Chapter 23 – Absorptive and Post-Absorptive Metabolism

Objectives

Given the synopsis in this chapter, competence in each objective will be demonstrated by writing short essays, drawing diagrams, and responding to multiple choices or matching questions, at the level of 85% or greater proficiency for each student.

A. To explain the absorptive metabolic pathways for the use of glucose, triglycerides, and amino acids.
B. To explain the post-absorptive metabolic pathways for the retrieval of glucose, and non-glucose sources of energy.
C. To explain the control of glucose metabolism by insulin.
D. To explain the control of glucose metabolism by glucagon.
E. To explain the control of glucose metabolism by epinephrine and sympathetic nerves.
F. To explain the control of metabolism by T3 and T4.
G. To explain the control of glucose metabolism by cortisol.
H. To synthesize the regulation of glucose metabolism by the various controlling hormones.

General Metabolic Processes

Glycolysis

Glycolysis occurs in the cytoplasm and breaks down glucose to two pyruvate molecules and yields ATP and reduced coenzymes.

- Glycolysis breaks down glucose (a six carbon molecule) to two pyruvate molecules (each a three carbon molecule) and yields ATP and reduced coenzymes
- Glycolysis requires ATP (adenosine triphosphate), NAD^+ (nicotinamide adenine dinucleotide), ADP (adenosine diphosphate), and P_i (inorganic phosphate).

$$\text{Glucose} + 2\ \text{ATP} \rightarrow \rightarrow 2\ \text{Phosphoglyceraldehyde} + 2\ NAD^+ + 2\ \text{ADP} + 2\ P_i \rightarrow$$

$$2\ \text{pyruvate} + \mathbf{2\ NADH + 2\ H^+} + 4\ \text{ATP (net } \underline{\text{2 ATP}}\text{)}$$

In anaerobic conditions (low oxygen), the electron transport system (see next page) is unable to regenerate NAD^+. In order to regenerate some NAD^+, pyruvate is converted to NAD^+ and produces lactate (lactic acid) as a byproduct. For this reason lactic acid builds up in skeletal muscle during anaerobic exercise.

$$\text{pyruvate} + \mathbf{NADH + H^+} \rightarrow NAD^+ + \text{lactate}$$

Decarboxylation

Decarboxylation occurs in the matrix of the mitochondria and uses pyruvate to acetylate coenzyme A and yields carbon dioxide and reduced coenzymes.

- Decarboxylation involves the formation of acetyl-coenzyme A from pyruvate and yields carbon dioxide and reduced coenzymes
- Decarboxylation requires coenzyme A (CoA) and NAD^+

$$2\ \text{Pyruvate} + 2\ \text{CoA} + 2\ NAD^+ \rightarrow 2\ \text{Acetyl-CoA} + 2\ CO_2 + \mathbf{2\ NADH + 2H^+}$$

Tricarboxylic acid (TCA) cycle (Krebs cycle)

The TCA cycle occurs in the matrix of the mitochondria and uses acetyl-CoA to yield carbon dioxide, reduced coenzymes and ATP.

- The TCA cycle uses acetyl-CoA to yield carbon dioxide, reduced coenzymes and ATP
- The TCA cycle requires NAD^+, FAD (flavin adenine dinucleotide), ADP, and P_i

$$2\ \text{Acetyl-CoA} + 6\ NAD^+ + 2\ \text{FAD} + 2\ \text{ADP} + 2\ P_i \rightarrow$$

$$4\ CO_2 + \mathbf{6\ NADH + 6\ H^+ + 2\ FADH_2} + \underline{\text{2 ATP}}$$

Electron transport system

The electron transport system is associated with the inner mitochondrial membrane where $FADH_2$ and NADH are oxidized by a chain of electron carriers. This process requires **oxygen**, and releases energy that is used to phosphorylate ADP. The formation of ATP is catalyzed by a large multi-protein complex called ATP synthase.

- Electron transport uses **oxygen** to yield ATP
- Electron transport requires NADH, H^+, $FADH_2$, O_2, ADP, and P_i.

$$\mathbf{10\ NADH + 10\ H^+ + 2\ FADH_2} + 6\ O_2 + 34\ ADP + 34\ P_i \rightarrow$$

$$\mathbf{10\ NAD^+ + 2\ FAD +}\ 12\ H_2O + \underline{34\ ATP}$$

Glucose storage and synthesis

In addition to glycolysis which is the breakdown of glucose, glucose can be stored, retrieved and synthesized from other molecules.

- **Glycolysis** is the breakdown of glucose to pyruvate
- **Glycogenesis** is the linkage of glucose to form glycogen
- **Glycogenolysis** is the breakdown of glycogen to glucose
- **Gluconeogenesis** is glucose synthesis from pyruvate and other three carbon molecules such as lactate or glycerol
    - **pyruvate** or **phosphoenopyruvate** can be converted to **glucose** *or* used to produce **acetyl CoA** for entry to the TCA cycle

Lipolysis

Lipids (triglycerides) are broken down by hydrolysis to glycerol and fatty acids.

- Triglycerides are hydrolyzed to glycerol and 3 Fatty acids
- Glycerol is converted to glycerol phosphate and then to pyruvate or glucose
- Fatty acids are converted by beta oxidation to acetyl CoA for entry to the TCA cycle
- Ketone bodies, which are byproducts of fat breakdown, are an alternate and critical energy source for the nervous system

Amino acid catabolism

Amino acids are broken down by removal of amino groups to produce ketoacids. It is important to note the ketoacids are different than ketones.

- Some amino acids are converted into pyruvate
- Some amino acids are converted to phosphoenopyruvate which can be converted to pyruvate or glucose
- Some amino acids are converted to acetyl CoA to enter the TCA cycle

Absorptive metabolic pathways

Once glucose, amino acids and triglycerides reach the blood they will be transported to various organs of the body and either used or stored for later use; the metabolic pathways involved are called absorptive metabolic pathways.

As we learned in anatomy, the blood supply to gastrointestinal tract is drained by the hepatic portal vein into the liver. Monosaccharides and amino acids are absorbed into the blood and thus pass into the liver before being returned to the heart. As a result, the liver has the opportunity to modify the nutritional composition of the blood before being distributed to the rest of the body. In contrast, the lymphatic vessel connects directly to the systemic veins. Fatty acids and monoglycerides are recombined to form triglycerides in chylomicrons which enter the lymphatic vessels. As a result, absorbed fat reaches other tissues before it has a chance to be modified by the liver. Figure 23.1 summarizes the major absorptive metabolic pathways.

Glucose

Varying amounts of glucose enter liver cells where it may be stored as glycogen or converted to triglycerides by way of fatty acid or α-glycerol intermediates. The remaining glucose is taken up by other cells and used for energy in most tissues, or stored as glycogen in skeletal muscle tissue, or stored as triglycerides in adipose tissue.

Triglycerides

As we saw earlier, during the absorption of lipids fatty acids and monoglycerides are rejoined to form triglycerides and coated in protein to form chylomicrons. The chylomicrons are treated very much like the VLDL produced by the liver, and are hydrolyzed by lipoprotein lipase located on the luminal surface of capillary endothelial cells, especially in adipose tissue. Fatty acids diffuse through the capillary wall and into the adipocytes where they combine with α-glycerol phosphate to produce triglycerides, which are stored.

Amino Acids

Some absorbed amino acids enter liver cells where they are used to synthesize a wide variety of proteins, including liver enzymes and plasma proteins; or they are converted to α-ketoacids by removal of the amino group. The amino groups are converted to urea and excreted by the kidney. The α-ketoacids can enter the Krebs cycle to provide energy for the liver, or converted to fatty acids for fat synthesis.

Most amino acids are taken up by other cells, especially skeletal muscle, and used for the synthesis of proteins. Importantly, excess amino acids are not stored as protein; rather they are converted to carbohydrate or fat.

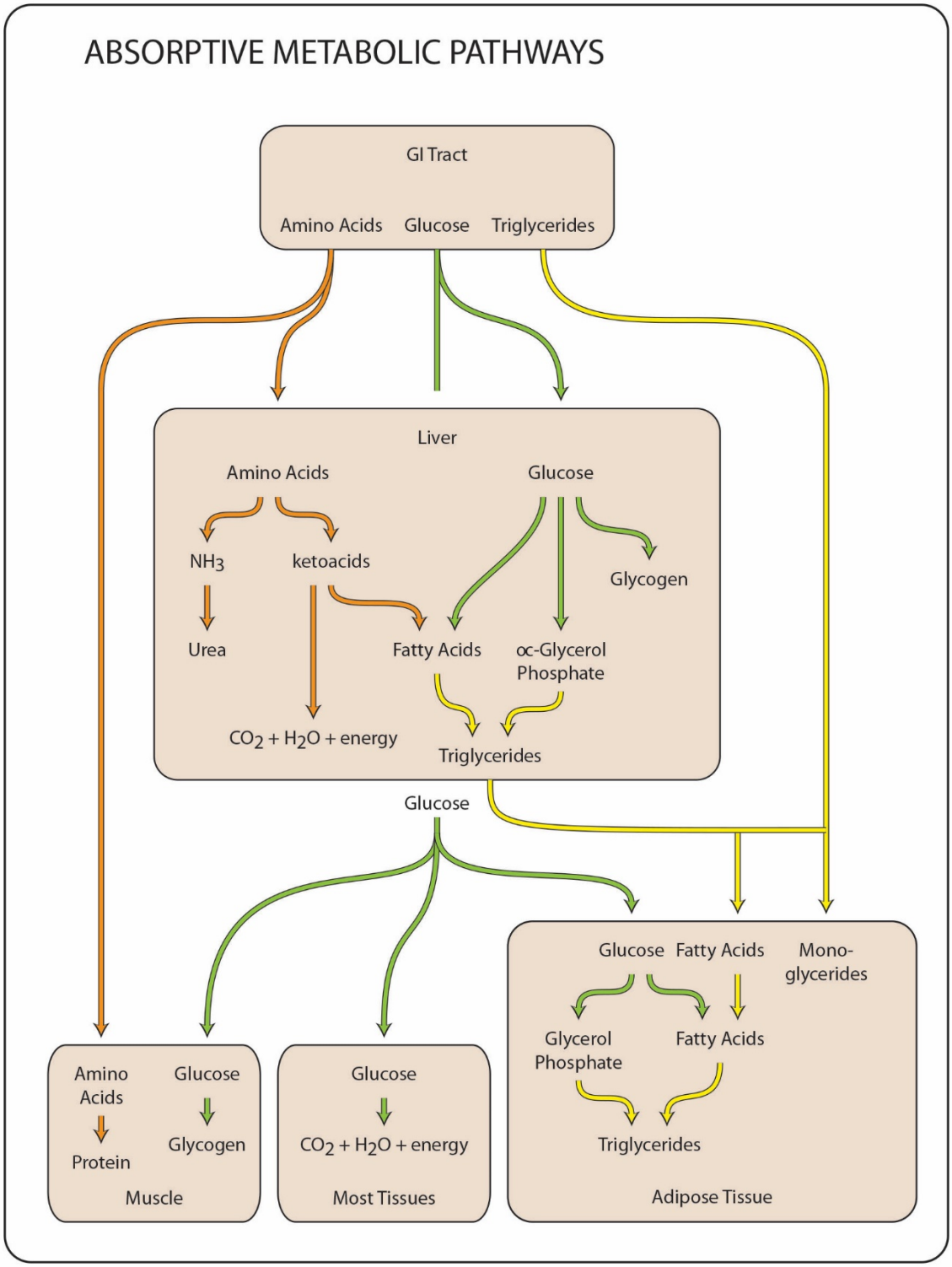


Figure 23.1 © 2016 David G. Ward, Ph.D.

Post-absorptive metabolic pathways

Nutrients that are stored must be retrieved in order to be used later; the metabolic pathways involved are called post-absorptive metabolic pathways.

As the absorptive period ends catabolism of glycogen, fat, and protein replaces their synthesis. In the post-absorptive state no glucose is being absorbed from the gastrointestinal tract, but blood glucose must be kept within normal range. Blood glucose is maintained by two types of processes; those that provide sources of glucose, and those that induce cellular use of fat rather than glucose (glucose sparing). Figure 23.2 summarizes the major post-absorptive metabolic pathways.

Sources of Glucose

A major source of glucose is via **glycogenolysis**, the hydrolysis of glycogen to glucose-6-phosphates. However, liver handles glucose-6-phosphate differently than skeletal muscle.

In liver, glucose-6-phosphate is enzymatically converted to glucose, which then enters the blood. Glycogenolysis in the liver begins within seconds of activation of the sympathetic nervous system, and is the first line of defense in maintaining blood glucose. Unfortunately the supply of glucose will last only a few hours.

In skeletal muscle, the enzyme necessary to convert glucose-6-phosphate to glucose is lacking. In skeletal muscle glucose-6-phosphate undergoes glycolysis to produce ATP, pyruvate and lactate. Some of the lactate enters the blood and is converted to glucose in the liver.

Another source for glucose is via **lipolysis**, the hydrolysis of triglycerides to glycerol and fatty acids. Lipolysis is most prominent in adipose tissue and yields glycerol and fatty acids that diffuse into the blood. Glycerol is converted to glucose in the liver.

A final source for glucose is via **gluconeogenesis**, a process which converts lactate, pyruvate, and glycerol, to glucose. Gluconeogenesis also involves the breakdown of protein to amino acids. The amino acids, in turn, enter the blood and may be converted to α-ketoacids, and then to glucose in the liver.

Glucose sparing

Instead of converting glycogen, fat and protein to glucose, it is possible to use ketones and fatty acids instead of glucose. Glycogenolysis and gluconeogenesis cannot supply all the body's needs in the post-absorptive state. Most organs and tissues reduce their glucose catabolism and increase their use of fats. This shift, often called **glucose sparing**, makes the glucose produced by the liver available for the nervous system.

The major process in glucose sparing is **lipolysis**, the hydrolysis of triglycerides to glycerol and fatty acids. Lipolysis is most prominent in adipose tissue and yields glycerol and fatty acids that diffuse into the blood. Circulating fatty acids are taken up and used by almost all tissues except in the nervous system. Beta oxidation of fatty acids produces hydrogen atoms and acetyl CoA. The hydrogen atoms go on to oxidative phosphorylation; the acetyl CoA enters the Krebs cycle.

The liver handles acetyl CoA differently, converting most to ketones (ketone bodies). The ketones can be used by many tissues, including the nervous system, in the Krebs cycle. As a matter of fact, some neurological diseases might be slowed by elevated ketones. Please make a special note that ketoacids are different than ketones. Ketoacids are derived from amino acids; ketones are derived from fatty acids.

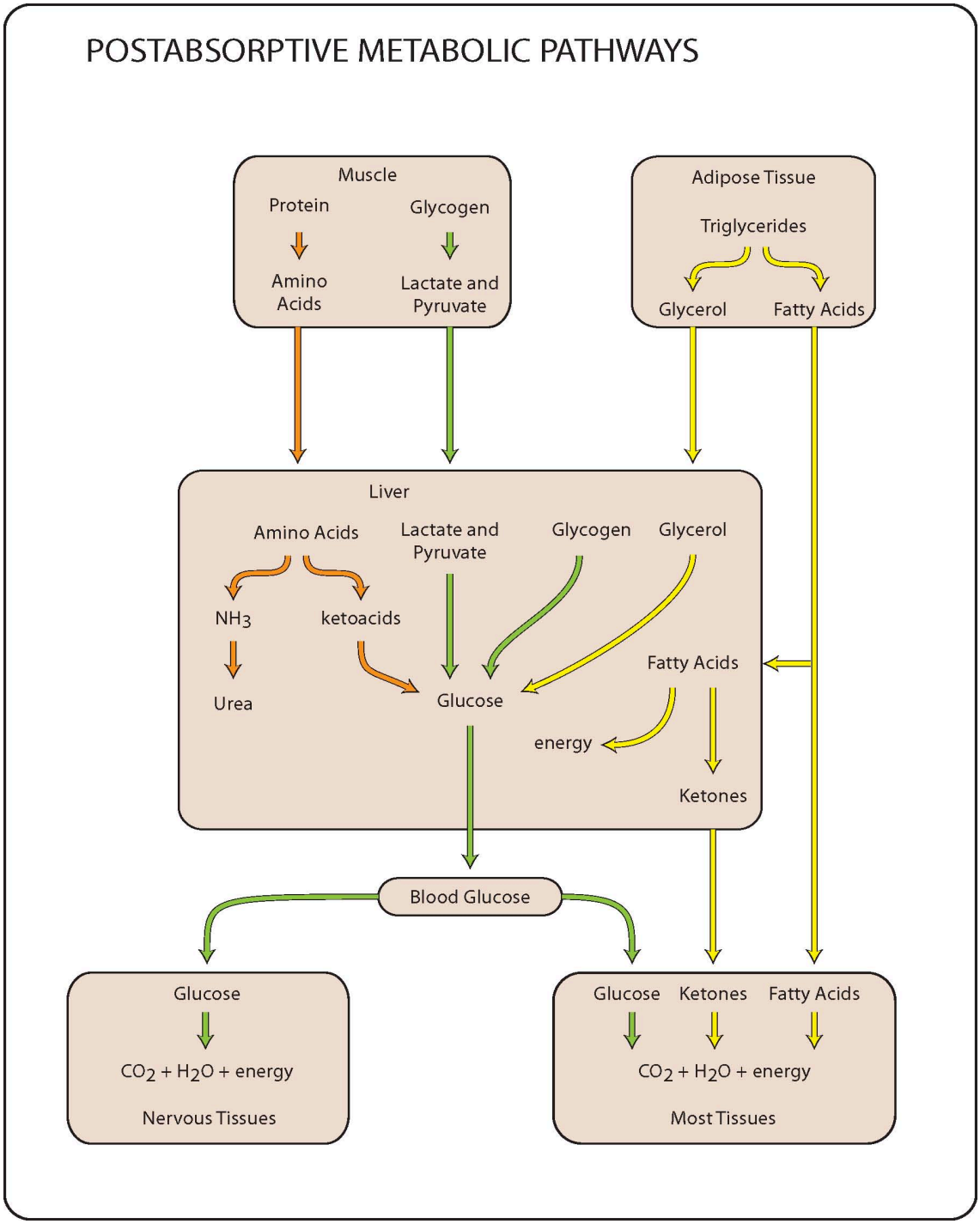


Figure 23.2 © 2007 David G. Ward, Ph.D.

Neural and Hormonal Control of Metabolism

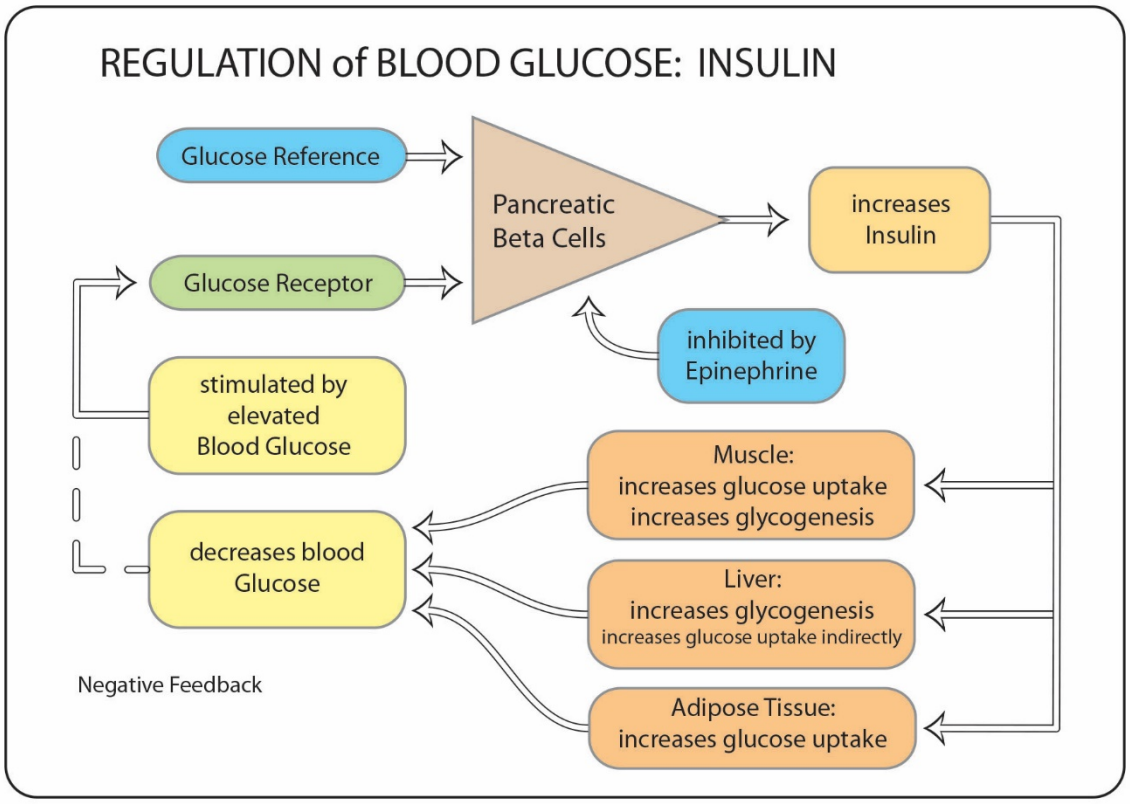
The transitioning between absorptive metabolism and post-absorptive metabolism, and vice versa, is dependent on several hormones and the sympathetic nervous system. The most critical are insulin and glucagon from the pancreas, epinephrine and cortisol from the adrenal gland, and sympathetic nerves to the liver and adipose tissues.

Insulin

The secretion of insulin is increased during the absorptive state and decreased during the post absorptive state. The metabolic effects of insulin are exerted mainly on skeletal muscle cells, adipose tissue cells, and liver cells. Insulin is produced by pancreatic beta cells and secreted in response to elevated blood glucose. Recall from chapter 14, Figure 14.7, the organization of the pancreas and pancreatic islets. Please refer to Appendix A, Table A.8 for the actions of the pancreatic hormones.

Insulin acts by binding to a tyrosine kinase linked receptor as shown in chapter 6, Figure 6.5. A major effect is to transfer glucose transporters (GLUT4) to the plasma membrane, which increases glucose uptake. These transporters are prominent in skeletal muscle and adipose tissue and absent in the liver and central nervous tissue. In each type of cell responding to insulin the responses are due to multiple actions and are often specific.

Figure 23.3 illustrates the regulation of blood glucose by insulin and shows some of its major actions. Glucose receptors in the plasma membrane of pancreatic beta cells respond to elevated blood glucose, as would be seen in the absorptive state. The beta cells respond by increasing their secretion of insulin, which in turn enters the blood. Insulin binds to insulin receptors, especially in skeletal muscle, adipose tissue, and liver. There is a direct increase in glucose uptake by cells in skeletal muscle and adipose tissue; and an indirect increase in glucose uptake in liver. Glycogenesis increases in skeletal muscle and liver. The end result is the uptake and storage of glucose, and a decline in blood glucose. The production of insulin by the beta cells is inhibited by epinephrine.



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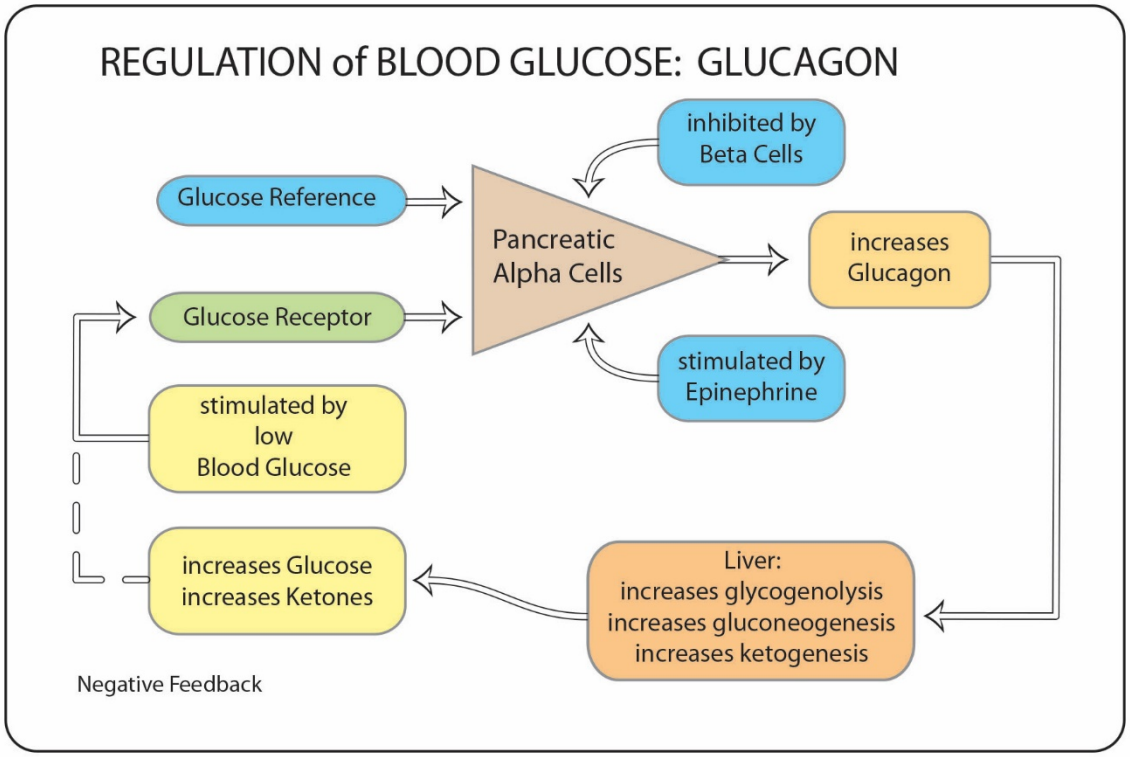
Glucagon

The secretion of glucagon is increased during the post-absorptive state and decreased during the absorptive state. The metabolic effects of glucagon are exerted mainly on the liver. Glucagon is produced by pancreatic alpha cells and secreted in response to low blood glucose. Recall from chapter 14, Figure 14.7, the organization of the pancreas and pancreatic islets. Please refer to Table 14.8 for the actions of the pancreatic hormones.

Glucagon acts by binding to a G-protein coupled receptor as shown in chapter 6, Figure 6.6. A major effect is to inhibit glycogen synthase and to activate glycogen phosphorylase which breaks down glycogen. Another effect is to activate cAMP response element binding protein (CREB) which in turn functions as a transcription factor to activate the expression of genes that code for enzymes involved in gluconeogenesis and ketogenesis.

Figure 23.4 illustrates the regulation of blood glucose by glucagon and shows some of its major actions. Glucose receptors in the plasma membrane of pancreatic alpha cells respond to low blood glucose, as would be seen in the post-absorptive state. The alpha cells respond by increasing their secretion of glucagon, which in turn enters the blood. Glucagon binds to glucagon receptors, especially in liver and increases glycogenolysis, gluconeogenesis, and ketogenesis. The end result is the efflux of glucose into the blood. The increase in glucose is supplemented by an increase in ketones. The production of glucagon by the alpha cells is inhibited by active beta cells and stimulated by epinephrine.



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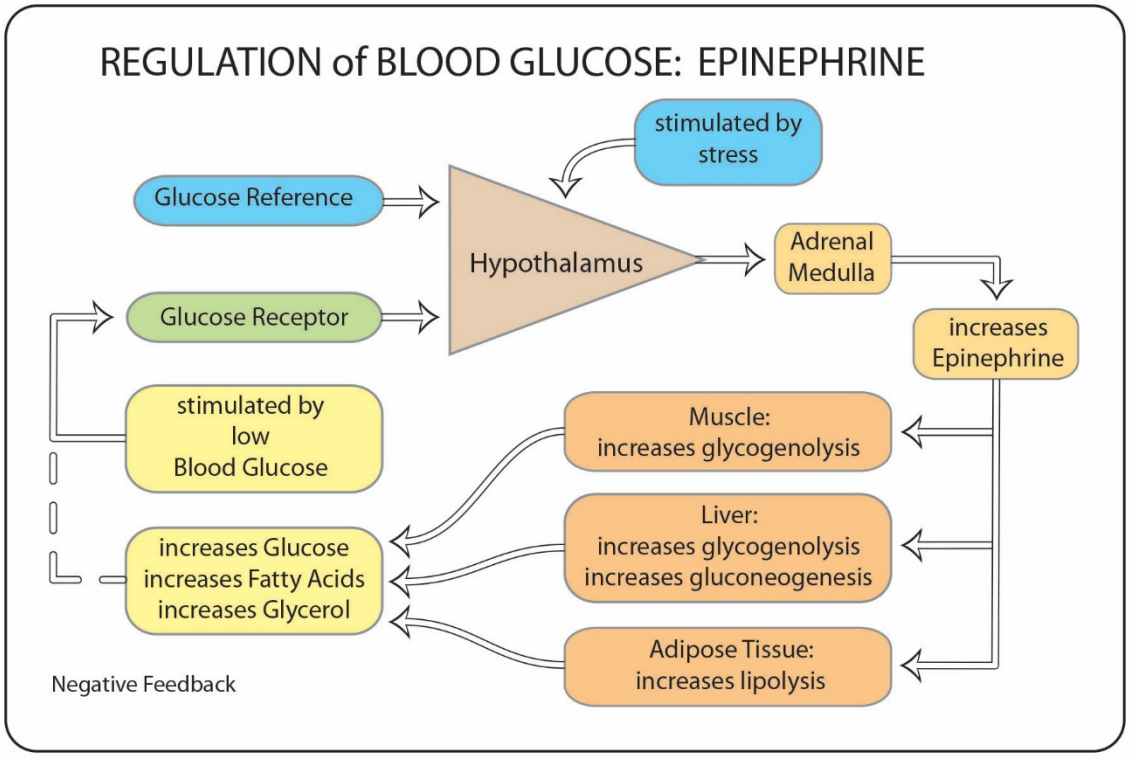
Epinephrine and sympathetic nerves

The secretion of epinephrine is increased during the post-absorptive state and decreased during the absorptive state. The metabolic effects of epinephrine are exerted on the liver, skeletal muscle and adipose tissue. Epinephrine is produced by adrenal medullary chromaffin cells and secreted in response to low blood glucose and other stressors. Recall from chapter 14, Figure 14.8, the organization of the adrenal gland. Please refer to Appendix A, Table A.6 for the actions of epinephrine and norepinephrine. See chapter 15 for the role of the sympathetic nervous system, pituitary, adrenal and thyroid in responding to stress.

Epinephrine acts similarly to glucagon by binding to a G-protein coupled receptor as shown in chapter 6, Figure 6.6. A major effect is to inhibit glycogen synthase and to activate glycogen phosphorylase which breaks down glycogen. Another effect is to activate hormone sensitive lipase (HSL) which breaks down fat. A final effect is to activate cAMP response element binding protein (CREB) which in turn functions as a transcription factor to activate the expression of genes that code for enzymes involved in gluconeogenesis.

Figure 23.5 illustrates the regulation of blood glucose by epinephrine and shows some of its major actions. Glucose receptors in the central nervous system and possibly the liver send signals to the hypothalamus. The hypothalamus activates the sympathetic

nervous which stimulates the chromaffin cells (ganglionic neurons) of the adrenal medulla. The chromaffin cells respond by increasing their secretion of epinephrine, which in turn enters the blood. Epinephrine binds mainly to beta receptors, in skeletal muscle, liver, and adipose tissue. There is an increase in glycogenolysis in skeletal muscle, an increase in, glycogenolysis and gluconeogenesis in liver, and an increase in lipolysis in adipose tissue. The end result is an efflux of glucose into blood. The increase in glucose is supplemented by an increase in fatty acids and glycerol.



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T3 and T4

The secretion of T3 and T4 is increased during the post-absorptive state and decreased during the absorptive state. Most of the metabolic effects of thyroid hormones are due to T3 (rather than T4) and are exerted on the liver, skeletal muscle, and adipose tissue. T3 and T4 is produced by the thyroid follicles of the thyroid gland in response to low body temperature, low blood glucose, low T3/T4 and other stressors. Recall from chapter 14, Figure 14.6, the organization of the thyroid gland. Please refer to Table A.4 of appendix A for the actions of the thyroid hormones. See chapter 15 for the role of the sympathetic nervous system, pituitary, thyroid, and adrenal in responding to stress.

T3 is lipid soluble and diffuses through the plasma membrane to bind to various thyroid hormone response element binding proteins (TREB proteins or TRs). T3-TR complexes function mainly as a transcription factors to activate the expression of genes

for synthesis of a wide variety of RNAs. These RNAs orchestrate the synthesis of enzymes involved in glycogenolysis, gluconeogenesis, and lipolysis.

Figure 23.6 illustrates the regulation of blood glucose by T3 and shows some of its major actions. Thermoreceptors and glucose receptors send signals to the hypothalamus. The hypothalamus releases thyrotropin releasing hormone (TRH) into the median eminence of the pituitary and from there it is carried to the anterior pituitary. In the anterior pituitary TRH stimulates the release of thyrotropin (TSH) from thyrotrophs. Thyrotropin enters the blood and signals the cells of the thyroid follicles of the thyroid gland to increase the synthesis and release of T3/T4, which in turn enters the blood. T3 binds mainly to TR receptors (thyroid hormone response elements) in liver, skeletal muscle, and adipose tissue. There is an increase in glucose uptake but a decrease in glycogenesis in skeletal muscle, an increase in gluconeogenesis and an increase in glucose efflux in liver, and an increase in lipolysis in adipose tissue. The end result is an increase in blood glucose, supplemented by an increase in amino acids and fatty acids.

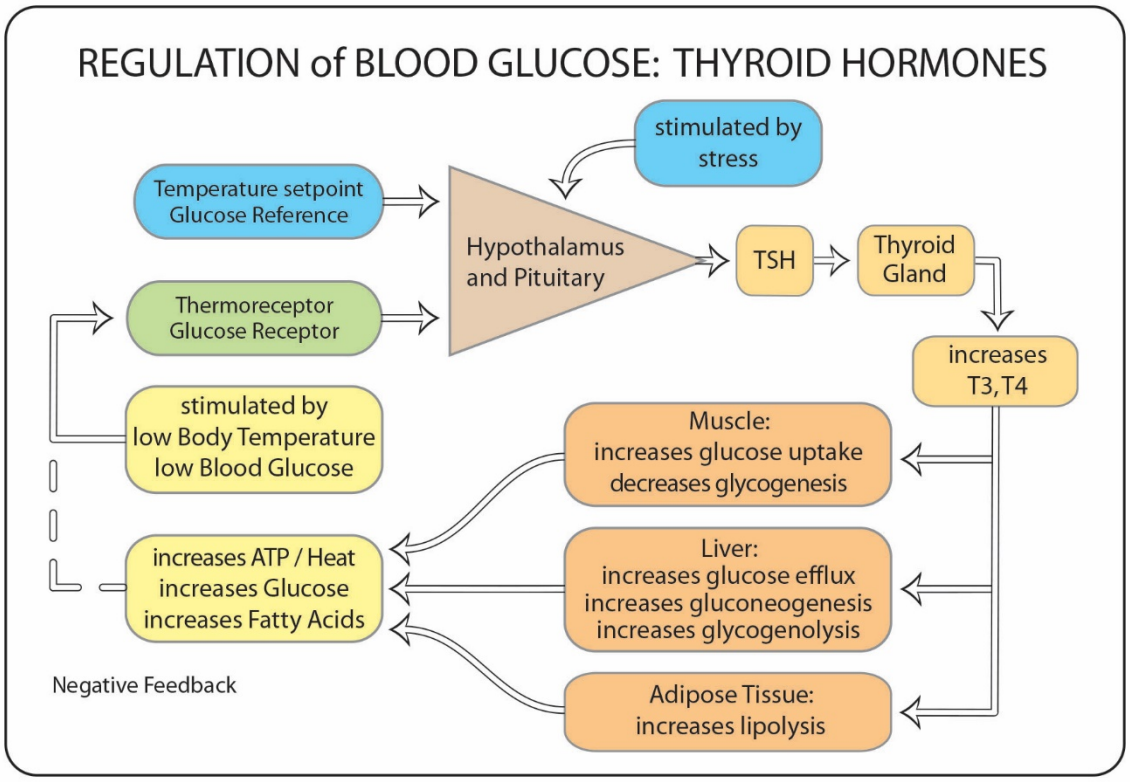


Figure 23.6 © 2016 David G. Ward, Ph.D.

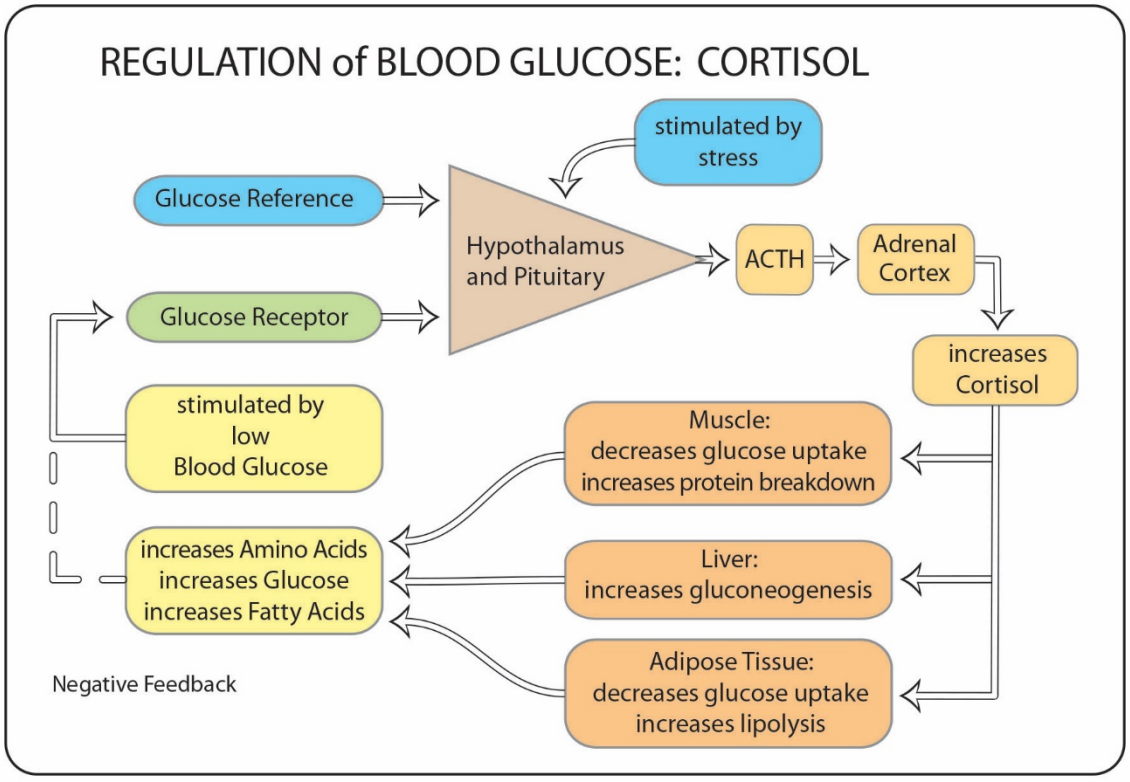
Cortisol

The secretion of cortisol is increased during the post-absorptive state and decreased during the absorptive state. The metabolic effects of cortisol are exerted on the liver, skeletal muscle and adipose tissue. Cortisol is produced by the zona fasciculata of the adrenal cortex in response to low blood glucose and other stressors. Recall from chapter 14, Figure 14.8, the organization of the adrenal gland. Please refer to Table A.7 of

appendix A for the actions of the adrenal cortical hormones. See chapter 15 for the role of the sympathetic nervous system, pituitary, thyroid, and adrenal in responding to stress.

Cortisol is lipid soluble and diffuses through the plasma membrane to bind to a glucocorticoid response element binding protein as shown in chapter 6, Figure 6.1. A major effect is to function as a transcription factor to activate the expression of genes that code for enzymes involved in gluconeogenesis, lipolysis and the breakdown of proteins.

Figure 23.7 illustrates the regulation of blood glucose by cortisol and shows some of its major actions. Glucose receptors in the central nervous system and possibly the liver send signals to the hypothalamus. The hypothalamus releases corticotropin releasing hormone (CRH) into the median eminence of the pituitary and from there it is carried to the anterior pituitary. In the anterior pituitary CRH stimulates the release of corticotropin from corticotrophs. Corticotropin enters the blood and signals the cells of the zona fasciculata of the adrenal cortex to increase the synthesis and release of cortisol, which in turn enters the blood. Cortisol binds mainly to glucocorticoid response elements in skeletal muscle, liver, and adipose tissue. There is a decrease in glucose uptake and an increase in protein breakdown in skeletal muscle; an increase in gluconeogenesis in liver; and a decrease in glucose uptake and an increase in lipolysis in adipose tissue. The end result is an increase in blood glucose. The increase in glucose is supplemented by an increase in amino acids and fatty acids.



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Summary of metabolic hormones

The actions of the major metabolic hormones are summarized in Table 23.1.

Insulin stimulates glucose uptake and glycogenesis. Insulin binds to tyrosine kinase linked receptors, and produces responses that are generally different than those seen with T3, glucagon, epinephrine, cortisol, or growth hormone.

- Insulin is the dominant hormone in the absorptive state

T3, glucagon, and epinephrine stimulate glycogenolysis, gluconeogenesis, and lipolysis. In addition, T3 stimulates glucose uptake in some organs. T3 binds to intracellular thyroid hormone response element binding proteins (TREB proteins or TRs), whereas epinephrine and glucagon bind to G-protein coupled receptors. Some actions of T3 on glucose metabolism may be due to synergistic interactions with epinephrine.

Cortisol and growth hormone inhibit glucose uptake, have little effect on glycogenolysis, and stimulate gluconeogenesis and lipolysis.

- Together, T3, glucagon, epinephrine, and cortisol are critical hormones in the post-absorptive state.

Table 23.1. Summary of Metabolic Hormones

Hormone	Glucose Uptake	Glycogenesis	Glycogenolysis	Gluconeogenesis	Lipolysis
Insulin	stimulate	stimulate			
T3	stimulate		stimulate	stimulate	stimulate
Glucagon			stimulate	stimulate	stimulate
Epinephrine			stimulate	stimulate	stimulate
Cortisol	inhibit			stimulate	stimulate
Growth hormone	inhibit			stimulate	stimulate

Quiz Yourself

1-5. Matching

A)	lipolysis	formation of glucose from amino acids or fatty acids	1) _____
B)	glycolysis	formation of glucose by the breakdown of glycogen	2) _____
C)	glycogenesis	formation of glycogen from glucose	3) _____
D)	glycogenolysis	breakdown of glucose	4) _____
E)	gluconeogenesis	breakdown of fat	5) _____

6-10. Matching

A)	glycolysis	use(s) oxygen	6) _____
B)	decarboxylation	produce(s) CO_2^+	7) _____
C)	Kreb's (TCA) cycle	produce(s) NADH	8) _____
D)	electron transport system	produce (s) 34 ATP	9) _____
E)	two or more of the above	produce(s) 2 net ATP	10) _____

11-15. Matching

A)	glucagon	is stimulated by low blood glucose	11) _____
B)	insulin	is stimulated by elevated blood glucose	12) _____
C)	none of the above	causes in increase in glucose uptake by cells	13) _____
		causes the breakdown of glycogen to glucose	14) _____
		is stimulated by glucose dependent insulinotropic H. (GDIH)	15) _____

16-20.

A)	Insulin	Increases gluconeogenesis	16) _____
B)	Cortisol	Decreases glucose uptake	17) _____
C)	Glucagon	Increases glucose uptake	18) _____
D)	Epinephrine	Increases glycogenolysis	19) _____
E)	Two or more of the above	Increases glycogenesis	20) _____

Fill in

21. _____.(a hormone) increases lipolysis and gluconeogenesis, and inhibits glucose uptake

22. _____ (a hormone) increases breakdown of glycogen.

23. _____.(a hormone) increases glucose uptake

24. _____ is a process that converts 2 Pyruvate into Glucose.

25. _____ (a hormone) increases cellular metabolism.

Study Questions

1. Explain the metabolic role of monosaccharides, amino acids, and fatty acids after they are absorbed into the blood (absorptive state).
2. Describe the major steps in the production of ATP from glucose.
3. Explain how stored glycogen, fat, and protein are metabolized to provide sources of energy (post-absorptive state).