9.6 The Adrenal Medulla and Integration of Metabolic Control

Learning Objectives

- Describe the relationship between the adrenal medulla and the sympathetic nervous system
- List the biochemical precursors of epinephrine in sequence of their synthesis
- Distinguish between the local effects of the sympathetic nervous systems and systemic effects
- Identify the signal transduction pathway for β adrenergic effects
- Identify the signal transduction pathways for α_1 and α_2 adrenergic effects
- List two enzymes involved in catecholamine degradation
- Describe the overall effect of epinephrine on carbohydrate metabolism
- Describe the overall effect of epinephrine on fat metabolism
- List the hyperglycemic hormones
- List the hypoglycemic hormones
- Describe in general terms the effects of hormones on intermediary metabolism, fat and protein stores in the body

THE ADRENAL MEDULLA IS PART OF THE SYMPATHETIC NERVOUS SYSTEM

The gross and histological appearance of the adrenal gland was described in Chapter 9.5, Figure 9.5.1. The innermost part of this gland is the medulla, which secretes the catecholamine **epinephrine** into the systemic circulation. It also secretes small amounts of norepinephrine, which is typically released at postganglionic nerve endings in the sympathetic nervous system and acts as a local neurotransmitter. Epinephrine released into the circulation therefore is a neuroendocrine hormone and has diverse effects on multiple organs. The medulla is actually an enlarged and specialized ganglion of the sympathetic nervous system, as recapitulated in Figure 9.6.1. Here, preganglionic sympathetic nerves exit the spinal cord at the lower thoracic level and release acetylcholine onto **chromaffin cells** in the adrenal medulla that synthesize and release epinephrine into the general circulation.

EPINEPHRINE DERIVES FROM TYROSINE

Epinephrine, dopamine, and norepinephrine are all catecholamines. Catechol is dihydroxy benzene, shown in Figure 9.6.2 along with the biosynthetic pathway for epinephrine. All of the enzymes involved in the synthesis are located in the cytoplasm, except for dopamine β hydroxylase that converts dopamine to norepinephrine. This occurs within vesicles in the chromaffin cells. Thus, dopamine is imported into the vesicles to be converted to norepinephrine and is exported back out of the vesicles to be converted into epinephrine, and then transported back into the vesicles for secretion. Uptake into the vesicles is mediated by the vesicular H-ATPase pump and carrier proteins called vesicular monoamine transporters (VMATs). The granulated vesicles contain dopamine β hydroxylase, ascorbic acid, ATP, and chromogranin A. The rate limiting step for synthesis of epinephrine is tyrosine hydroxylase, the first step that forms L-DOPA. Several of the enzymes are influenced by circulating concentrations of glucocorticoids, whereas epinephrine inhibits phenyl *N*-methyl transferase (PNMT) activity.

CATECHOLAMINES ARE RELEASED IN RESPONSE TO SYMPATHETIC STIMULATION

Preganglionic sympathetic fibers release acetylcholine onto the chromaffin cells in the adrenal medulla, and this activates nicotinic cholinergic receptors. The resulting depolarization, in turn, activates voltage-gated Ca^{2+} channels that raise intracellular $[Ca^{2+}]$. The increased $[Ca^{2+}]$ causes exocytosis of granules containing epinephrine and norepinephrine. Epinephrine makes up about 80% of the catecholamines released from normal adrenal medulla and norepinephrine, about 20%.

Secretion of epinephrine from the adrenal medulla is an integral part of the "**fight or flight**" response of the body to perceived emergency situations. Stimulation of adrenal secretion is induced by a number of conditions, such as:

- trauma
- pain

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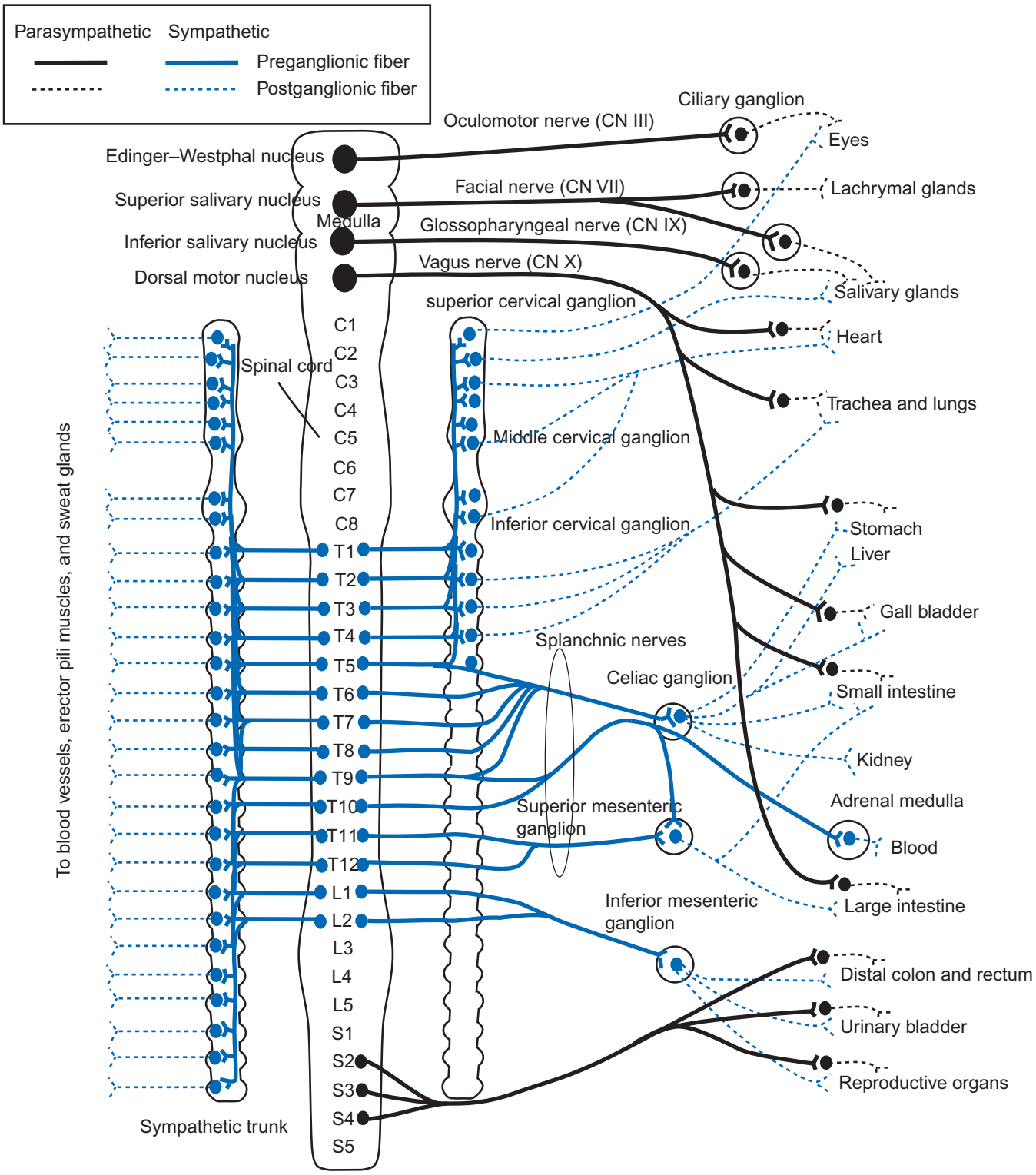

FIGURE 9.6.1 Connections of the sympathetic and parasympathetic nervous system. The sympathetic nervous system connections are shown in blue and the parasympathetic nervous system connections are shown in black.

- hypoglycemia
- hypotension
- anxiety
- temperature extremes
- severe exercise
- anoxia
- hypovolemia.

Figure 9.6.3 illustrates the different uses of epinephrine and norepinephrine by the sympathetic nervous system.

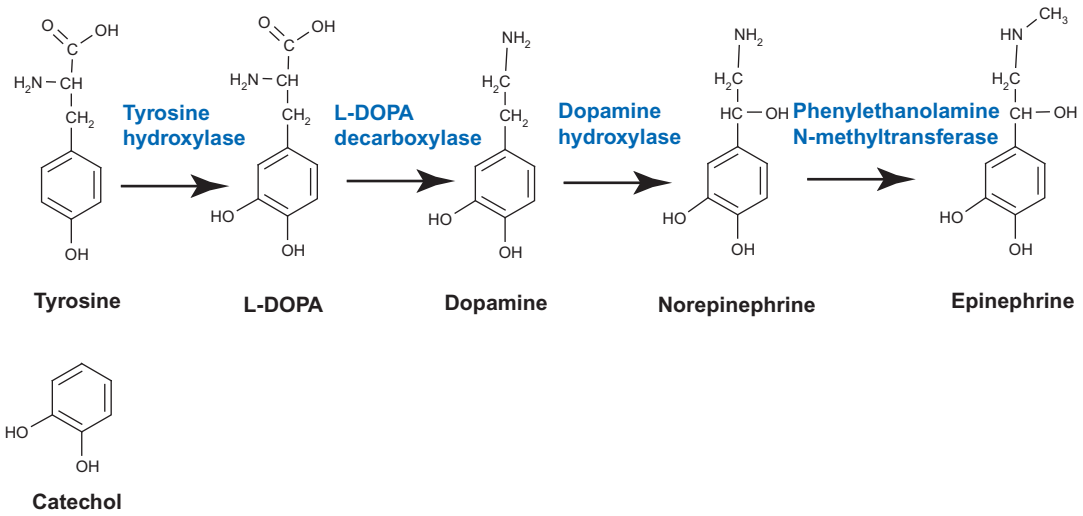

FIGURE 9.6.2 Synthesis of norepinephrine and epinephrine in the adrenal medulla.

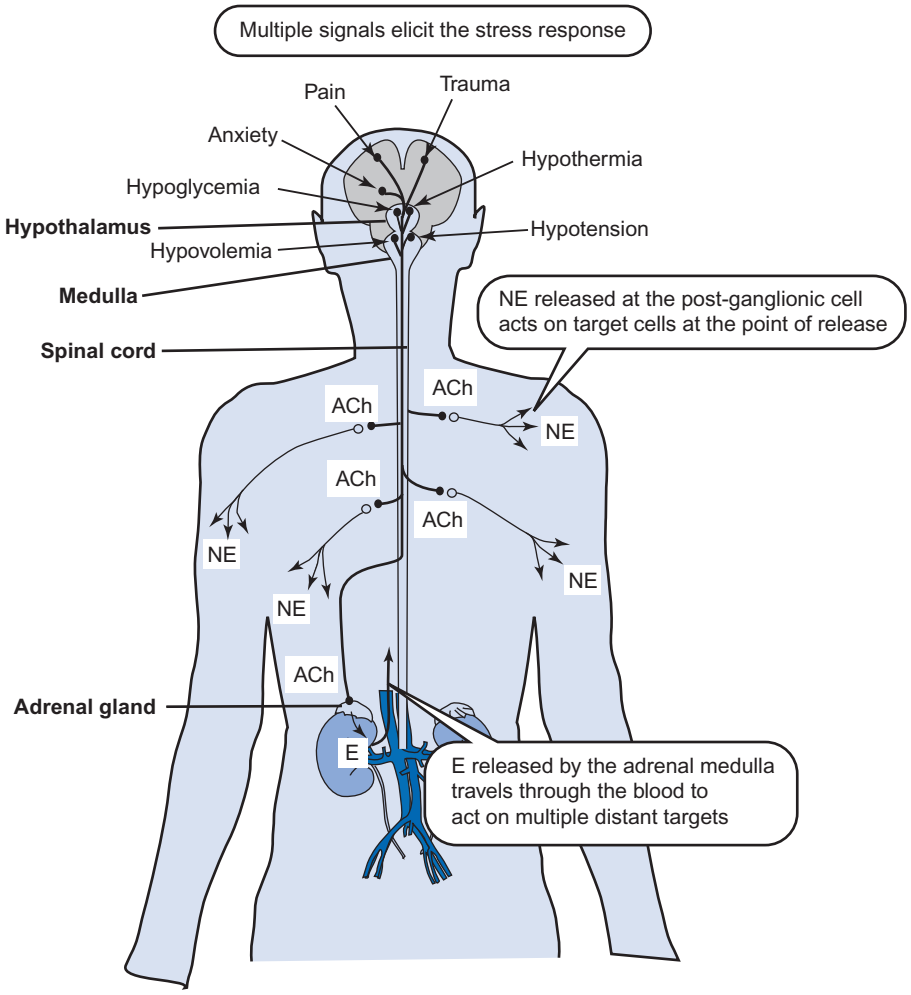

FIGURE 9.6.3 Different function of epinephrine (E) and norepinephrine (NE) in the stress response. A variety of signals can initiate the stress response including hypovolemia, hypotension, hypoglycemia, pain, trauma, anxiety, and hypothermia. These all activate the sympathetic nervous system. Some of the responses are mediated by norepinephrine, which is typically secreted in a widely dispersed network through preganglionic sympathetic fibers that use acetylcholine as a neurotransmitter to activate postganglionic fibers that release norepinephrine onto local target cells. Other responses are mediated by circulating epinephrine that is released from the adrenal medulla by sympathetic fibers carried in the preganglionic splanchnic nerves. These increase epinephrine release by depolarizing the chromaffin cells (those that secrete epinephrine) with acetylcholine.

CATECHOLAMINES ARE DEGRADED RAPIDLY

The basal circulating plasma epinephrine concentration ranges from 25 to 50 pg mL^{-1} (= about $1.5 - 3 \times 10^{-10}$ M) with an estimated daily secretion of 150 μg. Nearly all of the epinephrine in the circulation derives from the adrenal medulla, whereas most of the norepinephrine derives from sympathetic nerve terminals in the peripheral tissues and the brain. Most of the neurotransmitter is

retaken up by either the pre- or postsynaptic cell, but some escapes immediate uptake and leaks into the general circulation. Both epinephrine and norepinephrine remain in the circulation only a very short time: their half-lives are about 1–3 min and their metabolic clearances are from 2 to 6 L min^{-1}. Circulating epinephrine is degraded mostly in the liver and the kidney. The enzymes largely responsible for this degradation are catecholamine *O*-methyl transferase (COMT) and a combination of mono amine oxidase (MAO) and aldehyde oxidase (AO). The pathways for metabolism of the catecholamines are shown in Figure 9.6.4. Oxidation and *O*-methylation can occur in random order.

ACTIONS OF CATECHOLAMINES ARE MEDIATED BY ADRENERGIC RECEPTOR TYPES

All actions of epinephrine and norepinephrine are mediated through receptors on the surfaces of their target cells. As discussed in Chapters 4.2 and 4.9, these receptors are the **adrenergic receptors**. Ahlquist in 1948 classified them as α or β based on their response to epinephrine, norepinephrine, and isoproterenol. We now identify several subclasses of receptors: α_1 and α_2 and β_1, β_2, and β_3. These receptors differ in their relative responses to epinephrine and norepinephrine and also in their response to specific pharmacological agents. Some of these differences are summarized in Table 9.6.1. The β_1, β_2, and β_3 receptors are all G-coupled receptors whose occupancy stimulates adenylyl cyclase and so increases cAMP concentrations in the target cell: they are all G_s mechanisms because they stimulate adenylyl cyclase. The α_1 mechanism is a G_q mechanism. It is coupled to activation of phospholipase C in the surface membrane, which cleaves phosphatidyl inositol bisphosphate to release IP3 and diacylglycerol (DAG). The IP3 in turn binds to IP3 receptors on the endoplasmic reticulum membrane, causing them to release stored Ca^{2+}. The increase cytoplasmic $[Ca^{2+}]$ then activates specific cell responses. The DAG activates protein kinase C, which exerts its effects by phosphorylating target proteins. The α_2 receptors are coupled to a G_i mechanism, in which binding to the receptor inhibits adenylyl cyclase and therefore reduces cytoplasmic levels of cAMP.

The multitude of responses of target cells to epinephrine and norepinephrine derive from the distribution of these receptor types among the different tissues. For example, heart and liver tissue have β_1 receptors that are responsible for cardioacceleration and positive inotropy and glycogenolysis. Smooth muscles of the

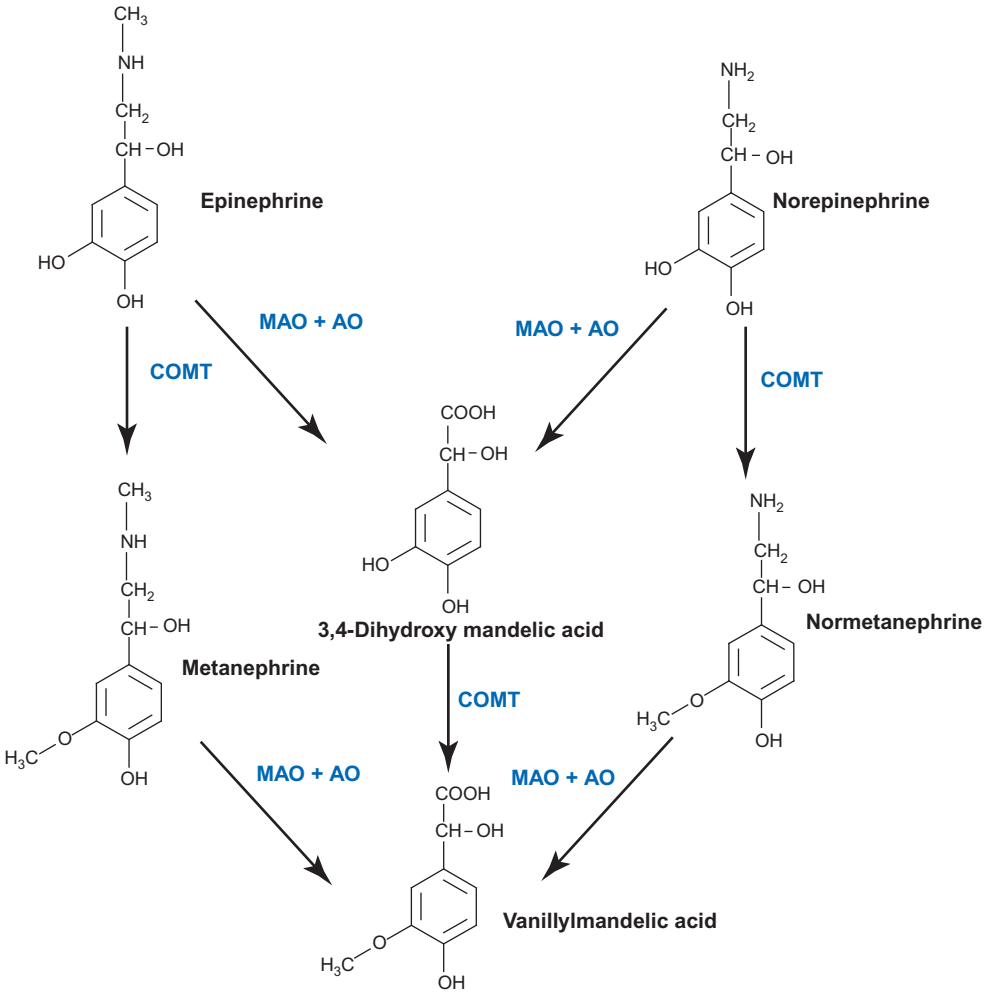

FIGURE 9.6.4 Catabolism of epinephrine and norepinephrine. Both catecholamines are degraded by a combination of catechol-*O*-methyl transferase (COMT), which incorporates a methyl group onto the *meta*-hydroxy position on the ring, and monoamine oxidase (MAO) and aldehyde oxidase (AO), which oxidize the amino group and then cleave it off, and then convert the aldehyde to a carboxyl group.

TABLE 9.6.1 Comparison of α- and β Adrenergic Receptors

Repeptor Type	Agonist Potency	Action of Agonist	Mechanism	Agonists	Antagonists
α_1	E>NE≫ISO	Smooth muscle contraction	G_q	Phenylephrine	Phentolamine prazosin phenoxybenzamine
α_2	E>NE≫ISO	Nerve terminal inhibition; smooth muscle contraction	G_i	Clonidine	Yohimbine
β_1	ISO>E = NE	Increased heart rate	G_s	Isoprenaline dobutamine	Atenolol metaprolol
β_2	ISO>E≫NE	Smooth muscle relaxation	G_s	Albuterol	Propranolol
β_3	ISO = E>NE	Increased lipolysis	G_s		

E, epinephrine; NE, norepinephrine; ISO, isoproterenol.

TABLE 9.6.2 Overview of the Physiological Actions of the Catecholamines

1. **Effects on carbohydrate metabolism**
   - 1.1 Overall effect is to increase plasma [glucose]
   - 1.1 Catecholamines increase liver glycogenolysis (β_1 and α_1)
   - 1.2 Catecholamines increase gluconeogenesis (β_2 and α_1)
   - 1.3 Epinephrine increases muscle glycogenolysis
   - 1.4 Norepinephrine decreases insulin secretion (α_2)
   - 1.5 Epinephrine increases insulin secretion (β_2)
   - 1.6 Catecholamines stimulate glucagon secretion (α)
2. **Effects on fat metabolism**
   - 2.1 Catecholamines increase lipolysis (β_3 and β_1)
   - 2.2 Catecholamines increase plasma levels of free fatty acids
3. **Effects on overall metabolism**
   - 3.1 Catecholamines increase BMR
   - 3.2 Catecholamines increase Q_{O_2}
   - 3.3 Catecholamines increase calorigenesis (β_1)
4. **Effects on the cardiovascular system**
   - 4.1 Catecholamines increase heart rate (β_1)
   - 4.2 Catecholamines increase cardiac contractility (β_1)
   - 4.3 Catecholamines increase conduction velocity (β_1)
   - 4.4 Catecholamines constrict arterioles in skin, kidney, GI tract, genitalia, spleen (α_1)
   - 4.5 Catecholamines dilate arterioles in skeletal and cardiac muscle, liver, and lungs (β_2)
   - 4.6 Net effect is to increase cardiac output and increase systolic (but generally not diastolic) pressure and to divert blood from splanchnic circulation to muscle
5. **Effects on the GI tract and sphnicters**
   - 5.1 Catecholamines relax smooth muscle in GI tract, urinary tract, and bronchioles (β_2)
   - 5.2 Catecholamines constrict GI and urinary sphincters (α_1)
6. **Other effects**
   - 6.1 Catecholamines cause pupillary dilation (α_1)
   - 6.2 Catecholamines cause emotional sweating
   - 6.3 Catecholamines increase platelet aggregation (α_2)

vasculature, intestine, uterus, and bronchi have β_2 receptors that are responsible for smooth muscle relaxation that causes vasodilation and bronchodilation. Vascular smooth muscle, pupillary dilator muscle, liver, and heart also have α_1 receptors that cause vasoconstriction, dilation of the pupil, glycogenolysis, and positive inotropy. Adipose tissue has β_3 receptors that cause lipolysis.

THE EFFECTS OF CATECHOLAMINES ARE TO PREPARE THE BODY FOR "FIGHT OR FLIGHT"

The concerted actions of the catecholamines have the net effect of preparing the body for emergency action. These actions are various and widely spread over the body systems. Table 9.6.2 summaries the wide variety of

physiological effects of the catecholamines. The heart rate accelerates due to an increase in the slope of the sinoatrial node pacemaker potential, caused by β_1 stimulation of the SA nodal cells with increases in I_f and L-type I_{Ca} (see Chapter 5.5). Stimulation of β_1 receptors on cardiomyocytes also phosphorylates a number of proteins in these cells that lead to increased inotropy (Chapter 5.7). This leads to an increased cardiac output and increased systolic pressure and mean arterial pressure. Simultaneously, the catecholamines constrict the blood vessels that supply the blood to organs that are inessential to emergency action: the GI tract, kidneys, and reproductive organs. Receptors on the bronchioles cause dilation of the airways to ready the respiratory system for increase air flow. The catecholamines mobilize liver and muscle glycogen, with only the liver glycogen contributing to the increase in blood levels of glucose. They also stimulate gluconeogenesis to further increase blood glucose and inhibit insulin release and stimulate glucagon release. The catecholamines also mobilize fat stores by increasing lipolysis and circulating levels of fatty acids. Dilation of the pupil, caused by sympathetic stimulation, enables better vision of distant objects. All of these actions prime the body for emergency action and also help rescue the body from trauma or hypoglycemia.

INTEGRATION OF METABOLIC CONTROL

Over the last few chapters, we have discussed several hormones that affect intermediary metabolism. These include: growth hormone, thyroxine, insulin, glucagon, cortisol, and the catecholamines. The purpose of this section is to attempt to integrate their effects on intermediary metabolism. First, we list here the general effects of each hormone on intermediary metabolism, and then we focus on the integrated effects of all of them on intermediary metabolism.

GROWTH HORMONE

1 Carbohydrate metabolism
- GH increases blood glucose (the "diabetogenic" effect of GH);
- GH mobilizes liver glycogen;
- GH increases insulin release;
- GH inhibits glucose uptake by muscle and adipose tissue.

2 Fat metabolism
- GH increases plasma free fatty acids;
- GH increases lipolysis;
- GH decreases glucose uptake into fat tissue;
- GH decreases body fat.

3 Protein metabolism
- GH increases total body nitrogen retention;
- GH increases lean body mass;
- GH increases uptake of amino acids into muscle, heart, and liver;
- GH stimulates protein synthesis.

THYROID HORMONE

1 Carbohydrate metabolism
- T3 potentiates the effect of epinephrine in the liver; increases liver glycogenolysis and gluconeogenesis;
- T3 therefore decreases liver glycogen and raises blood glucose;
- T3 potentiates the effect of insulin on muscle; it increases glucose uptake, utilization and storage of glucose.

2 Fat metabolism
- T3 potentiates the effect of insulin on adipose tissue;
- T3 increases plasma free fatty acids;
- T3 increases lipolysis.

3 Protein metabolism
- T3 promotes protein synthesis in a number of tissues.

INSULIN

1 Carbohydrate metabolism
- insulin increases glucose uptake by muscle and adipose tissue;
- increased uptake decreases plasma glucose concentration;
- insulin decreases glycogenolysis in liver and muscle;
- insulin decreases gluconeogenesis in liver and muscle.

2 Fat metabolism
- insulin increases lipogenesis;
- insulin decreases lipolysis;
- insulin decreases plasma free fatty acids.

3 Protein metabolism
- insulin increases amino acid uptake by liver and muscle;
- insulin increases protein synthesis and decreases protein breakdown.

GLUCAGON

1 Carbohydrate metabolism
- glucagon increases liver glycogenolysis and gluconeogenesis;
- glucagon increases plasma glucose concentration;
- glucagon does not affect glucose uptake or utilization by peripheral tissues.

2 Fat metabolism
- glucagon activates hormone-sensitive lipase, so increases lipolysis.

3 Protein metabolism
- glucagon promotes gluconeogenesis mainly in the liver.

GLUCOCORTICOIDS

1 Carbohydrate metabolism
- glucocorticoids raise plasma glucose concentrations;
- glucocorticoids increase gluconeogenesis;
- glucocorticoids raise liver glycogen stores;

TABLE 9.6.3 General Effects of the Various Hormones on Intermediary Metabolism and Fuel Stores

Hormone	Plasma [glucose]	Glycogen Stores		Gluconeo-genesis	Glucose Uptake, Utilization	Fat Stores in Adipose Tissue	Protein Content of Tissues
		Liver	Muscle				
Insulin	↓	↑	↑	↓	↑	↑	↑
Glucagon	↑	↓	→	↑	→	↓	→
GH	↑	↓	→	→	↓	↓	↑
Cortisol	↑	↑	→	↑	↓	↓	↓
Epinephrine	↑	↓	↓	↑	↓	↓	→
Thyroxine	↑	↓	↑	↑	↑	↓	→

- glucocorticoids reduce muscle and adipose tissue glucose utilization.

2 Fat metabolism
- glucocorticoids increase lipolysis;
- glucocorticoids increase plasma free fatty acids.

3 Protein metabolism
- glucocorticoids accelerate protein catabolism;
- glucocorticoids are "protein wasting" in the long term.

EPINEPHRINE

1 Carbohydrate metabolism
- epinephrine increases blood glucose concentration;
- epinephrine increases liver glycogenolysis;
- epinephrine increases muscle glycogenolysis;
- epinephrine increases gluconeogenesis.

2 Fat metabolism
- epinephrine increases lipolysis in adipose tissue;
- epinephrine increases plasma free fatty acid concentration.

3 Protein metabolism
- epinephrine increases gluconeogenesis.

These effects of hormones on intermediary metabolism are summarized in Table 9.6.3.

This table is not so formidable as it first appears. First, all of the listed hormones save insulin raise blood glucose. Because of the liver's importance in raising blood glucose, their effect on the liver is just the opposite: insulin raises liver glycogen and all others lower it. The one exception is cortisol because it raises blood glucose mainly through gluconeogenesis. Similarly, the effects on plasma glucose are opposite to the effects on fat stores: if blood glucose goes up, fat stores go down, and vice versa, with one exception: epinephrine mobilizes both carbohydrate and lipid stores.

Clinical application: Pheochromocytoma

Pheochromocytoma is an excess secretion of epinephrine and norepinephrine usually caused by a tumor of the adrenal medulla but sometimes due to extraadrenal production. Symptoms include elevated heart rate, palpitations, elevated blood pressure, anxiety resembling a panic attack, headache, excessive sweating, elevated blood glucose, and pallor. This is a rare condition, with about 1000 cases diagnosed in the United States each year, with a prevalence of 2–8 per million persons. It typically strikes in young to mid-adult persons. The disease is often associated with intermittent rather than continuous secretion of epinephrine, so that persons suffer sporadic attacks with a classic triad of severe headaches, palpitations, and diaphoresis (excessive sweating).

Diagnosis relies on high plasma levels of metanephrine or 24 h urine collections tested for epinephrine, total metanephrines, and creatinine. The purpose of measuring creatinine is to normalize the values for undercollection of urine. Plasma levels of epinephrine are unreliable because of the sporadic nature of the disease and the short half-life of circulating catecholamines.

Treatment is generally surgical. Preoperative care is essential as the victims are generally volume depleted. Patients are typically volume expanded with a high Na^+ diet and then treated with α blockers, followed by β blockers prior to surgery.

SUMMARY

The adrenal medulla is essentially a ganglion of the sympathetic nervous system that releases neurotransmitter into the blood instead of near local targets. Preganglionic sympathetic nervous fibers originating mainly in the thoracic spinal cord reach the adrenal medulla through the splanchnic nerves, and release acetylcholine onto chromaffin cells in the adrenal gland,

causing release of epinephrine into the blood; the epinephrine is then transported to distant targets. Epinephrine is synthesized from tyrosine in the sequence tyrosine–dihydroxyphenylalanine–dopamine–norepinephrine–epinephrine. Circulating epinephrine and norepinephrine are degraded by catechol-*O*-methyl transferase (COMT) and monoamine oxidase (MAO). A variety of stimuli increase epinephrine secretion including hypoglycemia, hypovolemia, hypotension, fear and anxiety, pain, and trauma.

The effects of epinephrine and norepinephrine are mediated through adrenergic receptors, of which there are at least five types. The α_1 receptors work through a G_q mechanism that activates smooth muscle contraction mainly in the arterioles of skin, GI system and kidney, and the urethral sphincter. Adrenergic α_2 receptors activate a G_i mechanism. All of the β adrenergic receptors exert their effects through a G_s mechanism.

The overall effect of adrenergic stimulation is to prepare the body for emergency action. The pupils dilate (α_1 receptors), blood pressure increases, bronchioles dilate (β_2 receptors), blood flow to inessential organs is reduced, heart rate and contractility are increased, and stored metabolic fuels, glycogen and triglycerides, are mobilized to increase plasma glucose and free fatty acids for metabolism.

REVIEW QUESTIONS

1. Where is the adrenal gland? Where is the medulla? What does it secrete? What stimulates its secretion?
2. What is the proportion of epinephrine and norepinephrine typically secreted by the adrenal gland?
3. From what amino acid is epinephrine synthesized?
4. What are adrenergic receptors? What mechanism is used by α_1 receptors, α_2 receptors, and β receptors?
5. Where are α_1 and β receptors located?
6. What effect does epinephrine have on heart rate, contractility, blood pressure, glucose levels, airway caliber, lipid mobilization, and liver glycogen stores? What is the mechanism in each of these?
7. Which hormones lower blood glucose? Which hormones raise it?