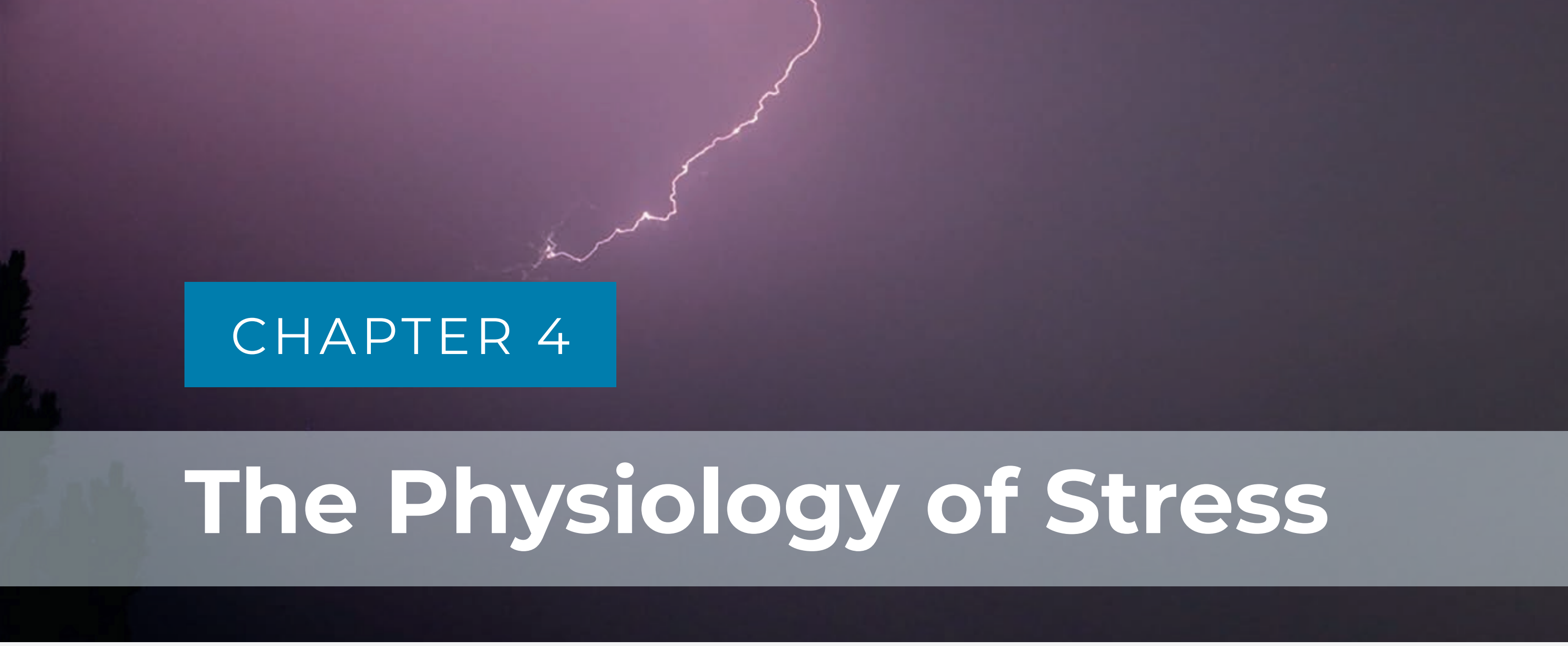

CHAPTER 4

The Physiology of Stress

It's not that stress kills us, it is our reaction to it that kills us.

—Hans Selye

CHAPTER LEARNING OBJECTIVES

Upon reading this chapter, the reader will be able to:

1. Identify the three layers of the brain related to the central nervous system.
2. Articulate the difference between the sympathetic and parasympathetic nervous systems.
3. Explain the importance of the vagus nerve associated with the relaxation response.
4. Explain the role of the endocrine system during the stress response.
5. List the three pathways associated with the stress response.
6. Explain new insights of brain physiology, including effect of stress on the amygdala and neuroplasticity.

Hans Selye's discovery of a direct relationship between chronic stress and the excessive wear and tear throughout the body laid the foundation for a clearer understanding of how physiological systems work in an extremely complex and integrative way. Perhaps because of this discovery and the fact that physical deterioration is so noticeable, much attention has been directed toward the physiology of stress. This chapter will take you through some basic concepts that explain the physiological dynamics involved with the stress response—specifically, the immediate, intermediate, and prolonged effects of stress on the body. These processes will be explained in terms of "pathways" that prompt the systematic and integrative steps of the stress response into action. Because physiology involves specific nomenclature outside the realm of your everyday vocabulary, you may find the nature of this chapter to be very specific and its contents very detailed. Most likely it will merit more than one reading to fully grasp, understand, and appreciate how the body responds to stress. The importance of a strong familiarity with human physiology as influenced by stressful stimuli becomes evident when the necessary steps are taken to effectively deal with the symptoms they produce, especially when using relaxation techniques. For example, it is important to know how the body functions when using specific imagery, visualization, music therapy, autogenic training, progressive muscular relaxation, and biofeedback.

In many circles, this topic of study is referred to as **psychophysiology**. This term reflects the fact that a sensory stimulus (perceived threat) that prompts the stress response must be processed at the mental level before it can cascade down one or more physiological pathways. In other words, the term

Psychophysiology A field of study based on the principle that the mind and body are one, where thoughts and perceptions affect potentially all aspects of physiology.

psychophysiology suggests that there is a mind–body relationship and supports the theory that many diseases and illnesses are psychosomatic, meaning that their origins lie in the mind through the higher brain centers. Although the mind–body dualism suggested by Descartes is no longer a viable model for a complete understanding of human physiology, to hold an appreciation of the "whole person" we must first examine the parts to understand how they connect to that whole.

Three systems are directly involved with the physiology of stress: the nervous system, the endocrine system, and the immune system, all of which can be triggered by perceived threats.

The Central Nervous System

The nervous system can be divided into two parts: the **central nervous system (CNS)**, which consists of the brain and spinal cord, and the peripheral nervous system (PNS), comprising all neural pathways to the extremities. The human brain is further divided into three levels: the vegetative level, the limbic system, and the neocortical level (**Fig. 4.1**).

The Vegetative Level

The lowest level of the brain consists of the reticular formation and the brain stem. The reticular formation, or more specifically the fibers that make up the **reticular activating system (RAS)**, is the link between the brain and the spinal cord. For this reason, it is considered the bridge joining the mind (brain) and the body as one; the RAS functions as a communications link between the mind and the body (**Fig. 4.2**). The brain stem, consisting of the pons, medulla oblongata, and mesencephalon, is responsible for involuntary functions of the human body, such as heartbeat, respiration, and vasomotor activity. It is considered the "automatic pilot" of the brain because it is responsible for maintaining the body's vital organs and vegetative processes at all times. This level is thought to be the most primitive section of the human brain because this portion of the brain is similar to those of all other mammals.

The Limbic System

The second, or midlevel, portion of the brain is the **limbic system**. The limbic system is the emotional control center. Several tissue centers in this level are directly responsible for the biochemical chain of events that constitutes the stress response Cannon observed in the early twentieth century. The limbic system consists of the thalamus, the hypothalamus, the amygdala, and the pituitary gland, which is also known as the master endocrine gland. These four glands work in unison to maintain a level of

Central nervous system (CNS) Portion of the nervous system that consists of the brain and the spinal cord.

Reticular activating system (RAS) The neural fibers that link the brain to the spinal column.

Limbic system The midlevel of the brain, including the hypothalamus and amygdala, that is thought to be responsible for emotional processing.

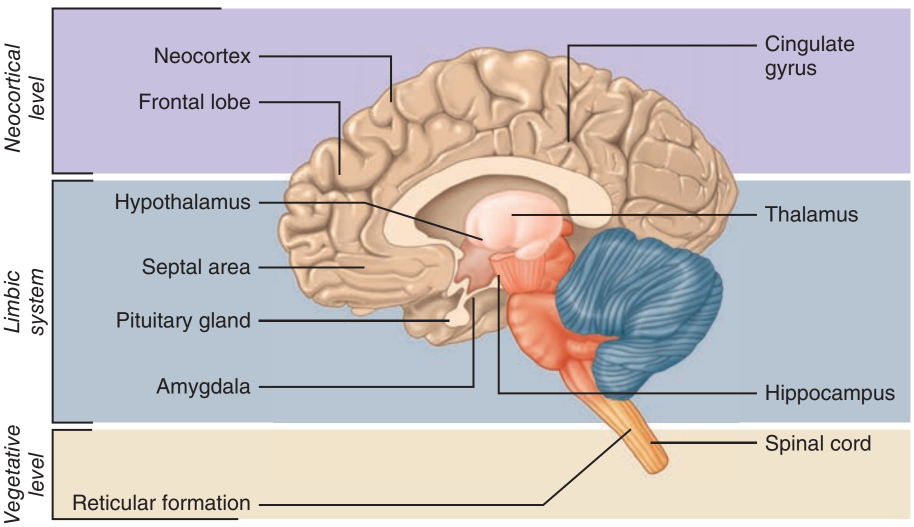

Figure 4.1 Three levels of the human brain: vegetative level, limbic system, and neocortical level.

Figure 4.2 Brain physiology at work.

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homeostasis within the body. For example, it is the hypothalamus that controls appetite and core body temperature. The hypothalamus also appears to be the center that registers pain and pleasure; for this reason, it is often referred to as the "seat of emotions." The combination of these functions in the hypothalamus may explain why hunger decreases when core body temperature increases in extreme ambient heat, or why appetite diminishes when you are extremely worried. This also explains why tempers (and violent crimes) flare up on extremely hot days during the summer months, as crime statistics prove each year. Fear is first registered in the amygdala. When a threat is encountered, the hypothalamus carries out four specific functions: (1) it activates the autonomic nervous system; (2) it stimulates the secretion of adrenocorticotropic hormone (ACTH); (3) it produces vasopressin, which is also called antidiuretic hormone (ADH); and (4) it stimulates the thyroid gland to produce thyroxine. All of these will be discussed in greater detail later.

The Neocortical Level

The neocortical level, or neocortex, is the highest and most sophisticated level of the brain. It is at this level that sensory information is processed (decoded) as a threat or a nonthreat and where cognition (thought processes) takes place. Housed within the neocortex are the neural mechanisms allowing one to employ analysis, imagination, creativity, intuition, logic, memory, and organization. It is this highly developed area of brain tissue that is thought to separate humans from all other species.

As Figure 4.1 illustrates, the positions of these structures are such that a higher level can override a lower level of the brain. Thus, conscious thought can influence emotional response, just as conscious thought can intercede in the involuntary control of the vegetative functions to control heart rate, ventilation, and even blood flow. This fact will become important to recognize when learning coping skills and relaxation techniques designed to override the stress response and facilitate physiological homeostasis.

Separate from the CNS is a network of neural fibers that feed into the CNS and work in close collaboration with it. This neural tract, the PNS, comprises two individual networks. The first is the somatic network, a bidirectional circuit responsible for transmitting sensory messages along the neural pathways between the five senses and the higher brain centers. These are called the efferent (toward periphery) and afferent (toward brain) neural pathways. The second branch of the PNS is the **autonomic nervous system (ANS)**. The ANS regulates visceral activities and vital organs, including circulation, digestion, respiration, and temperature regulation. It received the name autonomic because this system can function without conscious thought or voluntary control, and does so most, if not all, of the time.

Research conducted by endocrinologist Bruce McEwen (2002; McEwen et al., 1999) indicates that, initially, a stressful encounter is etched into the memory bank (so as to avoid it down the road), but that repeated episodes of stress decrease memory by weakening and shrinking hippocampal brain cells. Chronic stress is thought to wither the fragile connection between neurons in this part of the brain, resulting in "brain shrinkage" (**Box 4.1**).

Until recently it was believed that, unlike the voluntary somatic system involved in muscle movement, the ANS could not be intercepted by conscious thought, but now it is recognized that both systems can be influenced by higher mental processes (Green, 2010; Green & Green, 1989). The ANS works in close coordination with the CNS to maintain a favorable homeostatic condition

Autonomic nervous system (ANS) Subdivision of the peripheral nervous system that consists of the sympathetic (arousal) and parasympathetic (relaxed) nervous systems. This part of the central nervous system requires no conscious thought; actions such as breathing and heart rate are programmed to function automatically.

Box 4.1 A Closer Look at Panic Attacks

ABC's Nightline coanchor Dan Harris didn't plan on starting a daily meditation practice. In fact, it was the furthest thing from his mind, until he experienced a series of on-air panic attacks. In his search for peace of mind (and as a way to keep his career intact), he stumbled upon mindfulness meditation. In his best-selling book, *10% Happier* (2019), he not only tells his story, but uses his position of national notoriety to explain that meditation is a skill that everyone should include in their list of daily habits. For Dan Harris, it was a panic attack, but everyone today is riding a wave of adrenaline-based information overload.

Anyone can have a rush of fear come over them, but some people are prone to a more severe experience, often called a panic attack. A panic attack is often described as "the stress response on steroids." In short, it is the response of the sympathetic nervous system. Panic attacks can occur in any place, at any time, and often out of the blue. Physical symptoms of a panic attack include hyperventilation, a racing heart, sweating, chest pain, a choking feeling, nausea, chills, dizziness or feeling faint, tingling sensations, and muscle tremors or shaking. Some people describe it as feeling like they are having a heart attack. Other symptoms include a feeling of impending death, loss of sanity, or having a "nervous breakdown." Panic attacks are most common in early adulthood, but can occur at any age. Women are more prone to this condition than men (Casabianca 2022).

Panic attacks occur abruptly. They may seem like they last forever to those who experience them, but the duration is typically about 10 to 20 minutes (in rare cases over an hour). What is the cause of a panic attack? Although they seem to come out of the blue, every panic attack is triggered by some decoded sensory stimulus (or memory) that creates an intense fear or apprehension about some future event. Ironically, some panic attacks are brought on by fear of having another panic attack (Maher, 2022).

Some experts think that panic attacks may be hereditary, whereas others suggest that they may be due to abnormalities (hypersensitivity) in the amygdala and/or hypothalamus that control the fight-or-flight response (Maher, 2022). Some panic attacks are associated with substance abuse, but the vast majority are caused by stress (the interpretation of an exaggerated threat).

What is the best way to cope with a panic attack? The best strategy is to bring yourself back into the present moment and ground yourself. Experts suggest sitting on the floor with your back up against the wall, and then placing your hands and your feet firmly on the ground and taking several deep breaths. If you wish, repeat to yourself the phrase, "My hands and feet are firmly on the ground." If a panic attack occurs while driving, pull over, stop the car, place your hands down by your waist, and repeat the phrase, "My hands and feet are fully grounded." You can train yourself to avoid or minimize the effects of panic attacks by engaging in both effective coping skills and relaxation techniques (McDonagh, 2015).

throughout the body. Two branches of the ANS act to maintain this homeostatic balance, the **sympathetic** and **parasympathetic nervous systems**, both of which are activated by the hypothalamus. Most organs are innervated (stimulated) by nerve fibers of both the sympathetic and parasympathetic systems.

The Autonomic Nervous System

The Sympathetic and Parasympathetic Nervous Systems

The sympathetic nervous system is responsible for the responses associated with the fight-or-flight response (**Fig. 4.3**). Through the release of substances called catecholamines, specifically **epinephrine** (adrenaline) and **norepinephrine** (noradrenaline), at various neural synapses, a series of events occurs in several organ tissues to prepare the body for rapid metabolic change and physical movement. Sympathetic drive is associated with energy expenditure (e.g., jogging), a process known as **catabolic functioning**, whereby various metabolites are broken down for energy in

Sympathetic and **Parasympathetic nervous systems** The branch of the central nervous system that triggers the fight-or-flight response when some element of threat is present.

Epinephrine A neurochemical referred to as a catecholamine that is responsible for immediate physical readiness for stress, including increased heart rate and blood pressure. It works in unison with norepinephrine.

Norepinephrine A neurochemical referred to as a catecholamine that is responsible for immediate physical readiness to stress including increased heart rate and blood pressure. It works in unison with epinephrine.

Catabolic functioning A metabolic process in which metabolites are broken down for energy in preparation for, or in the process of, exercise (fight or flight).

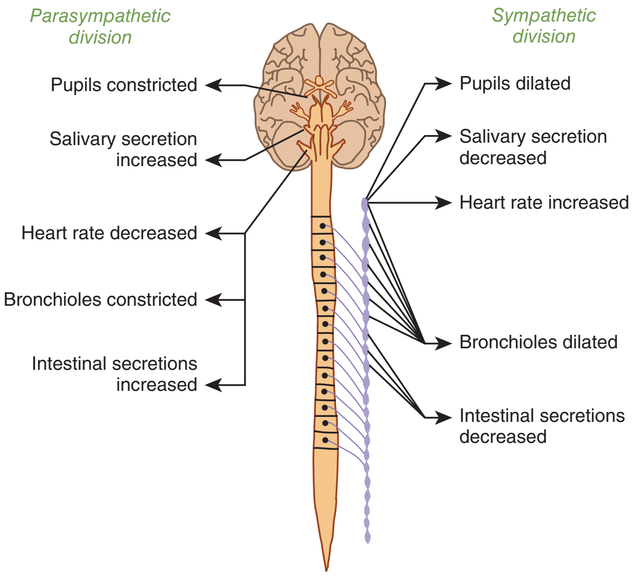

Figure 4.3 The sympathetic and parasympathetic systems. Internal organs are typically innervated by neural fibers from both sympathetic and parasympathetic divisions.

preparation for movement. It is this release of epinephrine and norepinephrine that causes the acceleration of heart rate, the increase in the force of myocardial contraction, vasodilation of the arteries throughout working muscles, vasoconstriction of arteries to nonworking muscles, dilation of pupils and bronchi, increased ventilation, reduction of digestive activity, released glucose from the liver, and several other functions that prepare the body to fight or flee. It is the sympathetic system that is responsible for supplying skeletal muscles with oxygenated, nutrient-rich blood for energy metabolism. Currently, it is thought that norepinephrine serves primarily to assist epinephrine, because the ratio of these two chemical substances released at neural synapses is 5:1 epinephrine to norepinephrine during the stress response. The effects of epinephrine and norepinephrine are very short, lasting only seconds. Because of their rapid release from neural endings, as well as their rapid influence on targeted organ tissue, the effects of the sympathetic nervous system are categorized as **immediate**.

12 Ways to Calm an Over-Active Sympathetic Nervous System

Here are 12 ideas to bring you into the present moment and help calm your sympathetic nervous system by engaging the vagus nerve and the parasympathetic nervous system:

1. Breathe a deep sigh, repeat after 10 seconds.
2. Hum a favorite tune for a few minutes.
3. Laugh at something funny, repeat often.
4. Doodle on paper with a pen or pencil for a few minutes.
5. Scan your body head to toe to release muscle tension, release tension as needed.
6. Sing the chorus of one of your favorite songs.
7. Aromatherapy (inhale a calming scent such as lavender or mint).
8. Listen to calm music (best if it's music without lyrics).
9. Hold a yoga pose or do a muscle stretch for 30 seconds.
10. Pet an animal (cat, dog).
11. Try body tapping, starting with the forehead, checks, upper lip, and chin.
12. Step outside into nature, feeling the sunshine on your face for 30 to 60 seconds.

Just as the sympathetic neural drive is associated with energy expenditure, the parasympathetic drive is responsible for energy conservation and relaxation. This is referred to as **anabolic functioning**, which allows the body cells to regenerate or grow. The parasympathetic nervous system is dominated by the 10th cranial nerve (the **vagus nerve**), which, in turn, is influenced by the brain stem. When activated, the parasympathetic nervous system releases **acetylcholine** (ACh), a neurochemical agent that decreases metabolic activity and returns the body to homeostasis. The influence of the parasympathetic drive is associated with a reduction in heart rate, ventilation, blood pressure, muscle tension, and several other functions. Both systems are partially active at all times; however, the sympathetic and parasympathetic systems are mutually exclusive in that they cannot dominate visceral activity simultaneously. These two systems allow for the precise regulation of visceral organ activity, much like the use of the accelerator and brake when driving. Sympathetic arousal, like a gas pedal pushed to the car floor, becomes the dominant force during stress, and parasympathetic tone holds

Immediate (effects of stress) A neural response to cognitive processing in which epinephrine and norepinephrine are released. The response lasts only seconds.

Anabolic functioning A physiological process in which various body cells (e.g., muscle tissue) regenerate or grow.

Vagus nerve The nerve that represents the main component of the parasympathetic system responsible for the regulation of internal organ function. Also known as the 10th cranial nerve. It creates vagal tone to promote homeostasis.

Acetylcholine A chemical substance released by the parasympathetic nervous system to help the body return to homeostasis from the stress response.

Stress with a Human Face


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George is 19 years old, yet the stress he has experienced in his first year serving as a Marine in Iraq makes him seem at least 10 years older—from the lines on his face to the tenor of his voice. I met George in Honolulu International Airport. We were both waiting to fly home to Colorado: me from vacation, George from the war. A delay in our scheduled departure allowed a friendly conversation at the gate's lounge, but for the most part, I just listened.

"You don't know what stress is until you are smack in the middle of a war. Your body is on alert 24 hours a day. You are constantly aroused even when you're trying to relax. You can never fully relax in a war zone. You can feel your heart pounding in your chest nearly all the time; a 24/7 adrenaline rush! I guess you just get used to it. All of your senses are heightened—never knowing what to expect, but always ready for something. This is my second visit home, and I am on guard right now as we speak. When I go into a restaurant back home, the first thing I do is scout out all the exits. It's survival mode. You can never be relaxed completely in a war zone. Sadly, this mentality stays with you outside the war zone, like right now.

"The stress of war is incredible. It only gets worse when your patrol has encountered an IED [improvised explosive device]. I have lost several buddies to these. You go right into reaction mode: Stop the bleeding! They train us all in emergency first aid, and you just pray you never have to use it. When one of these goes off you don't have time to be afraid. You just react. Stop the bleeding, whoever's bleeding, whatever's bleeding. Usually it's an arm or a leg blown off. I've seen stuff that would curl your hair. No matter what they tell you in basic training, there is nothing that can prepare you for war. I know several guys with PTSD [posttraumatic stress disorder]. I didn't believe in PTSD until I got to Iraq. I have crazy dreams at night. They say having nightmares is part of PTSD, but how can you not? After all it is a war zone ... your mind is processing all that's gone on in the course of the previous day. War is not the normal course of a typical day for most people, and definitely not Americans.

"Yes, they [the military leaders] hand out psychotropic drugs to keep soldiers up. Exponential Adrenaline Rush! I don't take 'em. I need all my wits about me when I am out there, outside the Green Zone ... even inside the Green Zone. ... Believe me ... war is the ultimate stress zone."

Box 4.2 Self-Care Immediate Stress Relief Toolbox

Engage Your Vagal Tone

Activating the vagus nerve helps intercept the stress response and calm the body. Try this: Close your eyes and take a slow deep belly breath. Repeat. After several slow deep breaths, sense how your body feels. Humming also activate the vagal nerve. Try humming a few bars of your favorite song.

Hormonal Imbalances

The endocrine system is an amazing yet delicate system of chemical properties aligned to ensure physiological homeostasis. The stress hormone dehydroepiandrosterone (DHEA), for example, is secreted from the adrenal gland. DHEA is also known as a precursor sex hormone that decreases in both production and secretion throughout the aging process. Some had speculated that supplementation of DHEA might increase stamina and memory and decrease the aging process in much the same way as the antioxidants beta-carotene, vitamin C, vitamin E, and selenium. Although DHEA supplements are considered beneficial for some, several studies have revealed only slight changes in these aspects with DHEA supplementation in either animals or humans (Carter, 2018). Supplementation is recommended only on the advice of your physician.

Serotonin and **melatonin** are not stress hormones, but they do seem to have an effect on mood. Decreases in both serotonin and melatonin are thought to be related to bouts of depression. Many things affect serotonin levels in the brain—from the natural and synthetic chemicals in the foods you eat, to the amount of sunlight you receive in the course of a day, to perhaps things we still don't know. Research is inconclusive about how serotonin affects mood, but it certainly plays a significant role. Most likely, stress affects serotonin levels as well (Bancroft, 2022).

Serotonin A neurotransmitter that is associated with mood. Low levels of this neurotransmitter are thought to be related to depression.

Melatonin A hormone secreted in the brain that is involved in regulating sleep, mood, and perhaps several other aspects of physiology and consciousness.

influence over the body at all other times to promote homeostasis. In other words, you cannot be physically aroused and relaxed at the same time (Fig. 4.3).

However, there are exceptions to the dynamics of these biochemical reactions. For example, it is sympathetic nerves, not parasympathetic nerves, that release ACh in the sweat glands to decrease core body temperature during arousal. In addition, stimulation of the salivary glands by the sympathetic and parasympathetic systems is not antagonistic; both influence the secretion of saliva. In addition, all blood vessels are influenced by sympathetic dominance, with the exception of the vasculature of the penis and clitoris, which is activated by parasympathetic innervation.

Rest and Digest: Thank You, Vagus Nerve!

When it comes to stress management, your vagus nerve may be your best friend. The vagus nerve is the 10th cranial nerve, and it is considered the longest nerve in the body. It begins at the base of the brain and runs the length of the spinal column to the internal organs of the abdomen and pelvis. More important, it is the vagus nerve that provides what is known as vagal tone, or the relaxation response, to the body. For this reason, the vagus nerve is sometimes referred to as the "queen of the parasympathetic nervous system," and from a neurological perspective, it is the tangible link between mind and body. Stimulating the vagus nerve decreases resting heart rate, blood pressure, and other physiological responses associated with the fight-or-flight response (**Box 4.3**). Deep breathing is known as one of the quickest ways to stimulate the vagus nerve, as is listening to some types of relaxing music (music therapy). "Fight or flight" may be the mantra for stress, but the mantra for the flip side of stress is "rest and digest." The vagus nerve sets the pathway for rest and digest into motion. The best way to activate the vagus nerve is with slow deep breaths to increase vagal tone (Heid, 2019; Vitale, 2019; Zimmerman 2019).

The Endocrine System

The endocrine system consists of a series of glands located throughout the body that regulate metabolic functions requiring endurance rather than speed. The endocrine system is a network of glands, hormones, circulation, and target organs. Endocrine glands manufacture and release biochemical substances called hormones. Hormones are chemical messengers made up of protein compounds that are programmed to attach to specific cell receptor sites to alter (increase or decrease) cell metabolism. Hormones are transported through the bloodstream from the glands that produced them to the target organs they are called upon to influence. The heart, skeletal muscle, and arteries are common targets for hormones that regulate metabolic functions.

The glands that are most closely involved with the stress response are the pituitary, thyroid, and adrenal glands. The **pituitary gland** is called the "master gland" because it manufactures several important hormones that then trigger the release of hormones in other organs. The **hypothalamus**, however, appears to have direct influence over the pituitary gland (**Fig. 4.4**). The thyroid gland increases the general metabolic rate.

Box 4.3 The Amygdala Revisited

The brain has many regions involved with consciousness, stress, and behavior. Over the past several years, the small almond-shaped portion of the brain known as the amygdala, a key structure in the limbic system, has proved to be of great interest with regard to functional magnetic resonance imaging (fMRI) research and stress. For decades scientists knew the amygdala was associated with aggressive behavior (anger), as well as feelings and behavior associated with fear and anxiety. Additionally, studies have found that the amygdala is responsible for the formation and consolidation of memories associated with events that provoked a strong emotional response (including anger and fear). The researchers suggest that these memories are imprinted via the neural synapses, perhaps as an ancestral survival dynamic (e.g., "beware of the rattlesnake") (McEwan, 2002; Peters, 2017). Through a complicated dynamic between the amygdala and the hippocampus, specific memories of past events can reprise the fight-or-flight response, merely by thinking about them. More recent findings have also linked the amygdala to binge drinking, most likely associated with stress (Crane et al., 2018).

Pituitary gland An endocrine gland often referred to as the "master gland" located below the hypothalamus that, upon command from the hypothalamus, releases ACTH and then commands the adrenal glands to secrete their stress hormones.

Hypothalamus Often called the "seat of the emotions," this endocrine gland is involved with emotional processing. When a thought is perceived as a threat, it secretes a substance called corticotropin-releasing factor (CRF) to the pituitary gland to activate the fight-or-flight response.

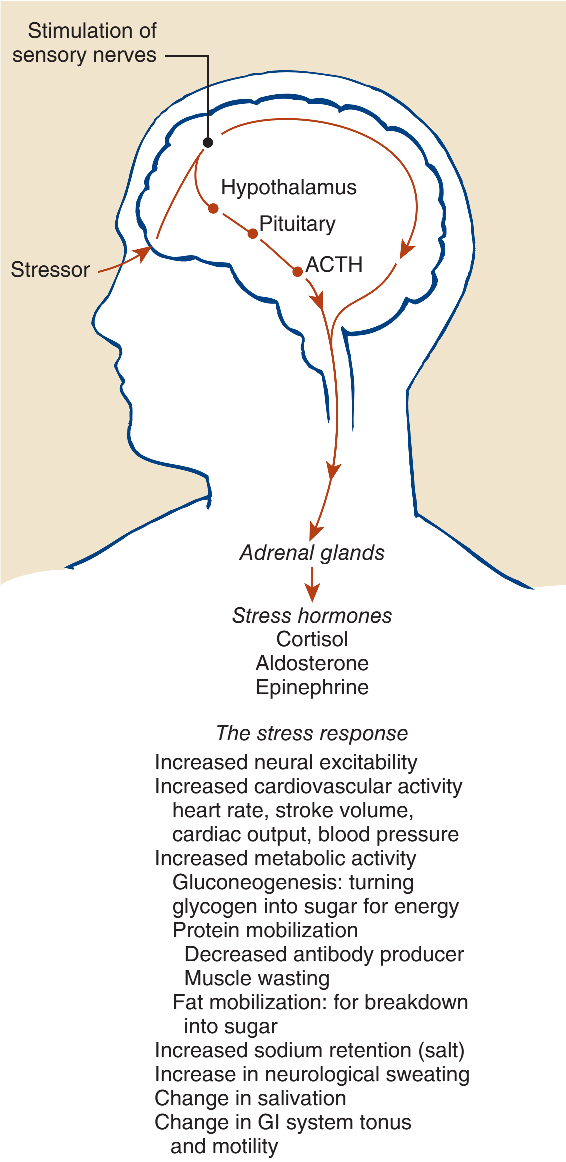

Figure 4.4 The physiological response to stress.

Perhaps the gland that has the most direct impact on the stress response, however, is the **adrenal gland** (**Fig. 4.5**). The adrenal gland, a cone-shaped mass of tissue about the size of a small grapefruit, sits on top of each kidney. The adrenal gland (also known as the "stress gland") has two distinct parts, each of which produces hormones with very different functions. The exterior of the adrenal gland is called the **adrenal cortex**, and it manufactures and releases hormones called **corticosteroids**. There are two types of corticosteroids: glucocorticoids and mineralocorticoids. **Glucocorticoids** are a family of biochemical agents that includes cortisol and cortisone, with cortisol being the primary one. Its function is to help to generate glucose, through the degradation of proteins (amino acids) during a process called gluconeogenesis in the liver, as an energy source for both the central nervous system

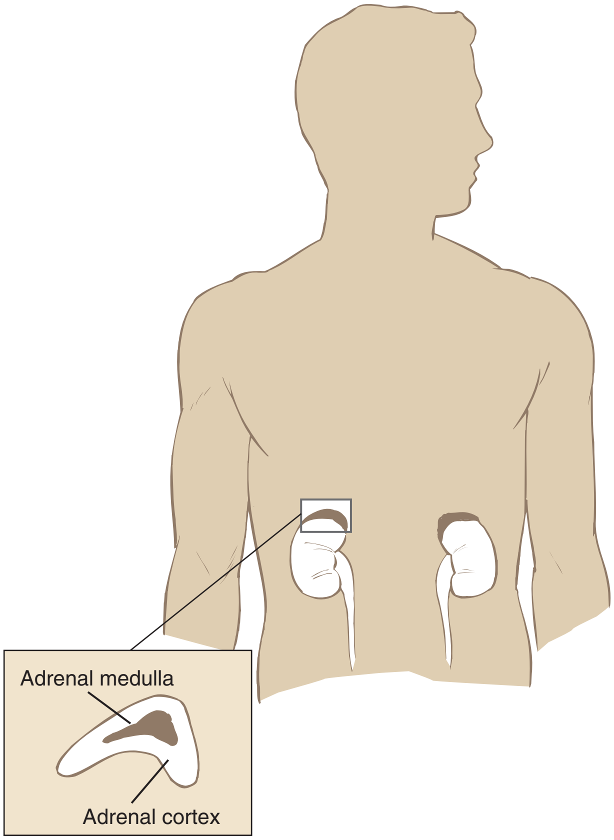

Figure 4.5 The adrenal gland, made up of the adrenal cortex and medulla, sits on the top of each kidney and is cone-shaped in appearance.

(the brain) and skeletal muscles during physical exercise. A metaphor to illustrate this process is the situation in which you resort to burning the furniture to keep warm once you exhaust your supply of firewood. **Cortisol** is also involved in the process of lipolysis, or the mobilization and breakdown of fats (fatty acids)

Adrenal gland The endocrine glands that are located on top of each kidney that house and release several stress hormones, including cortisol and the catecholamines epinephrine and norepinephrine. This gland is known as the "stress gland."

Adrenal cortex The portion of the adrenal gland that produces and secretes a host of corticosteroids (e.g., cortisol and aldosterone).

Corticosteroids Stress hormones released by the adrenal cortex, such as cortisol and cortisone.

Glucocorticoids A family of biochemical agents that includes cortisol and cortisone that are produced and released from the adrenal gland.

Cortisol A stress hormone released by the adrenal glands that helps the body prepare for fight or flight by promoting the release of glucose and lipids in the blood for energy metabolism.

for energy. It is well understood that prolonged increased levels of cortisol suppress the immune system (**Box 4.4**). In fact, organ transplant patients are prescribed cortisol to intentionally suppress the immune system so the transplanted organ won't be rejected. It appears that cortisol metabolizes (degrades) white blood cells. As the number of white blood cells decreases, the efficiency of the immune system decreases, setting the stage for illness and disease. Other studies have found that increased cortisol can direct excess amounts of cholesterol into the blood, thereby adding to associated artery plaque buildup and leading to hypertension and coronary heart disease (Lee et al., 2015). **Mineralocorticoids**, specifically aldosterone, are secreted to maintain plasma volume and electrolyte (sodium and potassium) balance, two essential functions in the regulation of circulation. (The exact mechanisms will be discussed later in this chapter.)

The inside of the adrenal gland is called the **adrenal medulla**. This portion of the gland secretes catecholamines (epinephrine and norepinephrine), which act in a similar fashion as those secreted at the endings of sympathetic nerves. The adrenal medulla releases 80 percent epinephrine and 20 percent norepinephrine. Under the influences of stress, up to 300 times the amount of epinephrine can be found in the blood compared to the amount in samples taken at rest (Sapolsky, 2010) (**Box 4.5**).

Box 4.4 Adrenal Fatigue and Adrenal Failure

With the alarming increase in chronic fatigue syndrome, the word in some medical circles is that many Americans also suffer from adrenal fatigue as a result of prolonged stress. What is adrenal fatigue? Chronic stress causes the adrenal glands to burn out from prolonged production of cortisol. Signs of exhaustion and the inability to produce and release the host of catecholamines and hormones needed for fight or flight appear to give credence to Hans Selye's general adaptation syndrome. Symptoms of adrenal insufficiency include fatigue, dizziness, low blood sugar (resulting in cravings and subsequent weight gain), poor libido, and depression. Weakened functioning of the adrenal glands has been associated with the incidence of autoimmune diseases, ranging from chronic fatigue syndrome and lupus to rheumatoid arthritis. Because of the complexities of human physiology, poor adrenal function has also been associated with aggravating the symptoms of menopause. Addison's disease is the name given to those with adrenal failure, a condition where the adrenal glands are no longer able to produce and secrete the necessary hormones for metabolic function (Campbell, 2019; Luther, 2015).

Data from Campbell, B. (2019). Do I have adrenal fatigue? Independently Published; Luther, M. (2015). The everything guide to adrenal fatigue. Simon & Schuster.

Mineralocorticoids A class of hormones that includes aldosterone that act to maintain plasma volume and electrolyte balance.

Adrenal medulla The portion of the adrenal gland responsible for the secretion of epinephrine and norepinephrine.

Box 4.5 Multitasking: Wired for Stress

The ability to multitask in this age of high technology certainly has its merits, but less recognizable are its long-range pitfalls. Sociologists are becoming increasingly alarmed by obsession with and addiction to smartphones, text messages, email, podcasts, and the Web among people of all ages. Sociologists and psychologists see dangers of a hyperkinetic mind that doesn't know how to unplug, turn off, and relax (Alter, 2018; Jackson, 2018; Newport, 2019). Habitual multitasking may condition the brain to an overexcited state, making it difficult for people to focus even when they want or need to. Add a dearth of patience to the mix with this Wi-Fi generation, and the stress response is compounded dramatically. As people begin to lose concentration skills, the end result is "chronic mental antsyness" (frustration).

The Myth of Multitasking

Sending a text message while watching (and voting for contestants on) *American Idol* and at the same time doing a Google search for research report content may seem like the height of organizational skills, but don't be fooled. Quantity is not quality. With the use of MRI technology, researchers, including Jordan Grafman, have identified one specific area of the brain's cortex, Brodmann's area 10, as the site specific for alternating attention from one task to another (Wallis, 2006). The prefrontal cortex, which houses Brodmann's area 10, is one of the last regions of the brain to mature and the first to decline as a result of the aging process. As such, youngsters up to age 22 and adults over the age of 60 do not multitask well. Research studies have revealed that when young adults perform two or more tasks simultaneously,

(continues)

Box 4.5 Multitasking: Wired for Stress *(continued)*

the amount of errors increases dramatically. Although there may be many causes for poor attention span (from the TV remote control to an abundance of toxic food chemicals), the combination of short attention span and the increased use of electronic devices becomes dangerous. The take-home message is that multitasking decreases efficiency (Wallis, 2006).

Although students may excel at locating and manipulating information via the Internet, their reach may be broad but ultimately quite shallow. Moreover, their ability to process the information in a deeper context is considered poor by most educational standards, states Claudia Koonz of Duke University: "It's like they have too many windows open on their hard drive. In order to have a taste for sifting through different layers of truth, you have to stay with the topic and pursue it deeply rather than go across the surface with your toolbar" (quoted in Wallis, 2006). What are the social implications of being wired for stress? Virtual conversations will never replace the nuances of face-to-face expressions and body language that humans have developed over thousands of years of cohabitation and community building. Experts have also noticed a decrease in interaction among family members with a rise in household electronic gadgets, further eroding the family structure. Furthermore, addiction to smartphones has even become a reason for marriage counseling and breakups (Winch, 2015). Studies on the topic of Alzheimer's support the theory that the brain needs stimulation to promote mental acuity. Stress research, however, validates the need for quiet time for the brain. When the brain is constantly stimulated (and overstimulated), these neurological impulses rewire the brain for perpetual stress (Alter, 2018).

Box 4.6 Self-Care Immediate Stress Relief Toolbox

Resetting the Stress Response: It has long been known that immediately after an animal survives a threat or attack, it will physically shake their entire body. It is thought that they do this to reset their nervous system, for they cannot maintain a heightened state of stress indefinitely. They must return to a sense of calm, foraging for food, or resting, etc. We can learn a lesson from this. Try it. Stand up, and shake your body. Initiate this coordinated shaking motion from your head, shoulders and hips for a few seconds. Then sit down and relax. Note how your body feels. Try this a few times throughout the day.

The Neuroendocrine Pathways

Evolutionary adaptations have provided several backup systems to ensure the survival of the human organism. Not all pathways act at the same speed, yet the ultimate goal is the same: physical survival. First, not only does the hypothalamus initiate activation of the sympathetic nervous system to cause an immediate effect (**Table 4.1**), but the posterior hypothalamus also has a direct neural pathway, called the sympathetic preganglionic neuron, that links it to the adrenal medulla. Next, upon stimulation by the posterior hypothalamus, the adrenal medulla secretes both epinephrine and norepinephrine. Once in the bloodstream, these catecholamines reinforce the efforts of the sympathetic drive, which has already released these same substances through sympathetic neural endings throughout the body. The release of epinephrine and norepinephrine from the adrenal medulla acts as a backup system for these biochemical agents to ensure the most efficient means of physical survival. The hormonal influences brought about by the adrenal medulla are called **intermediate stress effects**. Because their release is via the bloodstream rather than neural endings, travel time is longer (approximately 20 to 30 seconds), and unlike the release of these substances from sympathetic neural endings, the effects of catecholamines from the adrenal medulla can last as long as 2 hours when high levels of hormones are circulating in the bloodstream. These, along with hormones secreted from the adrenal gland, become a "toxic chemical cocktail" if they persist in the body for prolonged periods of time without being flushed out, primarily through exercise.

In addition, a third and potentially more potent system is available that joins the efforts of the nervous and endocrine systems to prepare the body for real or perceived danger if the perceived threat continues beyond several minutes. Neural impulses are received

Intermediate stress effects The hormonal response triggered by the neural aspects of the adrenal medulla that are released directly into the blood, lasting minutes to hours.

Table 4.1 Pathways of Stress Response

The body has several backup systems to help ensure physical survival. Here, these dynamics are broken down into categories based on the duration of their metabolic reactions.

Effects	Reaction	Time
Immediate effects	Epinephrine and norepinephrine from the sympathetic nervous system	2–3 seconds
Intermediate effects	Epinephrine and norepinephrine from the adrenal medulla	20–30 seconds, possibly minutes
Prolonged effects	ACTH, vasopressin, and thyroxine neuroendocrine pathways	Minutes, hours, days, or weeks

Modified from Allen, R. (1983). Human stress: Its nature and control. Burgess.

by the hypothalamus as potential threats create a chain of biochemical messages, which like a line of falling dominos cascade through the glands of the endocrine system. Because the half-life of these hormones and the speed of their metabolic reactions vary in length from hours to weeks in some cases, this chain of reactions is referred to as the **prolonged effect of stress**.

The ACTH Axis

Physiologically speaking, a biochemical pathway is referred to as an axis. In this section, we will discuss the ACTH axis. The other two axes, the **vasopressin axis** and the **thyroxine axis**, are covered in the following sections.

The **ACTH axis**, also known as the hypothalamic-pituitary-adrenal axis, or the **HPA axis** (**Fig. 4.6**), begins with the release of corticotropin-releasing factor (CRF) from the anterior hypothalamus. This substance activates the pituitary gland to

Prolonged effect of stress Hormonal effects that may take days or perhaps more than a week to be fully realized from the initial stress response.

Vasopressin axis A chain of physiological events stemming from the release of vasopressin, or antidiuretic hormone (ADH).

Thyroxine axis A chain of physiological events stemming from the release of thyroxine.

ACTH axis A physiological pathway whereby a message is sent from the hypothalamus to the pituitary, then on to the adrenal gland to release a flood of stress hormones for fight or flight.

HPA axis The hypothalamic-pituitary-adrenal axis, a term synonymous with the ACTH axis.

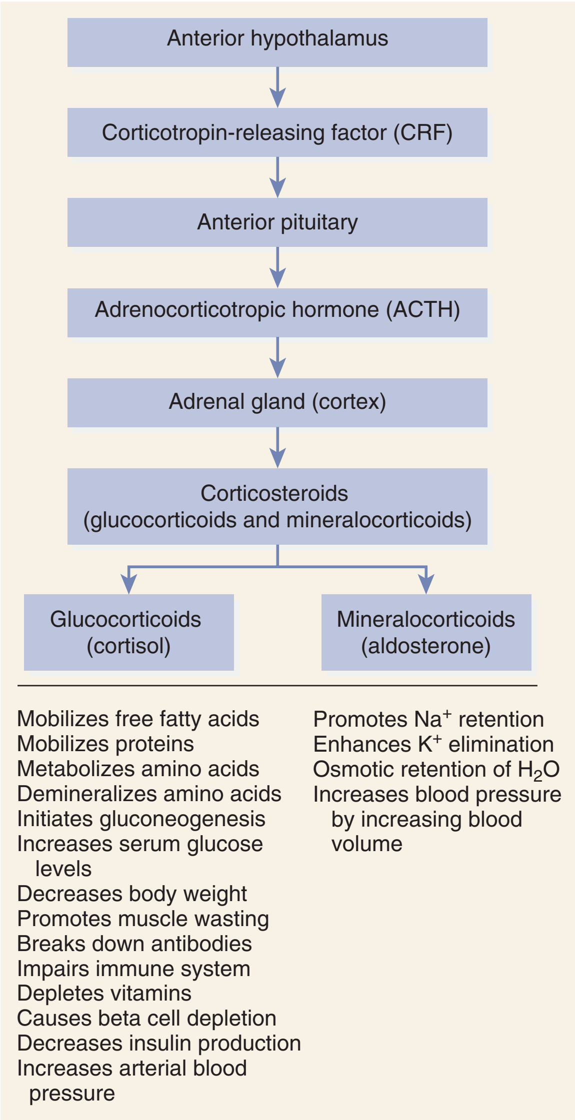

Figure 4.6 The ACTH axis.

release ACTH, which travels via the bloodstream to, in turn, activate the adrenal cortex. Upon stimulation by ACTH, the adrenal cortex releases a set of corticosteroids (cortisol and aldosterone) that act to increase metabolism and alter body fluids, and thus blood pressure. The effects of hormones released by the adrenal cortex are considered to be prolonged because they activate their functions for minutes to hours. Note that increased secretions of cortisol in the blood act primarily to ensure adequate supplies of blood glucose for energy metabolism. However, when increasingly high levels of cortisol are observed because of chronic stress, this hormone compromises the integrity of several physiological systems (**Box 4.7**).

Box 4.7 Insomnia and Brain Physiology

Brain chemistry is a complicated subject, and our understanding of it is embryonic at best, but some facts are clear with regard to how the brain works. Not only does an "active" mind release epinephrine and norepinephrine in the brain, compromising the ability to fall sleep, but other neurotransmitters—specifically, melatonin and serotonin—are affected by a host of daily rituals and behaviors, ranging from nutritional habits, caffeine intake, and sunlight exposure to smartphone use. Melatonin is a hormone secreted from the pituitary gland in the brain. This neurotransmitter is affected by real and artificial light and is thought to be associated with both sleep patterns and skin pigmentation. As daylight decreases, melatonin levels increase, giving rise to the belief that increases in melatonin help promote sleep. The brain neurotransmitter serotonin is partially affected by light. Decreases in light decrease serotonin levels, a factor that is thought to be associated with seasonal affective disorder (SAD) and depression.

Although the use of artificial evening light can alter serotonin levels, it can decrease melatonin levels, thus affecting natural sleep patterns (sleep patterns have changed dramatically since the turn of the twentieth century with the use of electricity). Smartphone use is thought to decrease melatonin with similar results. Increased consumption of carbohydrates (late-night snacks) also can increase serotonin levels, which may, in turn, affect melatonin levels. Medications for depression include selective serotonin reuptake inhibitors (SSRIs) that act to increase serotonin levels. This activity may, in fact, act to decrease melatonin levels, thus affecting a person's ability to get a full night's sleep (Seaward, 2016; Winter, 2017).

The Vasopressin Axis

Vasopressin, or antidiuretic hormone (ADH), is synthesized in the hypothalamus but is released by the pituitary through a special portal system. The primary purpose of vasopressin is to regulate fluid loss through the urinary tract. It does this in a number of ways, including water reabsorption and decreased perspiration. By altering blood volume, however, it also has a pronounced effect on stroke volume, or the amount of blood that is pumped through the left ventricle of the heart with each contraction. Consequently, vasopressin has a pronounced effect on blood pressure. Under normal circumstances, vasopressin regulates blood pressure by either increasing blood volume (changing the concentration of water in the blood) should it become too low, or decreasing blood volume when it becomes too high. Under the influence of chronic stress, however, many regulatory mechanisms in the body lose their ability to maintain physiological homeostasis. Consequently, the increased secretions of vasopressin produced under duress will increase blood pressure even when someone already has elevated resting values; this is known as hypertension. The purpose of vasopressin, as well as aldosterone, epinephrine, and norepinephrine, is to increase blood pressure to ensure that active muscles receive oxygenated blood, but under chronic stress in a resting state this hormonal response—the abundance of stress hormones—is literally overkill, leading to hypertension and ultimately death from coronary heart disease (CHD; **Box 4.8**).

Box 4.8 Physiology of Stress: The Take-Home Message

There is no doubt that the details of the physiology of stress can be overwhelming, but here is the take-home message: the stress response involves a cascade of chemicals/hormones in the body, most notably epinephrine and norepinephrine released from the neural endings of the sympathetic nervous system. Additionally, the stress hormone cortisol (secreted from the adrenal glands) plays a huge role in preparing the body for fight or flight. If stress persists, additional hormones are called into play. The strength of this stress hormone cocktail depends on the intensity and duration of the stressor(s), yet the effects can last far longer than the initial exposure/interpretation of the stressor. One notable effect of stress is that repeated stress tends to shrink brain cells. Medical science's love affair with functional magnetic resonance imaging continues to explore the brain under stress.

The Thyroxine Axis

Stimulation in the hypothalamus triggers the release of thyrotropic hormone–releasing factor (TRF). TRF is transported through a special portal system to the anterior portion of the pituitary, where it stimulates the secretion of thyrotropic hormone (TTH). Once in the bloodstream, TTH follows a path to the thyroid gland, which stimulates the release of two more hormones: thyroxine and triiodothyronine. The purpose of these two hormones is to increase overall metabolism, or the basal metabolic rate (BMR). Thyroxine is powerful enough to double one's metabolic rate. Note that the effects of this pathway are very prolonged. Because the production of thyroxine takes several days, it may be 10 days to 2 weeks before visible signs manifest as significant symptoms through this pathway. This explains why you may come down with a cold or flu a week after a very stressful encounter rather than the day after. The metabolic effects of thyroxine released through this pathway are increased workload on the heart muscle, increased gastrointestinal activity (e.g., gastritis), and, in some cases, a condition called **cerebration**, or cerebral excitivity, which is associated with anxiety attacks and/or insomnia.

A Parable of Psychophysiology

A metaphor can be used to illustrate the three pathways discussed earlier (**Fig. 4.7**). Let us say that your life is in danger because of a classified CIA document you inadvertently stumbled across, and you now pose a threat to national security. You want to deliver a message and a copy of this document to your family, who live a few hundred miles away, to let them know your life is in danger. This message is, of course, very important, and you want to make sure your family gets it, so you use a couple of methods to ensure its delivery. First, you immediately text message your parents because it is the quickest way to deliver the message, and the message is received instantaneously. This is like the action of the sympathetic nervous system. As a backup, you send an email in case no one responds to the text. This form of communication is fairly quick, taking perhaps minutes, and is equivalent to the preganglionic nerve to the adrenal medulla. And because you also need to send a copy of the document to further explain the contents of your message, you ship a package via overnight delivery. This means of communication allows more comprehensive information to be sent, but it takes much longer. It is like the neuroendocrine pathways. Similarly, our bodies are composed of several communication systems, each with its own time element and function, the overall purpose being to prepare the body for physical survival. As illustrated by this story, there are many backup systems, fast and slow, to get the message through.

Immediate effects	Intermediate effects	Prolonged effects
Text message or phone call	Email	Overnight delivery
Flushed face Rapid heart rate	Nauseous feeling in stomach Muscle tension	Suppressed immune system

Figure 4.7 Like communication networks that send and receive messages, the human body has several complex messenger systems, which not only see that the information gets through, but also ensure that the body will survive the perceived threat after the message is received.

In the short term, the combination of these various neural and hormonal pathways serves a very important purpose: physical survival. However, when these same pathways are employed continuously as a result of the influence of chronic stressors, the effects can be devastating to the body. In light of the fact that the body prepares physically for threats, whether they are of a physical, mental, emotional, or spiritual nature, repeated physical arousal suggests that the activation of the stress response is an obsolete mechanism for dealing with stressors that do not pertain to physical survival. The inability of the body to return to homeostasis can have significant effects on the cardiovascular system, the digestive system, the musculoskeletal system, and, research now indicates, the immune system. Organs locked into a pattern of overactive metabolic activity will eventually show signs of dysfunction. For instance, constant pressure and repeated wear and tear on the arteries and blood vessels can cause tissue damage to the inner lining of these organs. Numerous changes can also occur throughout the digestive system, including constipation, gastritis, diarrhea, and hemorrhoids. As was observed by Selye in his decades of research, the inability of the body to return to homeostasis can set the stage for signs and symptoms of disease and illness.

Cerebration A term used to describe the neurological excitability of the brain; associated with anxiety attacks and insomnia.

Four Decades of Brain Imaging Research

With the introduction of the MRI and fMRI to peek inside the brain noninvasively, as well as new technologies that can detect conscious thought without electrodes attached to the head, both the brain and the mind (conscious thought) have become a mecca of research studies over the past few decades. Moreover, this fascination in both mind and brain research shows no signs of stopping as it offers an incredible look at the mysteries of consciousness and human thought, including perceptions of stress, relaxation, creativity, and much more.

With the advancement of electromagnetic technology and magnetic resonance imaging (neuroimaging), thousands of studies have been conducted to determine which aspects of the brain are active in a variety of mental states and thought processes (Anderson, 2015). Despite news in 2016 that a bug was found in the computer program that analyzes fMRI data, suggesting that many of the findings were invalid, scientists continue to advocate the importance of brain research in unlocking one of the greatest mysteries known to humanity (Anderson, 2015). So enchanted have researchers become with brain physiology, as depicted through MRI technology, that a multitude of studies have been conducted on non-disease-related brain physiology. Although MRIs can help determine brain structure and specific physiology, it is electroencephalography (EEG) that currently holds the most promise to best understand brain function. Only recently have the dots been connected to provide a more accurate understanding of this most complex human organ. Bruce McEwen is one researcher working in this area. In his book *The End of Stress as We Know It* (McEwen, 2002; Peters et al., 2017), McEwen synthesizes much of this information, including the work of his protégé Robert Sapolsky, author of the acclaimed book *Why Zebras Don't Get Ulcers* (2004). Here are some highlights from McEwen's acclaimed research:

- The hippocampus and the amygdala together form conscious memories of emotional events.
- The hippocampus is highly sensitive to the stress hormone cortisol, which aids in memory formation of stress.
- The hippocampus region is rich in receptor sites for glucocorticoids.
- The amygdala is responsible for the emotional content of memory, particularly fear.
- Repeated excessive exposure to cortisol accelerates the aging process of the hippocampus and may, in fact, damage or shrink brain cells. Moreover, chronic stress may affect memory and learning processes. (In Vietnam vets with PTSD, this region of the brain was 26 percent smaller than in their peers without PTSD.)
- Research by Sapolsky (2010) revealed that damage to brain cells (in animals) caused by chronic stress appears to be irreversible.

McEwen concludes that the human brain is, indeed, wired for stress, or **allostatic load** as he calls it.

Neuroscientists have also discovered that the brain is far more "plastic" than previously thought, giving rise to a new term: neuroplasticity. We now know that the brain can generate new connections to various brain cells, recruit various brain tissue for a host of functions, and generate new cell growth (which was previously thought to be impossible) (Powell, 2007).

Based on the success of President Clinton's federally funded Genome DNA Project, President Obama launched the Brain Initiative Project in 2013. The purpose of this initiative was to help scientists explore the dynamics of the brain as a means to create a comprehensive understanding of everything from the creation of conscious thought and memory to the disease pathology of Alzheimer's, autism, Parkinson's, and several other disorders.

Allostatic load A term coined by stress researcher Bruce McEwen to replace the expression "stressed out"; the damage to the body when the allostatic (stress) response functions improperly or for prolonged states, causing physical damage to the body.

WRAP-UP

Summary

- Psychophysiology is the term used to describe the body's physiological reaction to perceived stressors, suggesting that the stress response is a mind–body phenomenon.
- Three physiological systems are directly involved in the stress response: the nervous system, the endocrine system, and the immune system.

- The nervous system has two main divisions: the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS includes three levels: the vegetative, the limbic, and the neocortical.
- The limbic system houses the hypothalamus, which controls many bodily functions, including appetite and emotions. The neocortical level processes and decodes all stimuli.
- The most important part of the PNS regarding the stress response is the autonomic nervous system, which activates sympathetic and parasympathetic neural drives. Sympathetic drive causes physical arousal (e.g., increased heart rate) through the secretion of epinephrine and norepinephrine, whereas parasympathetic drive maintains homeostasis through the release of ACh. The two neural drives are mutually exclusive, meaning that a person cannot be aroused and relaxed at the same time.
- Rest and digest is the opposite of fight or flight, and it appears that the vagus nerve commands the processes of relaxation that promote rest and digest (homeostasis).
- The endocrine system consists of a series of glands that secrete hormones that travel through the circulatory system and act on target organs. The major stress gland is the adrenal gland.
- The adrenal gland has two parts, each performing different functions. The adrenal cortex (outside) secretes cortisol and aldosterone; the adrenal medulla (inside) secretes epinephrine and norepinephrine.
- The nervous system and endocrine system join together to form three metabolic pathways or axes: the ACTH axis, the vasopressin axis, and the thyroxine axis.
- The body has several backup mechanisms to ensure physical survival. These systems are classified as immediate, lasting seconds (sympathetic drive); intermediate, lasting minutes (adrenal medulla); and prolonged, lasting hours if not weeks (neuroendocrine pathways). Each system is involved in several metabolic pathways.
- Stress is considered one of the primary factors associated with insomnia. Good sleep hygiene consists of behaviors that help promote a good night's sleep rather than detract from it, including decreased caffeine consumption, consistent bedtimes, and a host of effective relaxation techniques that enhance sleep quality.
- A decade of brain research reveals that humans are hardwired for stress through an intricate pattern of neural pathways designed for the fight-or-flight response. Research also suggests that chronic stress appears to atrophy brain tissue, specifically the hippocampus.

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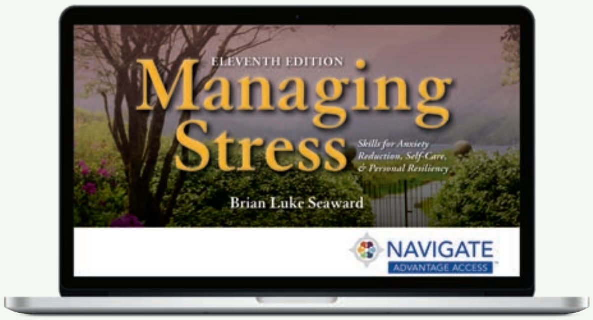

Study Guide Questions

1. What role does the nervous system play in the stress response?
2. What role does the endocrine system play in the stress response?
3. Name and explain the three pathways (axes) of stress physiology.
4. What role does the amygdala play in the stress response?
5. What nerve coordinates the rest and digest aspect of physiology?
6. What are panic attacks?
7. What does brain imaging tell us about stress physiology?
8. Explain the concept of neuroplasticity.
9. Identify the part of the brain that is associated with multitasking.

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