performs a stunning variety of metabolic activities. It receives blood containing dietary nutrients from the GI tract. It also uses lactate and alanine to synthesize glucose for export and glycogen for storage. The glucose in blood is preferentially delivered to glucose-dependent tissues (e.g., brain, red blood cells, and adrenal medulla). In addition to its key roles in carbohydrate, lipid, and amino acid metabolism, the liver monitors and regulates the chemical composition of blood and synthesizes several plasma proteins. The liver distributes several types of nutrient to other parts of the body. Because of its metabolic flexibility, the liver reduces the fluctuations in nutrient availability caused by drastic dietary changes and intermittent feeding and fasting. For example, a sudden shift from a high-carbohydrate diet to one that is rich in proteins increases (within hours) the synthesis of the enzymes required for amino acid metabolism and upregulates blood glucose levels via glycogenolysis and gluconeogenesis. Finally, the liver plays a critically important protective role in processing foreign molecules.

Muscle

Skeletal muscle, which is specialized to perform intermittent mechanical work, typically constitutes about one-half the body's mass. Therefore skeletal muscle consumes a large fraction of generated energy. The energy sources that provide ATP for muscle contraction are glucose from its own store of glycogen and from the bloodstream, fatty acids from adipose tissue, and ketone bodies from the liver. During fasting and prolonged starvation, some skeletal muscle protein is degraded to provide amino acids (e.g., alanine) to the liver for gluconeogenesis.

In contrast to skeletal muscle, cardiac muscle must continuously contract to sustain blood flow throughout the body. To maintain its continuous operation, cardiac muscle relies on glucose and fatty acids. It is not surprising, therefore, that cardiac muscle is densely packed with mitochondria. It can also use other energy sources, such as ketone bodies, pyruvate, and lactate. Lactate is produced only in small quantities in cardiac muscle because the isozyme of lactate dehydrogenase found in this tissue is inhibited by large concentrations of its substrate, pyruvate.

The limited production of lactate means that glycolysis alone cannot be sustained in cardiac muscle. Insulin activates glucose transport into skeletal and cardiac muscle cells by inducing the translocation of GLUT4 to the plasma membrane.

Adipose Tissue

The role of adipose tissue is primarily the storage of energy in the form of triacylglycerols. A typical human stores enough energy in adipose tissue to sustain life for several weeks to several months. Depending on current physiological conditions, adipocytes store fat derived from the diet and liver metabolism or degrade stored fat to supply fatty acids and glycerol to the circulation. Recall that these metabolic activities are regulated by several hormones (i.e., insulin and epinephrine). GLUT4 translocation is one of insulin's actions in adipocytes.

Adipocytes and macrophages within adipose tissue secrete a variety of peptide hormones, referred to as the adipokines. The adipokines include leptin and adiponectin. **Leptin** is a satiety-inducing protein, secreted into the bloodstream primarily by adipose tissue in proportion to adipose tissue mass. **Adiponectin** enhances glucose-stimulated insulin secretion and cellular responses to insulin (e.g., promoting fatty acid oxidation in skeletal muscle and suppressing glucose production by liver) primarily by activating AMP-dependent protein kinase (AMPK). Adiponectin blood levels are inversely proportional to body weight.

leptin A 16 kDa satiety-inducing protein secreted into the bloodstream primarily by adipose tissue.

adiponectin A peptide hormone that enhances glucose-stimulated insulin secretion and cellular responses to insulin.

Brain

The brain ultimately directs most metabolic processes in the body. Sensory information from numerous sources is integrated in several areas in the brain. These areas then direct the activities of the motor neurons that innervate muscles and glands. Much of the body's hormonal activity is controlled either directly or indirectly by the hypothalamus and the pituitary gland. The hypothalamus plays a pivotal role in energy balance as it integrates hormonal and neural signals and nutrient levels to promote or suppress feeding behavior.

Like the heart, the brain does not provide energy to other organs or tissues. Under normal conditions, the brain uses glucose as its sole fuel. It is noteworthy that the adult brain, about 2% of body mass, typically consumes about 20% of the body's energy resources. The brain is highly dependent on a continuous supply of glucose in the blood because it stores little glycogen. During prolonged starvation, the brain can adapt to using ketone bodies as an energy source.

Kidney

The kidney has several important functions that contribute significantly to maintaining a stable internal environment. These include the following:

1. filtration of blood plasma, which results in the excretion of water-soluble waste products (e.g., urea and certain foreign compounds);
2. reabsorption of electrolytes, sugars, and amino acids from the filtrate;
3. regulation of blood pH; and
4. regulation of the body's water content.

Considering the functions of the kidney, it is not surprising that much of the energy generated in this organ is consumed by transport processes. Energy is provided largely by fatty acids and glucose. Under normal conditions, the small amounts of glucose formed by gluconeogenesis are used only within kidney cells. The rate of gluconeogenesis increases during starvation and acidosis. The kidney uses glutamine and glutamate (via glutaminase and glutamate dehydrogenase, respectively) to generate ammonia, which is used in pH regulation. (Recall that NH_3 reversibly combines with H^+ to form NH_4^+.) The carbon skeletons of glutamine and glutamate can then be used by the kidney as a source of energy.

SUMMARY: Each organ in the mammalian system contributes to the body's overall function.