3 *Fundamentals of neuroscience*

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3.1 INTRODUCTION

The human brain contains approximately one trillion nerve cells (10^{12}), and each of them may communicate with between 10 and 10,000 other nerve cells. The messages transmitted between cells may involve the secretion of one or many chemical secretory messengers, and the nature of this chemical message is alterable. With a "wet weight" of only about 3 pounds, the human central nervous system is undoubtedly the most complex structure known to exist in the universe.

In spite of its complexity, a considerable understanding of the brain has been achieved through both reductionistic and organismic approaches. The actual term *neuroscience* originated with a group of "systems" and "components" scientists committed to the notion that any comprehensive understanding of the nervous system must include both molar and molecular concepts. This perspective has encouraged the conceptualization that the brain is composed of functional subsystems, and the principles governing one system frequently operate in others. The discoveries of general principles of interneuronal architecture and communication have been encouraging signs that we are beginning to understand some of the fundamental mechanisms of the brain. Central to these discoveries has been the application of modern biobehavioral technologies; these methods have accounted for much of the knowledge about the brain that has emerged over the last 100 years. Armed with such heuristics, neuroscience has made great strides in understanding what appears at first sight to be a hopelessly complex gelatinous mass.

A tremendous growth of knowledge about the basic anatomical and neurochemical mechanisms of the brain has occurred in the last 25 years. With this new knowledge has come a greater need to integrate these two aspects of the nervous system. A central tenet of this chapter is that the structure, neurochemistry, and physiology of the nervous system must be considered together to understand brain organization and function. Further, many areas of cross-fertilization between psychophysiology and neuroscience can emerge from interdisciplinary studies, but this can occur only if workers are familiar with both fields. It is our hope the new student of psychophysiology finds this chapter to be a foundation and a beginning toward this goal.

Complete coverage of the field of neuroscience cannot be achieved in one chapter, and our difficulty has been to select the areas to be covered and to provide an appropriate depth. The following is a combination of subjects from classical neuroscience and a selected set of more detailed descriptions of systems that may illustrate important principles or add specific information that is applicable to psychophysiology. Further, an attempt is made to identify important recent

developments in the field. The chapter makes no pretense of being a sufficient source of information, even for the beginning psychophysiologist. The interested reader is encouraged to pursue more extensive treatments found in many excellent texts on physiological psychology, psychopharmacology, and neuroscience. Four excellent sources are *Physiology of Behavior*, by N. Carlson (1986), *Fundamentals of Neuropsychopharmacology*, by R. S. Feldman and L. F. Quenzer (1984), *Principles of Neural Science*, edited by E. R. Kandel and J. H. Schwartz (1985), and *Medical Physiology*, edited by U. Mountcastle (1980). We begin our treatment by considering the general structure of the human nervous system. This is followed by an examination of the electrochemical basis of neuronal excitability and intercellular communication. Finally, we outline some of the major subsystems of the nervous system.

3.2 ANATOMY OF THE CENTRAL NERVOUS SYSTEM

3.2.1 *Neuroembryology*

Knowledge of the development of the nervous system can provide a conceptual framework for understanding the regional anatomy of the central nervous system (CNS). We therefore briefly consider the anatomy of the developing nervous system before examining the endpoint of that development, the regional anatomy of the adult human CNS.

The human embryo consists of three distinct layers of cells: the *endoderm* (inner layer), the *mesoderm* (middle layer), and the *ectoderm* (outer layer). The central nervous system derives from a specialized portion of the ectoderm called the *neural plate*. The neural plate lies on the dorsal (back) surface of the embryo and runs along the midline.

As development proceeds, the neural plate first invaginates and eventually closes to form an elongated tube called the *neural tube*. The neural tube is hollow, and the lumen is called the *central canal*. The central canal persists throughout development and eventually forms the *ventricular system* of the brain. The inner wall of the neural tube is lined with a thin layer of cells called epithelial cells. Through repeated mitotic cell divisions, the epithelial layer of the neural tube generates virtually all of the nerve cells (*neurons*) and supporting cells (*glia*) that form the adult nervous system. The generation of neurons is not uniform along the length of the neural tube; the rostral (toward the head) portion of the neural tube generates many more neurons than the caudal part (toward the "tail"). Consequently, as development proceeds, several enlargements in the neural tube form along its rostral end. These enlargements, called vesicles, develop into the brain. The caudal part of the neural tube, which retains its tubelike appearance throughout development, becomes the spinal cord. Initially, only three cephalic ("head") vesicles are present (Figure 3.1). The most rostral is called the *prosencephalon* (forebrain), the middle is called the *mesencephalon* (midbrain), and the most caudal is called the *rhombencephalon* (hindbrain). Later, five vesicles can be seen: the prosencephalon develops into two subdivisions, the *telencephalon* and the *diencephalon*, and rhombencephalon develops into the *metencephalon* and the *myelencephalon* (see Figure 3.1). The mesencephalon remains one vesicle throughout development. With these rudimentary aspects of the developing brain in mind, we turn to a consideration of the major derivatives of each vesicle in the adult brain.

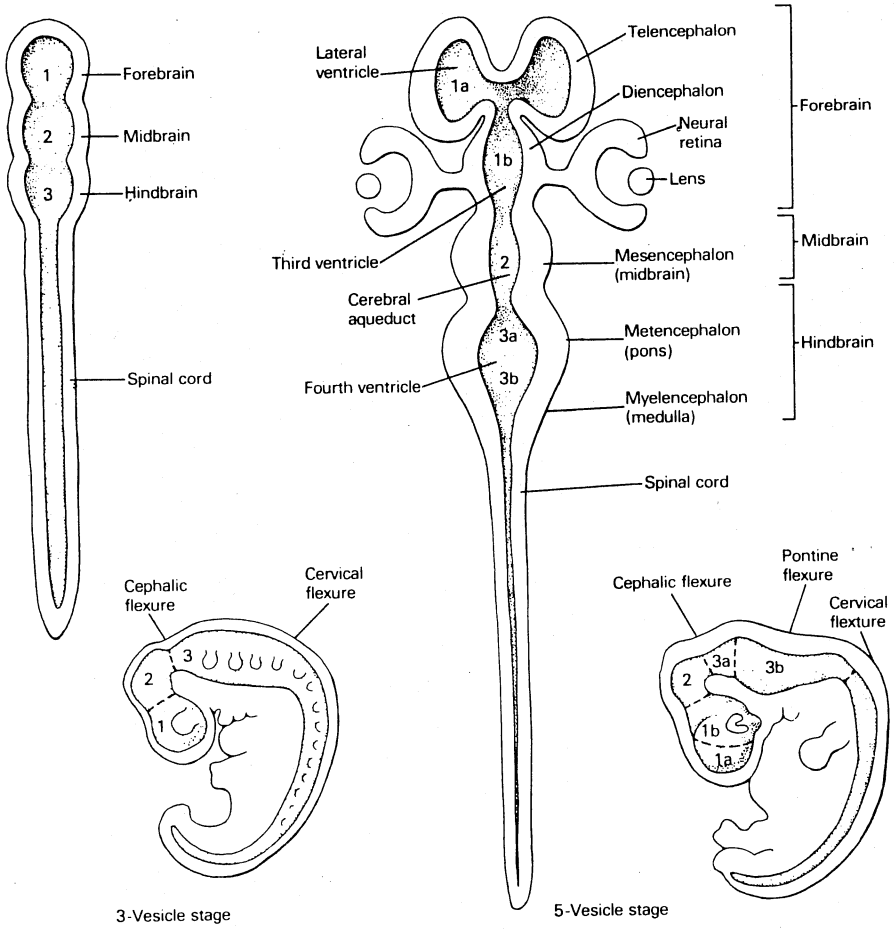

Figure 3.1. The brain and spinal cord develop from the neural tube. The brain arises from several enlargements, called vesicles, in the rostral portion of the neural tube. Early in development, three cephalic vesicles are present; later five cephalic vesicles differentiate into the various parts of the brain. In *Principles of neural science* (E. Kandel and J. Schwartz, Eds.), p. 246. Copyright 1985 by Elsevier Science.

3.2.2 *Telencephalon*

Major structures found in the telencephalon include the *lateral ventricles* (derived from the embryonic central canal), the *cerebral cortex*, the *basal ganglia* (which consist of the caudate, putamen, and globus pallidus), the *olfactory bulbs*, the *hippocampus*, the *fornix*, and the *amygdala*. Because of the great proliferation of neurons in the frontal and temporal lobes of the cerebrum, many of the forebrain structures are C-shaped; these include the lateral ventricles, the caudate nucleus, the hippocampus, and the fornix.

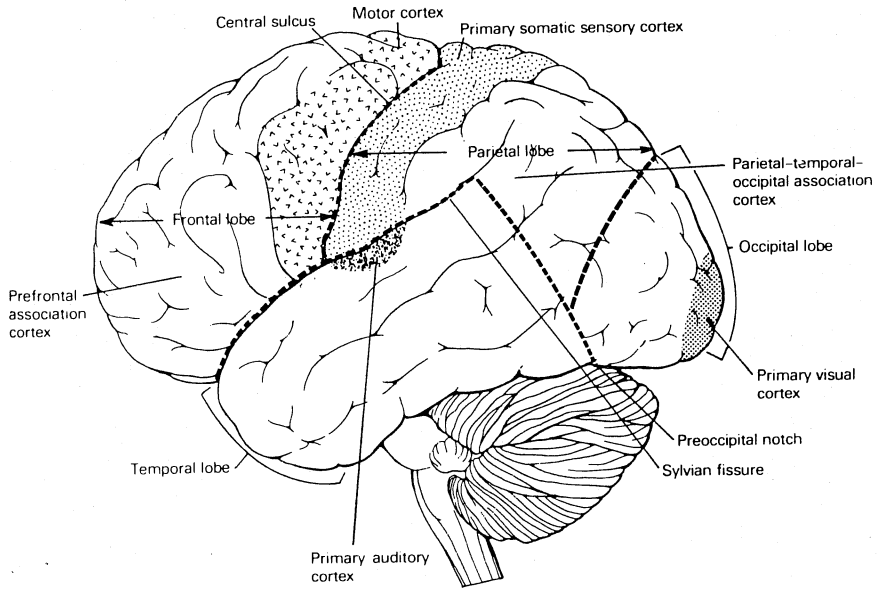

Figure 3.2. Lateral view of the brain showing major divisions of the cerebral cortex. (Reprinted by permission of the publisher from J. P. Kelly, Principles of the functional and anatomical organization of the nervous system, in *Principles of neural science*, E. Kandel and J. Schwartz, Eds., p. 214. Copyright 1985 by Elsevier Science.)

3.2.2.1 *Cerebral cortex*

The cerebral cortex covers most of the cerebrum and consists of two hemispheres interconnected by the *corpus callosum*. The cortex can be grossly subdivided into the frontal, parietal, temporal, and occipital lobes (Figure 3.2). Parts of the *frontal lobes* are involved in the generation of certain emotional states, motor functions, oculomotor control, speech production (Broca's area), and foresight (e.g., Kolb & Whishaw, 1980). The *temporal lobes* are associated with audition, auditory and visual recognition (e.g., Gross, Rocha-Miranda, & Bender, 1972; Iwai & Mishkin, 1968; Mishkin, 1979), and some of the perceptual aspects of language (comprehension and syntax). The *parietal cortex* contains the somatosensory projection fields (cortical representation of the skin senses and kinesthesia) as well as some areas related to visual processing and convergence of visual with somesthetic information. The parietal cortex may also play a role in some aspects of sensorimotor processing and visual attention (e.g., Lynch, Mountcastle, Talbot, & Yin, 1977; Posner, Walker, Friedrich, & Rafal, 1984; Robinson, Goldberg, & Stanton, 1978). The occipital lobes are associated with vision.

3.2.2.2 *Subcortical structures*

Telencephalic structures that lie beneath the cerebral cortex are often referred to as subcortical structures. These include the *caudate, putamen*, and *globus pallidus*, which lie below the corpus callosum and follow the course of the lateral ventricles

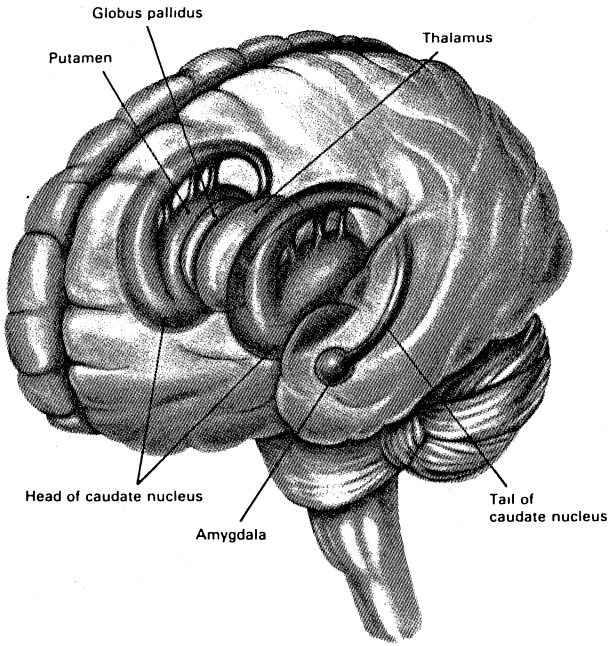

Figure 3.3. Subcortical telencephalic and diencephalic structures of the human brain. (Reprinted by permission of the publisher from N. R. Carlson, *Physiology of behavior,* p. 102. Copyright 1986 by Allyn and Bacon, Needham Hts., MA.)

(Figure 3.3). Collectively, these structures comprise the basal ganglia, a system involved in motor processing. The hippocampus, another subcortical structure, is part of an interconnected system of forebrain structures called the limbic system. Like the caudate, the hippocampus has a C shape because it follows the course of the lateral ventricles. The hippocampus is heavily interconnected with other limbic structures such as the *septal nuclei*, the amygdala, and the *mammillary bodies*. Many of the afferent and efferent connections of the hippocampus lie within the fornix, a large fiber bundle that arches from the hippocampus past the septal area and terminates within the hypothalamus. Limbic structures, such as the hippocampus, the mammillary bodies, and the amygdala, play an important role in memory (Olton, 1984; Squire, 1982; Zipser, 1985). The septum and parts of the amygdala appear to be involved in the elaboration of certain emotional states (especially fear and rage). Thus, lesions of the basolateral division of the amygdala produce docility, whereas stimulation produces affective attack (Hilton & Zbrozyna, 1963).

3.2.3 *Diencephalon*

The diencephalon derives primarily from a secondary vesicle of the prosencephalon. Major structures of the diencephalon include the *third ventricle*, the *thalamus*, and the *hypothalamus* (Figure 3.4). These structures lie below the hippocampus,

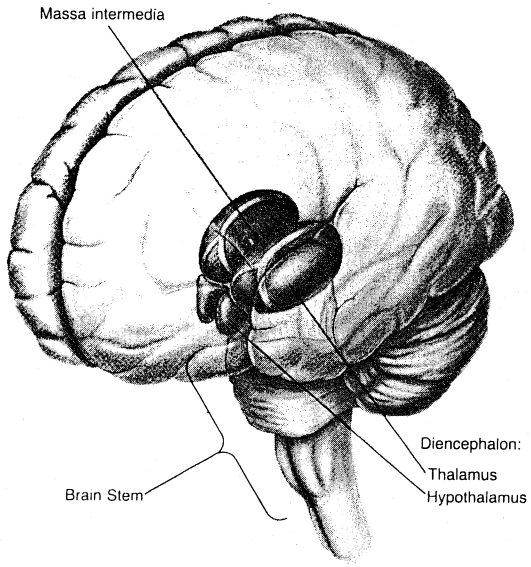

Figure 3.4. The location and structures of the diencephalon (thalamus and hypothalamus) of the brain. The massa intermedia connects the two thalami. (Reprinted by permission of the publisher from N. R. Carlson, *Physiology of behavior,* p. 103. Copyright 1986 by Allyn and Bacon, Needham Hts., MA.)

fornix, and caudate of the telencephalon. The thalamus can be regarded as the "gateway" to the cerebral cortex; almost all of the input to the cerebral cortex gains access via a synaptic relay in the thalamus. The thalamus actually consists of a number of identifiable nuclei, each of which projects to a fairly well-defined "cortical field" and has specific patterns of afferent (input) connections. This is most clearly seen in the *specific relay nuclei* of the thalamus. Each relay nucleus processes modality-specific sensory or motor information and transmits that information to the corresponding cortical projection field.

In contrast to the thalamus, the hypothalamus has no direct cortical connections. Lying beneath the thalamus (*hypo* = under), the hypothalamus is involved in homeostasis and related motivational states (e.g., hunger, thirst, and reproduction). The hypothalamus can also be viewed as an interface between sensory inputs and motor outflow for emotional and motivational behavior. Hypothalamic afferents (inputs) originate from the retina, frontal cortex, limbic structures such as the amygdala, septum, cingulum, and hippocampus, certain thalamic nuclei, and a variety of brainstem afferents including the solitary nucleus (which receives primary gustatory afferents). In addition, there are a variety of receptors that provide information concerning blood chemistry (e.g., glucose concentration) and osmolarity (associated with thirst). Some hypothalamic neurons clearly respond to a variety of sensory inputs arising both from internal sensory receptors (e.g., Anand & Brobeck, 1951) and exteroceptors such as vision and taste (e.g., Rolls, 1982).

Hypothalamic efferents are distributed to (1) parts of the thalamus, which in turn project to the frontal lobes as well as to the cingulate gyrus (providing feedback pathways to the already described fronto-hypothalamic and cingulo-hypothalamic projections), (2) the posterior lobe of the pituitary, and (3) a variety of zones within the midbrain, pons, and medulla. These latter areas in turn send projections to moto neurons of the somatic and autonomic motor systems. Not surprisingly, then, much of the hypothalamic output is directed toward regulation of the viscera and the endocrine system.

The *pituitary gland,* which is suspended by the infundibular stalk immediately below the hypothalamus, serves as a connection between the hypothalamus and the endocrine system. The pituitary is sometimes referred to as the "master gland" because it aids in the coordination of brain and bodily functions through the regulation of many other glands in the head and trunk. However, later it will become clear that the pituitary is really a mere storage and transducing mechanism since the brain dictates its activities; for this and other reasons, which will become clear later, the brain may be more deserving of the title "master gland."

3.2.4 *Mesencephalon*

The mesencephalon, or midbrain, can be divided into two general areas: the dorsal portion (called the *tectum, "roof")* and the ventral portion (called the *tegmentum,* "floor"). A small canal that comprises the midbrain's portion of the ventricular system courses through the center of the midbrain and demarcates the boundary between tectum and tegmentum. This canal is known as the *cerebral aqueduct,* or the *aqueduct of Sylvius.* Surrounding the cerebral aqueduct is the *periaqueductal gray* (PAG), an important area for the central inhibition of pain that operates through the release of opioid neurosecretory products. Two main structures comprise the tectum: the *superior colliculi,* which lie rostrally and play an important role in vision (especially with respect to eye movements), and the *inferior colliculi,* which lie behind the superior colliculi and play an important role in audition. From the cerebral aqueduct to the ventral surface of the midbrain is the midbrain tegmentum, sizable structure containing many nuclei including the *red nucleus* and *substantia nigra* (two nuclei involved in motor functions), the *midbrain reticular formation* (clusters of cells with varied functions, including control of arousal), the *oculomotor nucleus* (motoneurons for extra- and intraocular muscles), and the *cerebral peduncles* (a large bundle of fibers originating in the cortex and terminating in the midbrain, pons, medulla, and spinal cord; it is involved in the cerebral control of movement and in the modulation of incoming sensory information).

3.2.5 *Metencephalon*

Major structures in the metencephalon include the *fourth ventricle,* the *pons,* and the *cerebellum* (see Figure 3.5.). The pons contains several cranial nerve nuclei (both sensory and motor), the *pontine reticular formation* (again, involved in regulation of consciousness and sleep), and the *pontine nuclei* (which project to the cerebellum). The cerebellum overlies the pons and is involved in motor coordination and the control of posture. It is especially important in the control of ballistic movements and in the sensory control of motor output.

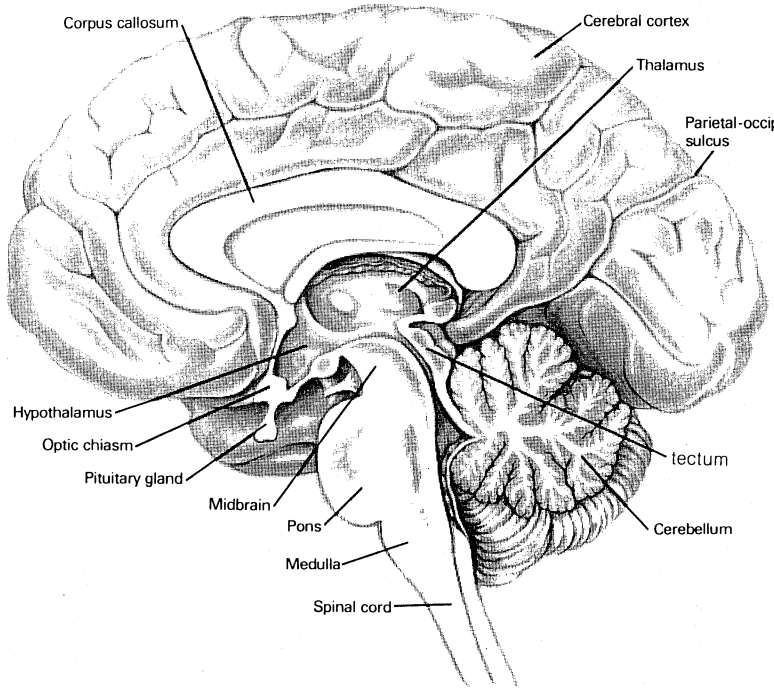

Figure 3.5. Sagittal section of the brain showing mesencephalic, metencephalic, and myelencephalic structures of the brain. The mesencephalon, or midbrain, includes the tectum (or roof) and tegmentum (or floor, which is the site labelled midbrain in the figure). Structures of the metencephalon include the cerebellum and pons. The myelencephalon is represented in the figure by the medulla. (Reprinted by permission of the publisher from J. P. Kelly, Principles of the functional and anatomical organization of the nervous system, in *Principles of neural science,* E. Kandel and J. Schwartz, Eds., p. 213. Copyright 1985 by Elsevier Science.)

3.2.6 *Myelencephalon*

The myelencephalon is the most caudal part of the brain and is usually referred to as the *medulla* (see Figure 3.5). A large portion of the medulla is comprised of the caudal portion of the reticular formation, called the *medullary reticular formation,* which receives inputs from interoceptors such as baroreceptors and chemoreceptors in the vasculature. Medullary reticular efferents project largely to the spinal cord (i.e., reticulo-spinal tracts). Thus, areas within the medullary reticular formation play an important role in the control of respiration, blood pressure, and maintenance of posture. In addition, there are a number of sensory and motor cranial nerve nuclei within the medulla. The *pyramidal tract,* a caudal extension of the cerebral peduncles, lies at the ventral surface of the medulla. It represents a subset of descending cortical fibers specifically destined for the spinal cord to control movement.

3.3 ANATOMY AND PHYSIOLOGY OF THE AUTONOMIC NERVOUS SYSTEM

Generally, a distinction is made between the *central nervous system* (CNS), comprised of the brain and spinal cord, and the *peripheral nervous system*, comprised of all the other nerve fibers. The peripheral nervous system is usually subdivided into two divisions: the *somatic nervous system* and the *autonomic nervous system*. The somatic nervous system consists of the nerves to and from motor and sensory organs whereas the autonomic nervous system innervates the viscera.

The autonomic nervous system regulates internal states. Emotions, cognitive activity, responses to environmental changes, and disease all involve complex regulation of internal activity; this is accomplished through interactions between the autonomic nervous system and the CNS. These interactions have been the focus of many psychophysiological studies and have illuminated some of the contributions of the autonomic nervous system to behavior.

The integrative mechanism in the autonomic nervous system serves a critical purpose for the maintenance of life by keeping the body's internal states within acceptable ranges. The principle governing this regulatory system is a process Walter B. Cannon (1935) called *homeostasis*. Homeostasis is often understood in the context of control theory (the systematic use of feedback to maintain a system at a desired state or set point). Thus, the essential elements of a controlled system are (1) feedback pathways that provide information about the state of the system, (2) a mechanism that defines the set point, (3) a comparison between the state of the system (as reflected in the feedback) and the desired state (as reflected by the set point), and (4) effectors that can modify systems parameters so as to minimize the difference between the set signal and the feedback signal. As described in what follows, the autonomic nervous system uses each of these components to set an appropriate internal state for each of life's varying circumstances. Certain areas of the brain, including many brainstem nuclei and the hypothalamus, play a crucial role in this process.

For a long time, the operation of the automatic nervous system and the attendant smooth muscles was thought to be "involuntary." This contrasted with the view of the "voluntary" control of the striate or skeletal muscles by the CNS. This distinction is less clear today due to demonstrations that visceral learning can take place (Miller, 1969); the underlying mechanisms for these effects remain controversial.

3.3.1 *Sympathetic and parasympathetic nervous system*

The autonomic nervous system can be divided into a *sympathetic division* (or thoracolumbar) and a *parasympathetic division* (or craniosacral). These antagonistic branches of the autonomic nervous system differ structurally, functionally, and chemically but work together to maintain homeostasis.

The major function of the sympathetic nervous system is to prepare the body for action, and each visceral change elicited by this system can be viewed as a step toward adapting to the action requirements of a situation. Stimulation of the sympathetic fibers, for instance, leads to dilation of the bronchioles and pupils, constriction of blood vessels supplying the skin, inhibition of the gastrointestinal system, and increases in blood pressure, stroke volume, cardiac output, and

sweating. These are all physiologically compatible responses that are observed in organisms that are either stressed or challenged. Cannon termed this the "fight-or-flight" response, an idea that has had enormous impact on the field of psychophysiology.

In contrast to the quick diffuse actions of the sympathetic nervous system, the parasympathetic nervous system works to restore and maintain bodily resources. Stimulation of parasympathetic fibers leads to decreases in heart rate and blood pressure, constriction of the bronchioles and pupils, and increases in digestive functions. Whereas the sympathetic nervous system often discharges as a whole, components of the parasympathetic division typically operate more independently and are less diffuse. There seems little reason, from an adaptive point of view, for the parasympathetic nervous system to discharge all at once as the sympathetic nervous system does in an emergency.

These functional differences between the sympathetic and parasympathetic divisions of the autonomic nervous system are supported by very clear anatomical differences between the two divisions (Figure 3.6). In both divisions, neurons exit the brain or spinal cord and make connections with other neurons in *ganglia*, collections of neuronal cell bodies outside the central nervous system. The first-order neuron is called the *preganglionic fiber*; the neuron connecting the ganglia to the organ is called the *postganglionic fiber*. Preganglionic fibers of the sympathetic nervous system emerge from the first thoracic to the third lumbar level of the spinal cord and are carried to a vertically oriented collection of ganglia called the *sympathetic chain*. Since the sympathetic chain is close to the spinal cord, the preganglionic sympathetic fibers are short and the postganglionic fibers are long. As the preganglionic fibers leave the spinal cord, they diverge considerably; some of them make connections with ganglia several segments above and/or below their point of origin. Thus, a single ganglion in the sympathetic chain receives input from several segments of the spinal cord. A number of ganglia fuse to produce large numbers of postganglionic neurons that travel to the visceral organs they innervate. With this diverging structural organization, one can see how an impulse from any portion of the sympathetic nervous system could potentially activate a large portion of the visceral system.

The fibers of the parasympathetic nervous system emerge either from cranial nerves or the sacral division of the spinal cord, but there are no interactions between the two. As a result, the parasympathetic nervous system produces more specific visceral changes than the sympathetic nervous system. The preganglionic fibers of the parasympathetic nervous system make connections in ganglia very close to or within the organs they innervate. Thus, in contrast to the sympathetic nervous system, the preganglionic fibers of the parasympathetic nervous system are long and the postganglionic fibers are short.

The details of the anatomy of the parasympathetic nervous system are shown in Figure 3.6. Note the major role played by the vagus nerve (cranial nerve X), which innervates nearly all the organs and glands of the trunk. The exceptions are the bladder, lower bowel, and genitalia, which are innervated by the pelvic nerve. The parasympathetic nerves arising from the oculomotor (III), the facial (VII), and the glossopharyngeal (IX) cranial nerves control the glands of the head.

Not only are the parasympathetic and sympathetic divisions structurally different, they release different chemical messengers as well. When preganglionic fibers

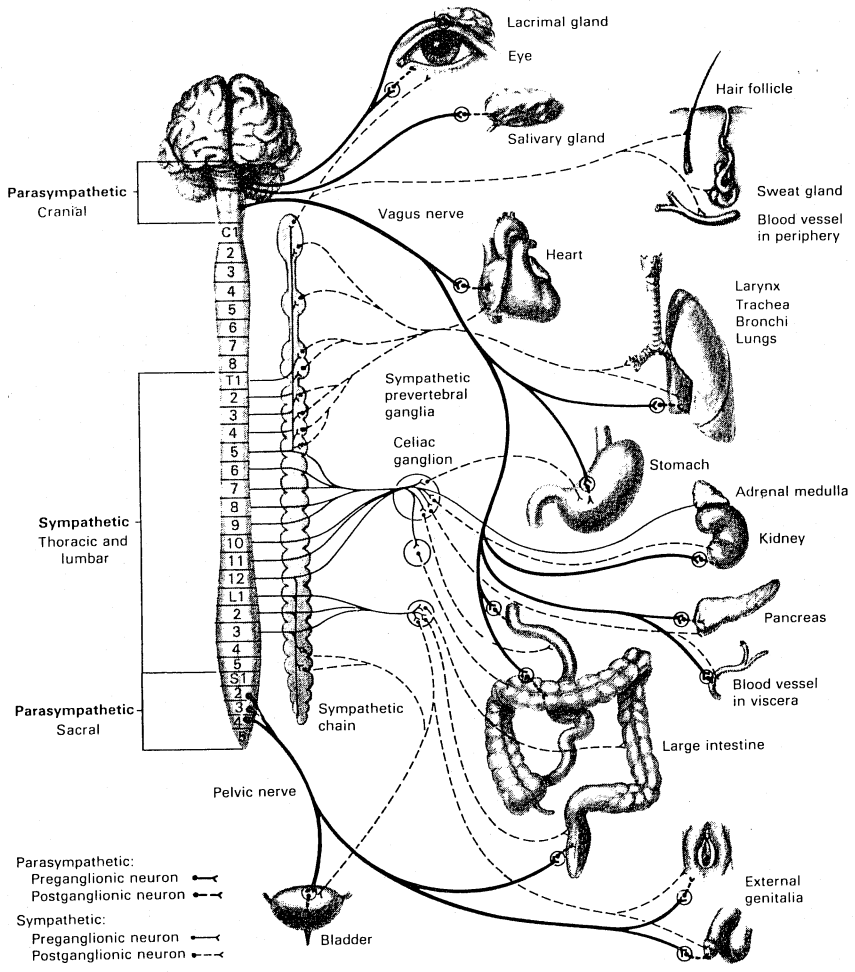

Figure 3.6. Target organs innervated by the parasympathetic and sympathetic divisions of the autonomic nervous system. (Reprinted by permission of the publisher from N. R. Carlson, *Physiology of behavior,* p. 117. Copyright 1986 by Allyn and Bacon, Needham Hts., MA.)

make connections with postganglionic fibers, they secrete acetylcholine (ACh) in both the sympathetic and the parasympathetic nervous system. Acetylcholine is also secreted by the postganglionic parasympathetic neurons. Postganglionic neurons in the sympathetic nervous system, however, secrete norepinephrine (NE), a substance similar to that secreted by the adrenal medulla. Thus, there is a chemical as well as a structural basis for diffuse sympathetic nervous system effects as opposed to more localized parasympathetic effects.

The considerable regularity in the particular chemical messengers used by different branches of the autonomic nervous system is not without exceptions,

however. The sweat glands, for instance, are innervated almost exclusively by the sympathetic nervous system, and acetylcholine, rather than NE, is the predominant chemical messenger. However, a minor adrenergic innervation is present (Shields, MacDowell, Fairchild, & Campbell, 1988). Hair follicles receive only sympathetic nervous innervation, and almost all blood vessels are innervated exclusively by the sympathetic division. Note, also, that the nature of chemical transmission in the autonomic nervous system is more complex than this overview would imply; details are provided after further discussion of chemical communication between neurous.

3.3.2 *Sympathetic–parasympathetic interactions*

The parasympathetic and the sympathetic divisions of the autonomic nervous system differ structurally, functionally, and chemically, and they often operate antagonistically. However, it is important to realize that both the sympathetic and parasympathetic divisions are always active. One is not "on" when the other is "off." The interactions are complex, and it is therefore not usually possible to ascertain which branch is responsible for a change in a particular visceral response from the response itself. Heart rate acceleration, for instance, may be attributed to an increase in sympathetic activation, a decrease in parasympathetic activity, or both. Generalizing about the sympathetic nervous system as a whole from a change in electrodermal activity (EDA; see Dawson, Schell, & Filion, chapter 11) is also difficult since the sweat glands are innervated primarily by atypical cholinergic sympathetic fibers.

Psychophysiologists have begun to outline ways to differentiate between the parasympathetic and sympathetic contributions to visceral change (e.g., Porges Bohrer, chapter 21), but at this point, it is difficult to do so using most non-invasive psychophysiological measures. To add further to the complexity, in some systems there is a clear lack of antagonism between the sympathetic and parasympathetic nervous system. Although very clear antagonistic relations are seen in the heart and lungs, supplementary interactions between sympathetic and parasympathetic nerves occur in the control of salivation and sexual reflexes.

The autonomic nervous system typically has direct effects on smooth muscles. However, those interested in the gut should note that an *enteric nervous system* also exists (cf. Costa, Furness, & Gibbins, 1986). The enteric nervous system is an extensive plexus of nerves within the bowel that is modulated by the autonomic nervous system. Costa et al. (1986) assert that there are more neurons in the enteric nervous system than in the spinal cord. This implies that understanding the neural control of the gut requires understanding the interplay between sympathetic and parasympathetic influences, the spontaneous activity of smooth muscle, and the physiology of the enteric nervous system (see Stern, Koch, & Vasey, chapter 16).

Any tendency to think of the autonomic nervous system as mostly motor output is to be avoided. Afferent neurons comprise at least half of the autonomic nervous system; the cell bodies of these autonomic afferents are found in the dorsal root ganglia along with those of sensory neurons arriving from the somatic nervous system (see Truex & Carpenter, 1969). These pathways provide information for autonomic reflexes, which perform complex regulatory functions in the autonomic nervous system. An excellent description of these reflexes may be found in Koizumi. and Brooks (1980).

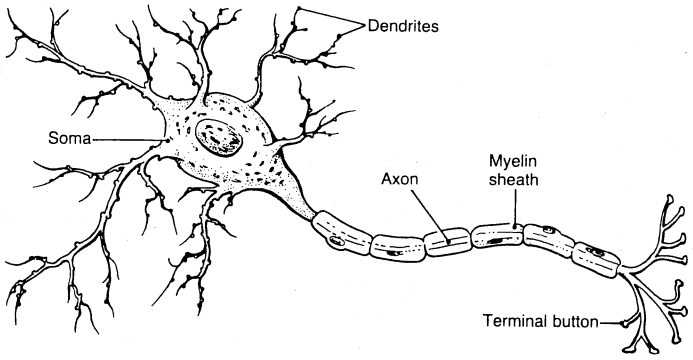

Figure 3.7. Morphology of a neuron. (Reprinted by permission of the publisher from N. R. Carlson, *Physiology of behavior*, p. 18. Copyright 1986 by Allyn and Bacon, Needham Hts., MA.)

3.4 NEURONAL EXCITABILITY AND SYNAPTIC TRANSMISSION

3.4.1 *Cell morphology*

Information is conveyed between nerve cells through chemical and electrical signals. This process of information transfer is called synaptic transmission. In order to understand how information is transferred between cells in the nervous system, some basic morphological features of nerve cells must be described. This review is by no means comprehensive and focuses on those aspects of the nerve cell that are important for cellular signaling.

The nerve cell, or *neuron*, is the fundamental unit of the nervous system (Figure 3.7). Neurons, like all cells, are closed bags with walls made out of proteins and lipids; the cell wall is called the *membrane*. The nerve cell membrane is much more than a wall, however; it has extraordinary electrochemical properties that are described in what follows. All nerve cells have a cell body, or *soma*, where energy is generated and other life-sustaining functions of the cell occur. Secretory products called *neurotransmitters* or *neuromodulators* are often, but not invariably, synthesized in the soma. Arborizations called *dendrites* extend from the cell body and receive signals from other neurons; these signals regulate the electrical state of the cell. Most neurons in the central nervous system have many dendrites, but some neurons have only a few or just one. The *axon* of a neuron is a stalklike structure that extends from the cell body for distances ranging from several micrometers to about a meter in the human adult. Each neuron has only one axon, but many axons send out branches (called *collaterals*) and arborize extensively at their ends. At the tips of these branches are bulbous structures called *terminal butons*, which form attachments with other neurons. A gap of approximately 200 Å, called the *synapse*, occurs between the terminal buton and the adjoining cell's membrane (Figure 3.8). The secretory products of the neuron (e.g., neurotransmitters) remain stored within the terminals in packets called *vesicles* until they are released as cellular signals. When released, the chemicals affect the electrochemical properties of the

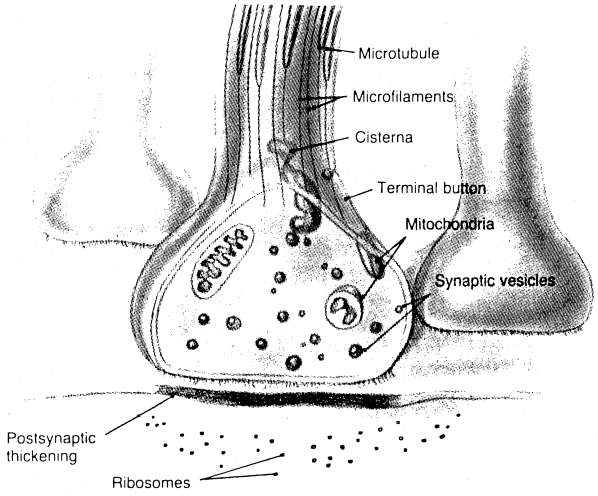

Figure 3.8. Details of a pre- and postsynaptic neuron at a synapse. The terminal button of the presynaptic neuron is shown above the postsynaptic cell. Microtubules and microfilaments form an internal network of tubes that interconnect various regions of the cell. Mitochondria provide energy for cellular functions. Neurotransmitters are synthesized and transported to the terminals through microtubules; in the terminals, neurotransmitters are stored in synaptic vesicles. The membrane of the postsynaptic cell is thicker at a synapse; this portion of the neuron is called the postsynaptic thickening. Ribosomes, which assist in protein synthesis, are shown in the postsynaptic neuron. (Reprinted by permission of the publisher from N. R. Carlson, *Physiology of behavior*, p. 53. Copyright 1986 by Allyn and Bacon, Needham Hts., MA.)

membrane of the adjacent cell. Synapses are found on dendrites, cell bodies, and axon terminals. An important morphological feature of the neuron is the *axon hillock*, which is located at the junction of the cell body and axon. The summation of information received from other cells at this site on the neuron determines whether or not that neuron will pass on a message to other cells.

3.4.2 *Electric and ionic mechanisms of nerve conduction*

3.4.2.1 *Generation of electrical potentials by ions*

A neuron may be thought of as one link in a vast communication network. In terms of its communicative functions, a neuron can be in one of three states: (1) at rest, neither receiving nor conveying a signals; (2) receiving a signal from another neuron or sensory receptor; or (3) conveying a signal to another neuron. These activity states can be described in terms of the electrical and chemical signals that are used by cells when they receive input from and pass on information to other cells.

Electrical signals in nerve cells are generated by *ions* (electrically charged atoms) that flow into and out of neurons. The generation of electricity results simply from the movement of these ions. Three ions are especially important in generating

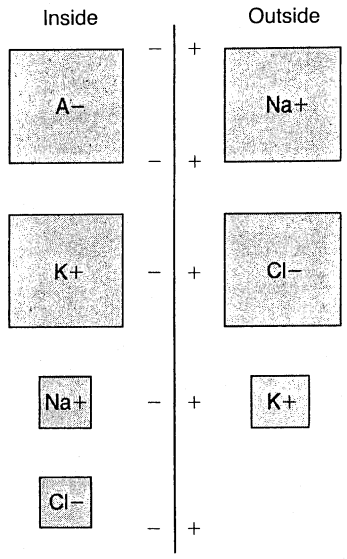

Figure 3.9. Distribution of important ions inside and outside of a model cell. Na^+ = sodium, K^+ = potassium, Cl^- = chloride, A^- = large anions. The vertical line in the center represents the neuronal membrane. (Reprinted by permission of the publisher from N. R. Carlson, *Physiology of behavior*, p. 36. Copyright 1986 by Allyn and Bacon, Needham Hts., MA.)

electrical signals in nerve cells: sodium (Na^+), potassium (K^+), and chloride (Cl^-). These ions are differentially distributed inside and outside of neurons (Figure 3.9), and ions move across the membrane through small pores called *ion channels* (cf. Hille, 1984). Ion channels are sometimes called *ionic gates* to indicate their function of determining whether or not an ion can cross the membrane. When the gate for a particular ion is closed, the membrane is impermeable to that ion. When the gate is open, ions of that type may move freely across the membrane. Given that the ion channel is open, whether an ion moves into or out of a cell depends largely on one of two passive physical forces; a diffusional force and an electrochemical force. The diffusional force, called the *concentration gradient*, operates upon each type of ion *independently*, favoring the flow of an ion from regions of high concentration to regions of low concentration. For example, since K^+ is found in high concentrations inside the neuron, the concentration gradient tends to move K^+ out of the cell. The electrochemical force, the *electrical gradient*, favors the attraction of oppositely charged species (e.g., + and −) and the repulsion of like-charged species (e.g., − and −, + and +), a process that maintains electrical neutrality in most physical systems. Since large negatively charged proteins are trapped inside neurons, electrochemical forces favor the flow of positively charged ions, such as K^+, from outside to inside the cell to neutralize the electrical imbalance. This however, opposes the concentration gradient, which tends to push K^+ out of the cell. A compromise condition (*equilibrium*) occurs such that neither force "wins": Neither electrical neutrality nor total diffusion of ions occurs.

It should be noted that in addition to the influence of physical forces, ions may move through the cell membrane at random due to the leaky nature of the porous cell wall. To compensate for the leakiness of the cell membrane to Na^+ and K^+, neurons actively control ionic movement through a mechanism referred to simply as a pump. Unlike diffusional and electrochemical forces that are passive, the pump requires energy from the neuron to operate. Thus, passive physical forces and a cellular pump control the flow of ions across the cell membrane, which in turn generates electrical potentials. These forces are summarized in Figure 3.9.

When the gates for a particular ion are open, the membrane potential moves toward a particular voltage specific to that ion (*equilibrium potential*) that balances out the various forces described in the preceding paragraphs. The equilibrium potential for an ion can be calculated from the *Nernst equation* if the concentration of the ion inside and outside the cell is known (Koester, 1985; cf. Kuffler, Nicholls, & Martin, 1984). The values for particular ions have been calculated and compared to experimentally measured values during different activity states of neurons (e.g., when the neuron is at rest). This line of investigation is important because when the predicted and measured values are comparable, one can conclude that (1) the membrane is likely to be permeable to that ion during that activity state and (2) that ion may be important in generating the observed electrical potential. Conversely, if there is a discrepancy between the predicted and measured values, the membrane is probably not permeable to that ion and that ion probably is not responsible for the electrical potential.

3.4.2.2 *Types of electrical potential in neurons*

Resting potential. Three types of electrical signals are generated by neurons, each corresponding to one of the three activity states of a neuron (receiving, sending, or resting). The potential that can be measured across the cell membrane when the neuron is at rest is called the *resting potential.* The value of the resting potential (about −70 mV) is close to the K^+ equilibrium potential predicted by the Nernst equation, and experimental studies have confirmed that alterations in K^+ are followed by changes in the resting potential. The small discrepancy between the K^+ potential and the resting potential is due to a small leakage of Na^+. This illustrates that the membrane potential is the result of the combination of the equilibrium potentials for each ion and the permeability of the membrane to each ion. This relationship is formally described in the Goldman–Hodgkin–Katz equation (see DeVoe & Maloney, 1980; cf. Hille, 1984). Thus in a resting state, the membrane potential is largely governed by K^+, reflecting the permeability of the membrane to K^+.

Graded potential. A second type of electrical potential is associated with cells when they are receiving information. This type of electrical potential is called a *graded potential.* Graded potentials can be subdivided into two types: synaptic potentials and receptor potentials. *Synaptic potentials* are generated when a neuron receives signals from other cells. Synaptic potentials are normally referred to as *inhibitory postsynaptic potentials* (IPSPs) or *excitatory postsynaptic potentials* (EPSPs), depending on whether the chemical input tends to inhibit or excite the cell on which it acts. Electroencephalograms, potentials that are commonly recorded from the scalp by

psychophysiologists, are the sum of synaptic potentials from all of the neurons in the vicinity of the electrode (cf. Thompson & Patterson, 1974). *Receptor potentials* are generated when first-order sensory neurons (*primary afferents*) receive input from sensory receptors.

Graded potentials spread from their point of origin, acting at a distance to control the state of the neuron. Therefore, understanding synaptic physiology requires an appreciation of the properties of graded potentials. First, the initial size of a graded potential is proportional to the size of the triggering stimulus. Second, as graded potentials spread away from their point of origin, they decrease in strength due to the cable properties of neurons (e.g., the presence of leakage, resistance, and capacitance). Finally, graded potentials are summed over both space and time at the axon hillock. Thus, at this junction of the soma and the axon, the overall effect of all the messages being received by the cell are weighed to determine the type of signal the neuron will pass on to other cells. If many more excitatory than inhibitory inputs are received by the cell (due to many excitatory inputs at different locations on the cell or to a fast sequence of excitatory inputs), the neuron passes on a message. On the other hand, if many more inhibitory than excitatory inputs are received by the cell, the cell will be inhibited and thus prevented from sending a chemical signal. It should be recognized that cellular inhibition is itself a form of communication, one that is primary in the regulation of many neuronal systems.

Action potentials. When neurons are excited into sending a message, a third type of electrical potential can be measured, the *action potential.* During an action potential, the membrane voltage swing from −70 mV to approximately +40 mV and back again over a period of time that ranges from 0.5 to 5 msec for different cells. The action potential is sometimes called "spike" because of its appearance on an oscilloscope. Figure 3.10 illustrates the characteristic waveform of an action potential. The initial rising portion of the waveform is carried mainly by the influx of sodium ions (Na^+); the falling portion of the waveform is associated with the efflux of potassium ions (K^+). When an action potential occurs, the cell is said to discharge, fire, or produce an impulse.

Action potentials are generated when the sum of graded potentials drives the resting membrane potential positive by about 15 mV. Although action potentials occur when the cell is more positive, the membrane voltage (having a resting value that is negative) is decreased; hence, the neuron is excited when it is *depolarized.* For a particular neuron, an action potential occurs at a specific membrane voltage called the *threshold voltage.* When the threshold is crossed, an action potential is generated; when the membrane potential is more negative than the threshold, no action potential is generated. Unlike the amplitude of a graded potential, the size of an action potential is not affected by the amplitude of the triggering stimulus, although the latency of the action potential is proportional to the size of the excitatory stimulus once the threshold is reached. Thus, in a given cell, a stimulus just over threshold will generate the same size action potential as a stimulus much over threshold. Therefore, action potentials are said to be *all or none:* Action potentials either occur (when the membrane voltage is above threshold) or they do not occur (when the membrane voltage is below threshold).

Action potentials travel from the cell body to the terminals, a process called *propagation.* Unlike graded potentials, which "fade" as they spread away from the point of origin, action potentials exhibit no decrement as they move down an axon

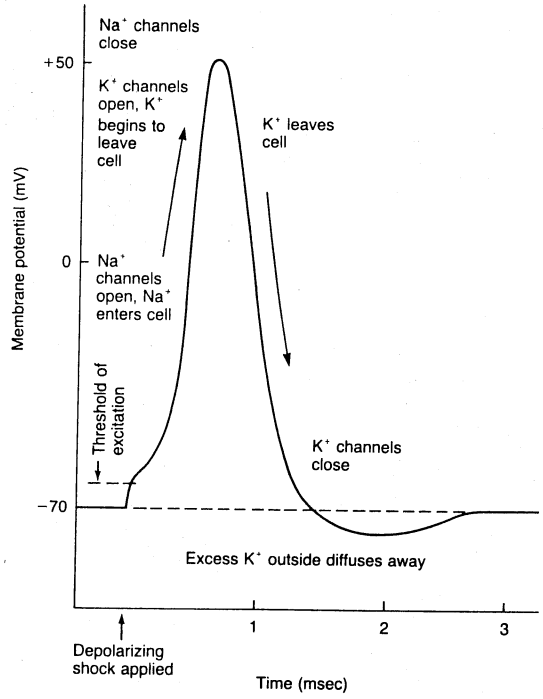

Figure 3.10. A typical action potential and the ionic fluxes associated with various components of the waveform. (Reprinted by permission of the publisher from N. R. Carlson, *Physiology of behavior,* p. 42. Copyright 1986 by Allyn and Bacon, Needham Hts., MA.)

toward the nerve terminals. This movement is really the generation of successive action potentials along the length of an axon. This occurs through the electrical current spread during an action potential that depolarizes the adjacent membrane.

Many axons are sheathed with a lipid insulator called myelin, which is interrupted at regular intervals to expose the axon. At these gaps, the *nodes of Ranvier,* the axon is susceptible to depolarization. Because the sheathed part of the axon is insulated, action potentials jump from one node to the next, a process called *saltatory conduction.* This jumping action greatly increases propagation velocity, the rate of which ranges from about 3 to 120 m/s. Two factors largely determine the speed of propagation: the diameter of the axon and whether or not it is myelinated. Myelinated axons with wide diameters conduct the fastest, whereas fine caliber unmyelinated axons conduct the slowest.

Action potentials are followed by refractory periods during which the membrane becomes electrically unresponsive. At first, the membrane cannot generate another action potential at all (*absolute refractory period*); later, a greater than normal positive change in membrane voltage is required to generate another action potential (*relative refractory period*).

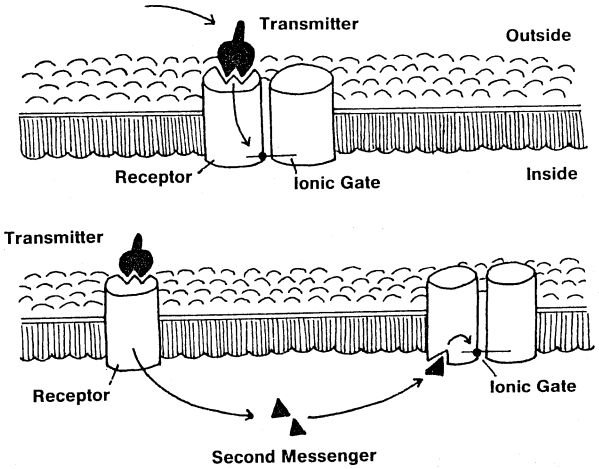

Figure 3.11. Activation of ion channels by neurotransmitters. Panel *a* shows direct activation of an ion channel by the binding of a transmitter, such as acetylcholine, to the receptor; panel *b* shows indirect activation of an ion channel by a transmitter. In the latter case, second messenger molecules serve as the connection between the actions of the neurotransmitter (primary messenger) and activation of the ion channel.

3.4.3 *Neurotransmission*

Action potentials lead to the release of neurotransmitters from the cell. When action potentials propagate down the axon, they cause voltage-sensitive Ca^{2+} channels at the nerve terminals to open. Calcium ions rush into the terminal, where they bind with the enzyme, calmodulin. This enzyme facilitates the release of neurotransmitters from the terminal (*exocytosis*) into the synaptic cleft. In this context, the cell releasing the transmitter is called the *presynaptic* cell, and the cell upon which the transmitter acts is called the *postsynaptic* cell.

Transmitters affect the membrane voltage of the postsynaptic neuron by binding to receptor molecules, specific proteins that span the postsynaptic cell membrane. Neurons generally possess many different types of receptors so that they may respond to each of the possible transmitters released from the many synapses usually present. The receptor molecules have a three-dimensional structure that matches the three-dimensional structure of the transmitter molecule, much like the three-dimensional structure of a lock matches the three-dimensional structure of a key. Thus, different types of neurotransmitters interact with different classes of receptor. For instance, dopamine molecules fit into certain receptor proteins (dopamine receptors) that are different in three-dimensional structure from the receptor proteins for other neurotransmitters. When binding occurs, the neurotransmitter alters the three-dimensional structure of the receptor, which leads to a series of events inside the postsynaptic neuron, resulting in alterations in ionic conductance. Although the typical description of the action of transmitters is postsynaptically on the soma or dendrites, transmitters may also bind to receptors on the presynaptic cell (*autoreceptors*), a form of neuronal feedback control.

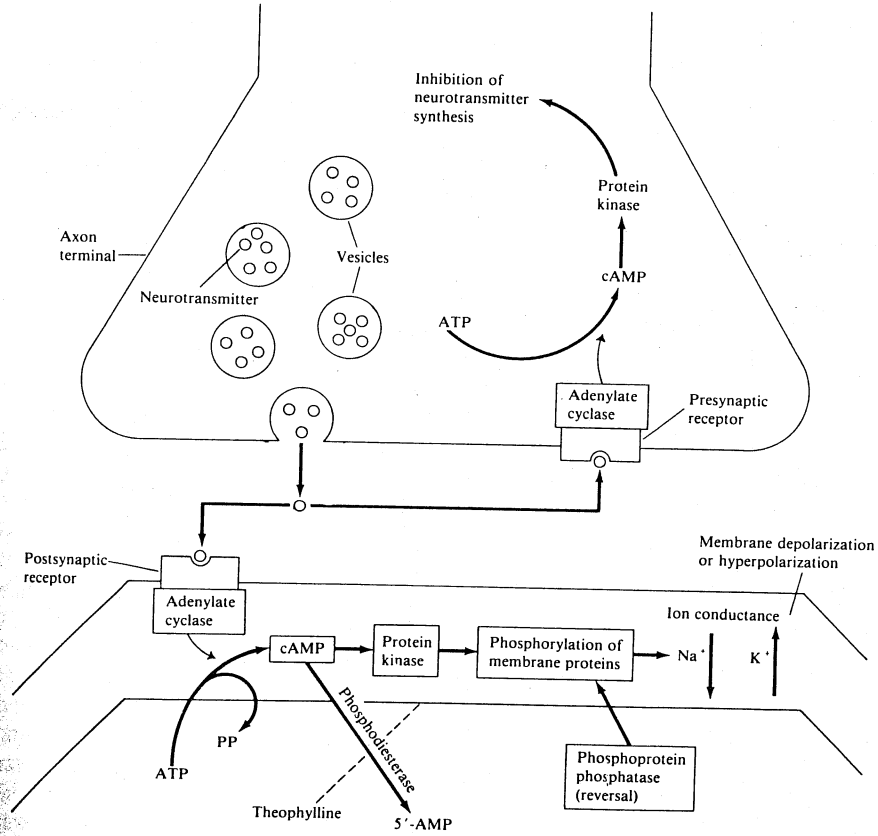

Figure 3.12. Chemical reactions involved in the activation of an ion channel by cyclic AMP. (Reprinted by permission of the publisher from R. S. Feldman and L. F. Quenzer, *Fundamentals of neuropsychopharmacology*, p. 109. Copyright 1984 by Sinauer Associates, Sunderland, MA.)

The binding of a transmitter to a postsynaptic receptor results in the generation of graded potentials (IPSPs and EPSPs) through the opening and closing of particular ion channels. Some transmitters, such as acetylcholine, directly activate ion channels when they bind to receptors (Karlin et al., 1983). This occurs because the ion channel and the receptor are part of the same protein. Some ion channels, however, are located on a separate part of the cell membrane, away from the receptor protein. In these instances, intracellular chemical signals coordinate the functioning of the two (see Figure 3.11). The intermediary molecules used for this purpose are called *second messengers*. Thus, when receptor proteins spanning the cell membrane are bound by the appropriate transmitters, second messengers on the inside of the cell are activated and go through a series of chemical reactions that eventually lead to the opening or closing of an ion channel. Two second messenger systems have been well characterized. They are cyclic adenosine monophosphate (cAMP) and phosphoinositol (PI).

The activation of an ion channel via cAMP involves several steps (Greengard, 1976, 1979) (Figure 3.12). First, a neurotransmitter or hormone binds to a receptor on

the extracellular side of the cell membrane. This frees the catalytic subunit of adenylate cyclase inside the cell, thus forming the active state of the enzyme. The activated adenylate cyclase than catalyzes the formation of cAMP from adenosine triphosphate (ATP). Cyclic AMP then activates a cAMP-dependent protein kinase (protein kinase A) that can catelyze the phosphorylation of an ion channel, which alters its conformation and opens or closes the channel (see the bottom portion of Figure 3.12).

The PI system (Berridge, 1987; Berridge & Irvine, 1984) is somewhat more complex because at least two molecules carry out the transduction. One of these is diacylglycerol, which activates protein kinase C, which then can phosphorylate an ion channel as in the cAMP system. The second transducing molecule in the PI system is inositol triphosphate. Inositol triphosphate is involved in a number of receptor-mediated events such as mobilization and release of intracellular Ca^{2+} from nonmitochondrial stores (a process associated with Ca^{2+}-sensitive processes such as secretion and muscle contractions).

Recently, G proteins, another group of modulatory chemicals, have been found to link some receptors to a second messenger system (Gilman, 1987; Stryer & Bourne, 1986). Two types of proteins are particularly important: G_s stimulates adenylate cyclase activity, while G_i inhibits the enzyme. Recent evidence shows that these G proteins can affect the transduction of cAMP-dependent signals to ion channels (Hescheler et al., 1986, 1987). Other G proteins transduce signals between receptors and ion channels via intermediaries in the PI system (Ewald et al., 1988, Brown et al., 1984). Although G Proteins usually indirectly modify ion channels through second messengers, they apparently directly activate some K^+ and Ca^2+ channels (Brown & Birnbaumer, 1988).

The interaction between transmitter and receptor does not involve a long-lasting covalent bond; rather it involves an ionic bond, and after a time, the transmitter dissociates from the receptor and returns to the extracellular space. At that time, the transmitter may be taken into the presynaptic terminal for recycling and reuse or it may be broken down by enzymes and excreted. In either case, the synaptic action of the transmitter is terminated.

3.4.4 *Summary*

After a transmitter is released from a presynaptic cell, it binds to a receptor protein on the postsynaptic neuron. This leads to the opening or closing of ion channels, either through a direct coupling between the receptor and the ion channel or through the activation of a second messenger. The flow of ions into and out of the cell causes the voltage across the cell membrane to either increase or decrease. These changes in membrane voltage are measured as graded potentials. Graded potentials (IPSPs and EPSPs) are summed at the axon hillock. If the overall input onto that cell is inhibitory, the cell will be prevented from passing on a chemical message to other cells. If the overall input, however, is both excitatory and exceeds the critical firing threshold, an action potential is generated and propagates down the axon. When the action potential reaches the terminals, voltage-sensitive calcium channels are opened. Calcium ions in the extracellular space enter the terminal and bind calmodulin. Transmitter is then released from the cell through a process called exocytosis. The transmitter molecules released into the synaptic cleft can then bind to receptor proteins on the postsynaptic membrane and the process repeats itself.

3.5 THE SYNAPTIC MESSAGE

Only recently have we begun to understand the complexity of the synaptic message and how it applies to function. As we discuss in what follows, relatively recent discoveries about synaptic messages blur the previous simple conception of synaptic signaling. Although these findings have complicated matters, they have led to a better understanding of the fundamental properties of brain function. The analysis of synaptic messages has become an important new way of studying the nervous system and moves us away from a purely connectionistic/electronic-circuit view. We now know that a neuron may secrete many messenger molecules, and it may alter the mix of secretory products as a result of experience. You might say that we used to think that neurons speak in words, but now we know they speak in sentences. Further, we now know that the brain responds as a target organ for certain hormones; and some neuronal release products act more like hormones than the electronically fast neurotransmitters we tend to think of in the nervous system. These findings have profoundly altered the way we think about the nervous system and therefore have important implications for research in psychophysiology.

3.5.1 *Classes of neurotransmitters*

Let us begin the discussion of neurotransmitters with a current list of the classes of chemicals thought to be released from neurons (cf. Feldman and Quenzer, 1984; see Table 3.1). Acetylcholine was the first substance shown to mediate chemical transmission across the synapse (Loewi, 1921). Subsequently, several monoamines were identified: norepinephrine, epinephrine, dopamine, and serotonin (5-hydroxytryptamine). Some neurons use amino acids as transmitters. Some of these amino acids, such as glycine and glutamate, are found in all cells for use in protein synthesis, while others, such as gamma-aminobutyric acid (GABA), are modified from one of the 20 or so standard amino acids. In recent years, investigators have increasingly recognized the importance of polypeptide neurotransmitters (or simply peptides, or neuropeptides). Peptides are cleaved from proteins into products; thus peptides are in fact small proteins. Close to 100 such substances have been discovered and postulated to be transmitters. Several other substances such as adenosine and several purines including the ubiquitous ATP have also been postulated to act as neurotransmitters.

In a few cases, the discovery of specific receptors for a drug led to the implication that an endogenous ligand (or transmitter) for the receptor must be present. This logic led to the discovery of the opioid peptides or endorphins (cf. Akil et al., 1984). Currently, the most prominent example of a receptor in search of a neurotransmitter is the benzodiazepine receptor (cf. Tallman & Gallager 1985). This receptor apparently mediates the actions of valiumlike anxiolytic drugs and a remarkable class of opposite-acting compounds (β-carbolines) that elicit reports of feelings of panic in humans (Dorow, Horowski, Paschelke, Amin, & Beastrup, 1983) and learned helplessness in rats (Drugan, Maier, Skolnick, Paul, & Crawley, 1985). More than six endogenous substances have been proposed as the putative endogenous ligand for benzodiazepine receptors, but a definite role as a neurotransmitter has not been established for any of them (e.g. Ferrero, Guidotti, Conti-Troconi, & Costa, 1984; Skolnick & Paul, 1982). Another receptor in search of a transmitter is the so-called haloperidol-sensitive σ receptor (cf. Walker et al., 1988). This receptor binds many antipsychotic drugs and a variety of (+)-morphinans and (+)-benzomorphans,

Table 3.1. *Major neurotransmitters and neuromodulators*

Acetylcholine (ACh) Monoamines
Dopamine (DA)
Norepinephrine (NE noradrenalin)
Epinephrine (E, adrenalin)
Serotonin (5-hydroxytryptamine, 5HT)
Amino acids
Aspartic acid
Glutamic acid
Homocysteic acid
β-Alanine
Gamma-aminobutyric acid (GABA)
Taurine
Peptides
Alpha-neoendorphin
Alpha-melanocyte stimulating hormone (α-MSH)
Angiotensin II
Cholecystokinin (CCK)
Corticotropin-releasing factor
Dynorphin
β-endorphin
Enkephalin
Leutinizing hormone-releasing hormone
Neuropeptide Y (NPY)
Somatostatin
Substance P
Vasoactive intestinal polypeptide
Vasopressin (antidiuretic hormone, ADH)
Other
Histamine
Adenosine
Various purines

some of which produce psychosislike effects in humans. Recent evidence suggests that this system may mediate some of the antipsychotic actions or motor side effects of neuroleptic drugs. Presumably, certain neurons in the brain release transmitters for these receptors (Contreras, DiMaggio, & O'Donohue, 1987).

3.5.2 *Complex synaptic messages*

3.5.2.1 *Neuromodulation*

A "wiring diagram" of nervous structures can no longer be considered sufficient to make inferences about function because the message at the synapse is much more complex than previously assumed. In recent years, the term *neuromodulator* has come into increasing use for neuronal release products that do not fit the standard definition of short-acting, hyper-, or depolarizing neurotransmitters.

The term neuromodulator is sometimes used to refer to compounds that modify the actions of other secretory products (Barker, 1976; Barker, Neale, Smith, & MacDonald, 1978). Neuromodulators of this sort do not exert direct effects on the postsynaptic membrane but alter the efficacy of another substance. For example,

enkephalin (an opioid peptide) applied iontophoretically to mouse spinal neurons depresses glutamate-evoked responses. This action is unusual because the inhibition of glutamate occurs independently of any direct effect of enkephalin on membrane conductance. Although in some cells, enkephalin directly alters ionic gates like a typical neurotransmitter, in this case, it acts as a neuromodulator by altering conductance changes associated with the actions of another transmitter.

The term neuromodulator is also used to refer to substances that show an unusually long time course. For example, β-endorphin is a very potent opioid peptide that produces long-lasting cellular and behavioral effects (e.g., Walker et al., 1977). This substance is directly relevant to psychophysiological work because it is released from neurons arising in two important centers of autonomic integration, the hypothalamus and the nucleus tractus solitarius (cf. Akil et al., 1984). Very low doses of the substance can cause alterations in pain sensitivity that last an hour or more. In view of its distinctly hormonelike action in the central nervous system, perhaps it is not surprising that β-endorphin is also released as a hormone from the pituitary gland. Indeed, some development studies indicate that hormone-producing endocrine cells and peptide-secreting neurons have a common embryonic origin (Pearse, 1976).

In related research, Sandman et al. (1971) demonstrated long-lasting EEG effects of analogs of alpha-melanocyte-stimulating hormone, a further indication that some neuronal products exert potent long-term actions characteristic of hormones. A number of other centrally acting peptides also exert unusually long-lasting effects including substance P, cholecystokinin, vasopressin, and others (e.g., Krnjevic & Morris, 1974; Meck, Church, & Wenk, 1986; Mueller & Hsiao, 1978; cf. Sandman et al., 1971). These hormonelike neuromodulatory effects suggest that certain functions in the nervous system that exhibit long time constants (e.g., mood shifts) may be mediated by hormonelike neuromodulators rather than ill-defined and yet to be identified reverberating circuits frequently postulated in the past.

One unexpected finding from studies of the relationship between hormones and neurotransmitters was that the brain sometimes reverses roles with the glands. In other words, the brain becomes the target organ under the command of the glands. For example, the work of Lewis, Tordoff, Sherman, and Liebeskind (1982) suggests that opioids released along with catecholamines from the adrenal gland may then be transported to the brain via the blood to produce analgesia. This conclusion is based on studies that showed that opioid stress-induced analgesia depends upon the integrity of the adrenal medullary axis. Further support that the brain is sometimes the target organ derives from studies of angiotensin II (Severs & Daniels-Severs, 1973) and cholecystokinin (CCK; see Mueller & Hsiao, 1978), two peripheral hormones that may enter the brain from the systemic circulation and affect behavior upon commands from peripheral organs.

3.5.2.2 *Multiple release of transmitters*

At one time, most introductory neuroscience courses taught a rule called Dale's Principle. Dale's Principle asserts that each neuron secretes one and only one neurotransmitter. The principle is wrong on two counts. First, Dale never postulated this principle; Dale thought that all branches of the same neuron have the same secretary product(s) (Dale, 1935). Second, many (perhaps most) neurons secrete many substances (cf. Hokfelt et al., 1986). The evidence for multiple release is

practically indisputable, and the new principle (multiple release) has important ramifications because the proportions of the release products can vary as function of experience.

The earliest clear sign of multiple neuromodulators per cell came from studies of neurons that produce opioid peptides. Biochemists and molecular biologists (Nakanishi et al., 1979) found that the potent opioid peptide β-endorphin was derived from a protein precursor that produced a whole array of interesting peptides. The entire molecular structure of this precursor (called proopiomelanocortin, POMC) was eventually determined, and we now know a good deal about the products that are released from neurons that use β-endorphin. In particular, we know that neurons that secrete β-endorphin also secrete α-melanocyte-stimulating hormone (referred to previously), gamma-melanocyte-stimulating hormone, and several other peptides.

In the case of β-endorphin, the functional significance of multiple release has been determined to at least some extent (Akil, Young, Walker, & Watson, 1986; Walker et al., 1987). These studies used analgesia as a dependent measure because β-endorphin apparently serves naturally to modulate pain sensitivity. Studies of the behavioral properties of other products of the β-endorphin precursor show that they too affect pain sensitivity (e.g., Walker, Akil, & Watson, 1980). Some products act as analgesics but do not have an opiate pharmacology (Walker, Berntson, Sandman, Kastin, & Akil, 1981). Other products are potentiators; they have no analgesic properties of their own but enhance the analgesia produced by other products. At least one of the release products may act as an antagonist; this peptide (β-endorphin$_{1-27}$, the first 27 amino acids of β-endorphin) significantly reduces the analgesia produced by β-endorphin.

The significance of these findings for behavior was further suggested by studies of stress-induced analgesia (Akil et al., 1986). Uncontrollable footshock under appropriate conditions causes animals to become analgesic. However, with repeated administration the animal shows behavioral tolerance, and the analgesic effect of stress is diminished. Biochemical studies have shown that this alteration in stress-induced analgesia is accompanied by a change in the chemical release patterns of β-endorphin-containing neurons. These neurons normally secrete little of the opiate-attenuator molecule (β-endorphin$_{1-27}$). However, after repeated stresses, the neurons switch to producing little β-endorphin and much more of the attenuator substance. These findings indicate that the synaptic message is modifiable in terms of the transmitter products released. The words of the synaptic sentence have been changed.

3.5.2.3 *Autonomic nervous system: differential release as a function of firing rate*

The multiple-release phenomenon is not limited to the central nervous system. This mode of synaptic transmission occurs widely in the autonomic nervous system as well. In fact, studies of chemical transmission in the autonomic nervous system have substantially clarified our understanding of multiple release. This is not surprising; historically, the autonomic nervous system has provided a model for the central nervous system because it is much easier to isolate secretory products and analyze their actions in the autonomic nervous system. These studies indicate a frequency-dependent release of different transmitters that sometimes exert opposite effects postsynaptically.

DeGroat and colleagues (1985, 1984) suggested such a frequency-dependent release of different transmitters from studies of the preganglionic innervation of the urinary bladder. In these neurons, acetylcholine is colocalized with enkephalin and the other half dozen or more products of the enkephalin precursor. They found that the usual postganglionic discharge elicited by stimulation of a branch of the pelvic nerve is inhibited by repetitive (20–30 Hz, 3–5 sec) stimulation of another branch of the same nerve. This effect is blocked by naloxone, a specific opiate antagonist, suggesting that at low stimulation frequencies acetylcholine is preferentially released and at higher frequencies enkephalin (which is sensitive to naloxone) is released. Since enkephalin and acetylcholine exhert opposite effects on the bladder, the chemical mix released at a given frequency is an important source of information beyond the electrical activity alone.

Another example of frequency-dependent release of different transmitters in the autonomic nervous system derives from the studies of Lundberg and Hokfelt (1986; see also Lundberg, Rudehill, Sollevi, Theodorsson-Norheim, & Hamberger, 1986). They demonstrated that low-frequency stimulation of the splenic nerve (sympathetic postganglionic) results in the release of NE. At higher frequencies of stimulation, a peptide (neuropeptide Y) that is costored with NE is preferentially released. Psychophysiologists may take additional interest in the vasoconstrictor responses produced by neuropeptide Y and the observation that burstlike firing in these nerves produces a greater vasoconstrictor response than the same number of action potentials in regular firing nerve. These studies suggest that higher frequency bursts may normally be associated with the preferential release of peptide products, many of which exert hormonelike actions.

We tend to associate a state of rest with the parasympathetic division of the autonomic nervous system and a state of emergency, the "fight or flight" responses, with the sympathetic division of the autonomic nervous system. Clearly, the data described in the preceding paragraphs indicate that the postsynaptic actions of autonomic nerves may change as a function of firing rate through the release of opposite-acting transmitters. These observations would thus appear to be applicable to psychophysiological models of the autonomic nervous system, especially if measures of burst firing in autonomic nerves can be developed.

3.5.2.4 *Multiple release and the vascular system*

The experiments described in the previous section further imply that some release products regulate blood flow. Indeed, the vasculature in the brain responds to increased neuronal firing by increasing blood flow to the local area (e.g., Lassen, Ingvar, & Skinhoj, 1978). Increasingly, it appears that this change in local blood flow is mediated by chemical products released from nerve cells that leave the synapse and bind to receptors or the vascular walls. Many vasoactive peptides are present in neurons, and biochemists have demonstrated the presence of receptors for these substances on vascular membranes. Some release products from neurons may accomplish a vascular function secondary to a postsynaptic action, whereas others may serve only a vascular function. In addition, vascular effects of some breakdown products of neuromodulators suggest that release products may convey a synaptic message while metabolites convey a corresponding vascular message. These findings suggest that we should look outside the synapse as well as at the postsynaptic membrane when considering the functions of multiple release.

3.6 ORGANIZING PRINCIPLES OF THE CENTRAL NERVOUS SYSTEM

Undoubtedly, the case for a neurochemical understanding of the nervous system cannot be isolated from the elegant wiring of the nervous system. Indeed, it may be self-evident that chemical transmitters and neuroanatomical connections must be considered together to understand neural mechanisms. Thus, the afferent (input) and efferent (output) connections of neurons provide important clues to the functional organization of neural systems. A great deal of anatomical order exists within many levels of analysis, ranging from major axonal pathways between nuclei down to specific patterns of synaptic contacts on individual neurons. In this section, we describe some of the general principles of anatomical organization. Here we delineate some of the major systems and discuss patterns of organization found within them. We will divide the central nervous system into (1) sensory systems, (2) motor systems, and (3) integrative systems. We hasten to note, however, that there exists a great deal of anatomical and functional interplay between these divisions, and many structures lie along the interfaces of these divisions.

3.6.1 *Sensory systems*

An important division between sensory systems is based on the orgin of the stimulus. The five special senses are called *exteroceptive* because the driving energy arrives from the outside world. However, anyone who has suffered from appendicitis can confirm that we have many sensors that report the state of our internal environment (*interoceptors*). These include not only pain sensors (nociceptors) but also baroreceptors, CO_2 receptors, joint position detectors, muscle spindles, and others. Many of these latter receptors apparently do not receive representations in the cerebral cortex, which is presumably why their activity does not reach subjective consciousness (see Reed, Harver, & Katkin, chapter 9).

3.6.1.1 *Sensory transduction, receptive fields, and lateral inhibition*

Several common features of all sensory systems have been discovered. Sensory systems always involve a transducer function that selectively converts a form of energy into electrochemical currents in the transducing cell. This function can occur either in specialized receptor cells (e.g., photoreceptors, haircells) or in distal processes of primary sensory neurons. The connections between the set of these receptor cells and the set of primary afferents are spatiotopically precise. That is to say, individual nerve cells only receive inputs from a small and usually contiguous subset of sensory receptors. As a result, individual sensory neurons will only respond to stimulation of a particular region of receptor surface (e.g., a particular portion of the skin). This small region of the receptor surface that elicits some response when stimulated is called the neuron's *receptive field*. The concept of the receptive field is central to any understanding of sensory systems. Indeed, the discipline of sensory physiology has as its principal concern the development of accurate descriptions of receptive fields of sensory neurons, since such a description is a prerequisite to understanding how the brain encodes, processes, and interprets sensory inputs.

One universal feature of receptive fields is termed *lateral inhibition*: The effects of activity in one sensory receptor are usually opposed by simultaneous stimulation of the surrounding receptors. Lateral inhibition was first described by H. K. Hartline

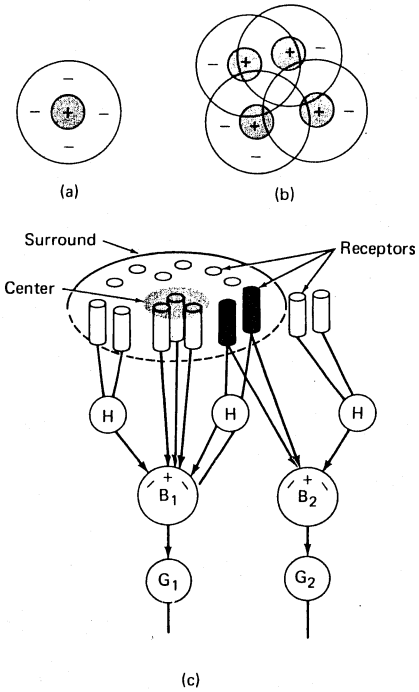

Figure 3.13. The center–surround receptive field organization of retinal ganglion cells. Note that regions in the center of a receptive field and in the surrounding doughnut-shaped area exert opposing influences as in *a*. This is accomplished as shown in the bottom panel. Inhibition by the surround region occurs in the retina through the interactions of horizontal cells (labelled *H*) that inhibit the bipolar cells (labelled *B*). (Reprinted by permission of Kurt Schlesinger, University of Colorado, Boulder.)

(1949) in the compound eye of the primitive invertebrate *Limulus* (the horseshoe crab). In this species, the receptor cells are directly interconnected via a fiber plexus, and Hartline's early work clearly showed that the light-induced activity in a receptor was attenuated by stimulation of an adjacent receptor via these lateral connections (Hartline & Ratliff, 1957). In vertebrate systems, this inhibition usually is mediated by an interneuron. The basic circuit that produces lateral inhibition in the vertebrate retina is schematically illustrated in Figure 3.13.

A general characteristic of all sensory (and probably nonsensory) neural systems, lateral inhibition has the important consequence of *accentuating differences* in stimulus intensity in adjacent areas while simultaneously attenuating responses to spatially uniform stimuli. In the case of vision, lateral inhibition enhances sensitivity to contours (see Figure 3.13) while it reduces sensitivity to gradual changes in luminance. The importance of lateral inhibition can be inferred from its occurrence at the first opportunity in retinal processing: the second-order neuron (bipolar cell; see Figure 3.13). Indeed, sensory systems generally implemented some form of lateral inhibition at the level of the first synaptic station (which is, of course, the first opportunity to include interneurons); lateral inhibition therefore character-

izes all second-order sensor cells (e.g., cells in the cochlear nucleus in the auditory system and dorsal column nuclei in the somesthetic system). Techniques exactly analogous to the center–surround antagonism first described in the vertebrate eye by Kuffler (1953) are now routinely used to enhance contrast in digital image processing.

We have seen how lateral inhibition sharpens the spatial profile of sensory activity produced by stimulation of adjacent regions of the receptor surface. Despite the obvious differences between sensory systems, the consequence of these lateral interactions is always to enhance the system's ability to discriminate sites of activity within the mosaic of sensory receptors. For example, in the auditory system, tonal frequency is largely encoded by the place of activity on the basilar membrane (the receptor surface of the auditory system). Therefore, lateral inhibition results in what is known as *two-tone inhibition* (Greenwood & Maruyama, 1965). The important point to recognize is that two-tone inhibition enhances tonal discrimination capacity in the same manner that center–surround antagonism enhances spatial resolution in vision.

The central connections of primary afferents always preserve the topology of the receptor mosaic. As a result, neurons with nearby receptive fields also tend to be in close spatial proximity. When we consider the three-dimensional structure of a sensory nucleus within the brain, we find that the distribution of receptive fields within the nucleus recapitulates (often with astonishing precision) the receptor mosaic. This property is called receptotopic organization. We will have more to say about these receptotopic patterns shortly. For now we simply point out that the *locus* of activity within a nucleus is in fact part of the neural code for stimulus quality.

We should make one more point with respect to the organization of receptive fields. It is often the case that as we examine the response characteristics of progressively higher order sensory neurons, the receptive field characteristics become increasing more specific with respect to the spatio-temporal distribution of effective stimuli. When studying the highest levels of sensory systems, the cells often become very difficult to "drive" with sensory inputs, making it difficult to address the issue of how higher order percepts are encoded by individual neurons or by ensembles of neurons. Eventually, this increase in receptive field complexity is accompanied by an increase in receptive field size. Thus the receptotopic order described in the preceding paragraph ultimately gives way to representations that are not closely tied to the particular location of the eliciting stimulus. This is apparently a consequence of progressive convergence and is often regarded as evidence that the processing has gone from a strict receptor-based coordinate system to a nonreceptotopic system that one usually associates with higher order percepts (i.e., components of the system respond to intrinsic features of a given stimulus regardless of its position on the receptor surface).

3.6.1.2 *Central distribution of sensory inputs*

The central distribution of sensory inputs can be generally characterized as taking three specific routes. First, all primary sensory afferents contribute to reflex pathways that are localized in the spinal cord and brainstem. Second, sensory pathways influence the cerebellum, which has motor functions. Third, sensory afferents form multisynaptic pathways that synapse in the thalamus, which then projects to specific sensory areas of the cortex.

Reflex pathways. Reflexes involve relatively stereotyped sensorimotor behavioral patterns that are supported by specific neuronal pathways. Reflexes vary in complexity from the simplest direct connections between sensory and motor neurons to multisynaptic circuits involving many interneurons. Both exteroceptive and interoceptive reflexes are commonplace. Examples of exteroceptive reflexes include the monosynaptic myotatic reflex (described in more detail in what follows), the constriction of the pupil of the eye in response to light (the pupillary light reflex), and the contraction of the tensor tympani and stapedius muscles (which protect the cochlea by dampening the motion of the middle ear ossicles) in response to intense auditory inputs. Interoceptive examples include the baroreceptor reflex (which controls vasoconstriction and heart rate in response to changes in blood pressure) and changes in respiration resulting from chemoreceptors that sample CO_2 concentration in the blood. Reflexes are by definition relatively simple sensorimotor pathways; yet even the simplest of these circuits is subject to a variety of modulating influences. The monosynaptic stretch reflex, for example, is subject to modulatory influences based on adaptive constraints such as body posture and center of gravity (Nashner, 1976).

Cerebellar pathways. The cerebellum ("little brain") receives information from virtually all sensory systems. In general, these cerebellar circuits lie in parallel with the reflex pathways previously discussed and, in some cases, modulate reflex activity in important ways. For example, consider the vestibulo-ocular reflex (VOR). The afferent limb of this reflex originates in the semicircular canals of the inner ear, which sense acceleration of the head in any plane. These pathways terminate on second-order neurons in the vestibular complex of the medulla. The second-order neurons project in turn onto motoneurons that control eye position through their connections on the extraocular muscles. Through these connections, this reflex produces compensatory changes in eye position in response to angular rotation of the head, so that the visual image on the retina remains stable during head movements.

The VOR is a marvelous feat of nature's engineering. One of the most interesting aspects of this reflex is its remarkable degree of plasticity. If a person wears left–right inverting prisms, the world is turned backward and the old movements of the eyes from the reflex are likewise backward. However, after a time, the relationship between the motion of the head and the movements of the eyes is somehow reversed, restoring the adaptive value of the reflex. Remarkably, this "plasticity" of the VOR is dependent on a particular region of the cerebellum that receives primary afferent input from the semicircular canals and projects in turn to vestibular nuclei of the medulla. Lesions of this "vestibulo-cerebellum" result in a reversal of the reflex in adapted animals back to the unadapted state and prevent any further adaptation from occurring (Robinson, 1976).

Thalamocortical projection systems. All of the exteroceptive sensory afferents contribute to pathways whose ultimate destination is the cerebral cortex. These cortical pathways are associated with the conscious perception of sensory events, and the associated circuits are important to the processes of recognition and discrimination and to the perception of the external environment. Indeed, a substantial domain of neuroscience is concerned with the cortical mechanisms subserving the sensory and motor functions of the cerebral cortex.

Most of the inputs to the cerebral cortex originate in the thalamus of the diencephalon. Every sensory modality except smell (touch, taste, audition, balance, and vision) projects to a specific thalamic nucleus, which in turn projects to relatively specific cortical targets or "projection fields." As a result, each sensory modality has a specific cortical representation (i.e., visual cortex auditory cortex, somatosensory cortex; see Figure 3.2). There have been dramatic advances in our understanding of the general organization of sensory areas of the cortex over the past 10–15 years. We now turn to a brief consideration of these advances.

The traditional view of the cortical organization of sensory systems was that each modality gained access to the cerebral cortex through its representation in one particular thalamic relay nucleus. For example, in vision, the retinal ganglion cells project to the lateral geniculate nucleus of the thalamus (LGN). The dorsal division of this nucleus (LGNd) in turn projects to a cortical area variously known as area 17, striate cortex, or visual cortical area 1 (V1). Some readers may be familiar with the general organization of this geniculo-striate system as it has been delineated primarily through the classic work of Hubel and Wiesel (1977); space does not allow us to present their findings here. Also note that the designation "area 17" originates from studies by the German neuroanatomist Brodmann (1909), who designated different areas of cortex with numbers based upon the pattern of distribution of morphologically distinct neurons (Figure 3.14). Area 17 contains a complete representation of the contralateral visual field, so that visually responsive neurons are laid out on the cortex in a spatial pattern that corresponds to the spatial pattern of visual space at the eye. The term V1 refers to this so-called visuotopic organization, whose boundaries correspond exactly with cytoarchitectural boundaries.

In primates (presumably including humans), the vast majority of geniculate projections are confined to this cortical target (V1). However, surrounding area 17 is another cytoarchitecturally defined cortical field called area 18, and for many years area 18 was known to also contain a representation of the contralateral visual hemifield. For this reason, area 18 is often referred to as V2 (visual area 2). Beyond area 18 is a third cortical field, area 19. The conceptualization of area 19 has changed dramatically in the last 10 years, however, and these later developments in many ways serve to illustrate new insights into the cortical organization of sensory systems more generally.

3.6.1.3 *Parallel thalamocortical pathways*

As indicated in the preceding section, the geniculo-striate system was regarded at one time to be the sole route through which visual information could reach the neocortex. This view is implicit in the term *primary visual cortex*. In fact, this notion was not restricted to visual cortex, but to somatosensory and auditory cortices as well. The cortical fields surrounding the primary sensory fields were thought to depend on the primary fields for their principal inputs and were therefore regarded as "higher order" stages in sensory processing. Thus, with respect to visual processing, areas 18 and 19 were regarded as visual association cortex and were thought to subserve more "perceptual" functions. The association cortex was classically defined as lacking a thalamic input: It simply processed the inputs from the primary projection areas. Thus, the cortical processing of sensory information was viewed very much in terms of serial processing. When anatomists discovered that in fact all neocortex receives a

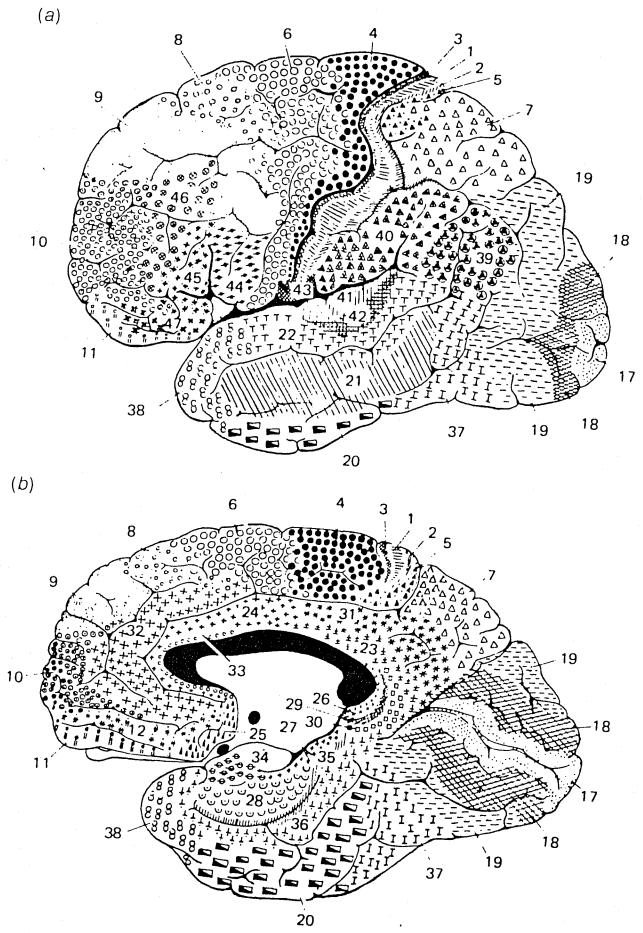

Figure 3.14. Lateral view of the cerebral cortex showing Broadmann's divisions. The areas outlined by Broadmann are based on differences in cytoarchitecture, the typical morphological features of the neurons found in a region. (Reprinted by permission of the publisher from J. Kelly, Anatomical basis of sensory perception and motor coordination, in *Principles of neural science,* E. Kandel and J. Schwartz, Eds., p. 237. Copyright 1985 by Elsevier Science.)

thalamic projection, the definition of association areas was simply extended to include those thalamic nuclei that were known to project to association areas, and these were referred to as *association nuclei of the thalamus*. The defining characteristic of association areas (either cortical or thalamic) was that the afferents depended on the primary visual cortex for their inputs. Areas 18 and 19 receive a thalamic input from a massive nucleus called the pulvinar; so when it was discovered that the pulvinar received a projection from the superior colliculus (a major visual structure in the midbrain that receives direct input from the retina), it was recognized that even the modified definition of association cortex was no longer tenable. Thus, areas 18 and 19 were recognized as receiving visual information via

at least two parallel pathways; first via the geniculo-striate system and second via the newly discovered pathway from the retina to the colliculus, thence to the pulvinar (cf. Diamond & Hall, 1969). This parallel thalamocortical organization is now recognized as a ubiquitous feature of cortical systems (Woolsey, 1982).

3.6.1.4 *Multiplicty of visual cortical areas*

Following these developments, physiological studies revealed a previously unrecognized complexity in the visuotopic order of cortical areas surrounding area 17. Rather than consisting of one representation of the visual hemifield that was coexistensive with the cytoarchitectural field of area 19, it was discovered that area 19 actually consisted of nine or more discrete representations of the visual field (cf. Van Essen, 1979; Woolsey, 1982)! A great deal of recent work has focused on the functional properties of cells in these different regions as well as the specific afferent and efferent patterns that exist. Not surprisingly, there appears to be some degree of functional specialization between these areas (some areas seem specialized for color or movement; see Livingstone, 1988). Moreover, this multiplicity of representation is a general feature of the cortical organization of all sensory systems (Woolsey, 1982).

3.6.1.5 *Some functional considerations*

As previously indicated, the cerebral cortex is often regarded as essential to processes such as recognition, discrimination, and conscious awareness of sensory events. Here, we briefly point out two phenomena that support this position. First, based on studies using an evoked response technique (see Coles, Gratton, & Fabani, chapter 13), Libet and colleagues (Libet, Alberts, Wright, & Feinstein, 1967) assert that the cortex is necessary for conscious awareness. Evoked responses are alterations in the electroencephalogram (EEG) that are locked to stimuli. Typically, the EEG is averaged using a computer, and the averaging is time locked to the onset of the stimulus. Components of the EEG that are consistently elicited by the stimulus "grow", whereas random components average to zero. In the work reported by Libet et al. (1967), however, this averaging was not necessary as the evoked responses were recorded with fine electrodes that were actually implanted in the cortex itself. These workers show that a specific component of the evoked response in primary somatosensory cortex (S1) correlates with conscious awareness of a cutaneous sensation. Following an initial biphasic wave, this component occurs relatively late (approximate latency of 300 ms), and it invariably happens when a detectable stimulus (in these experiments, a mild electric shock) is applied to the skin. If, however, an electrical pulse is delivered to the somatosensory thalamic relay nucleus, the early components of the cortical evoked response occur, but the later components may not be present (their occurrence depends on the duration of the electrical pulse train to the thalamus). Libet et al. (1967) report that human subjects experience a conscious sensory event that is referred to a specific portion of the body (entirely predictable based on the receptotopic order) only when the late component of the evoked response is present, indicating that a substantial amount of neural processing must occur in the somatosensory cortex in order to produce a conscious cutaneous sensation (a process he refers to as achieving neuronal adequacy).

A second example of the role of sensory cortex in conscious awareness derives from the work of Wieskrantz and colleagues (Weiskrantz, Warrington, Sanders, & Marshall, 1974) on visual discrimination performance in human patients following removal of primary visual cortex. These surgeries are sometimes performed to remove life-threatening brain tumors. Damage in the primary visual cortex in humans produces a dramatic decrease in visual sensitivity in the contralateral visual field, a condition referred to as a scotoma or cortical blindness. This blindness is, from the point of view of the patient, quite dense: Such patients fall to report visual events that occur in the affected portion of the visual field. However, Weiskrantz et al. (1974) report that if forced to make binary choices concerning the identity of visual stimuli presented within this area of blindness (e.g., to guess whether a luminous bar was horizontal or verticall), such patients are correct on as many as 90 percent of the trails despite their insistence that they are unaware that a stimulus was presented at all! Not surprisingly, Weiskrantz has called this phenomenon "blind sight." While some have raised the possibility that these demonstrations of residual capacity within a cortical scotoma are artifactual (Campion, Latto, & Smith, 1983), others have countered with demonstrations of blind sight when the potential for such artifacts had presumably been eliminated (Stoerig, Huber, & Poppel, 1985). In any case, since these residual capacities are clearly not possible with more extensive damage to the visual areas of the neocortex, these findings illustrate the importance of cortex for conscious sensory processing. The important remaining issue is the location (striate or extrastriate?) and nature of the neural mechanisms that support residual vision.

3.6.2 *Motor systems*

As early as 1906, Sherrington proposed that simple movements beginning with reflexes serve as building blocks that are sequentially executed to form complex motor acts. Other early theorists recognized that the activity of many muscles must be coordinated to accomplish a particular task. We know today that voluntary movements require coordination of many levels of the neural axis. The first portion of this section outlines some basic properties of muscles and how they interact with the central nervous system to elicit basic movements. Later sections describe supraspinal mechanisms that are involved in the control of movement.

3.6.2.1 *Motoneurons*

Motoneurons are neurons that innervate muscles. Two types of motoneurons, alpha- and gamma-motoneurons, project from the ventral horn of the spinal cord to muscles. These neurons release the neurotransmitter acetylcholine, which produces muscular contractions (Dale et al., 1936).

Alpha- and gamma-motoneurons innervate different types of muscle fibers and are thus associated with different functions. *Alpha-motoneurons* are very large myelinated neurons that innervate extrafusal fibers. *Extrafusal fibers* are the large muscle fibers that do the bulk of the work. Thus, alpha–motoneurons are important in regulating contractions in the muscle bulk responsible for most of the work under a load. A *motor unit*, the smallest functional unit controlled by the nervous system, is comprised of one alpha-motoneuron and all the muscle fibers it innervates.

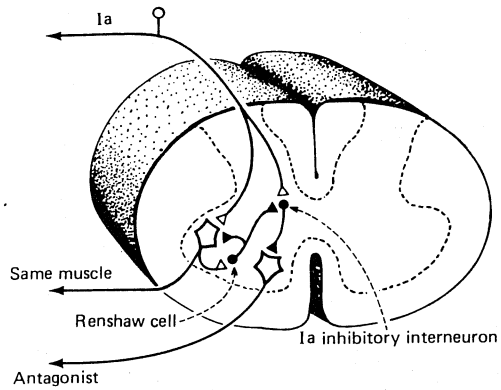

Figure 3.15. Schematic showing the neural basis for recurrent collateral inhibition involving Renshaw cells. (Reprinted by permission of the publisher from T. Carew, The control of reflex action, in *Principles of neural science,* E. Kandel and J. Schwartz, Eds., p. 459. Copyright 1985 by Elsevier Science.)

Since alpha-motoneurons are constantly receiving inputs, they are in danger of overstimulation. However, overstimulation does not occur because alpha-motoneurons have axon collaterals that terminate on interneurons called Renshaw cells. These Renshaw cells synapse on the same alpha-motoneuron and inhibit it (Figure 3.15). This arrangement, called recurrent collateral inhibition, results in a sharing of the load among all the motor units. This concept is similar to that of a refractory period in an axon, the period immediately following an action potential during which no other action potentials can propagate. Both arrangements protect neurons from overstimulation; Renshaw inhibition additionally protects muscle fibers from overstimulation.

In contrast to alpha-motoneurons, which innervate extrafusal fibers, *gamma-motoneurons* innervate *intrafusal muscle fibers,* which work together to set the position of a limb under varying loads. Through spinal reflex mechanisms, gamma-motoneurons and stretchreceptors use feedback control to maintain the extrafusal muscle at a present length. Gamma-motoneurons, through reflex circuity (involving 1a afferents), can also indirectly activate extrafusal (load-bearing) muscle fibers. The synaptic arrangement is diagrammed in Figure 3.16.

3.6.2.2 *Coding*

When a motoneuron fires, it releases acetylcholine, which binds to receptors on muscle cell membranes. Muscle cells are very similar to nerve cells in their electrical properties, and when the transmitter binds, the muscle is depolarized. With sufficient depolarization a *muscle action potential* is produced; this results in the contraction of the muscle fiber. The force of a muscular contraction is governed by recruitment and firing rate. The more motoneurons that are active during a contraction (*recruitment*), the greater the force of the muscle contraction. Also, the faster the motoneurons fire, the greater the force. Changes in the force of muscle contraction through either recruitment or firing rate are associated with changes in the electrical activity of the muscle. These voltage fluxes, called *electromyograms,* or

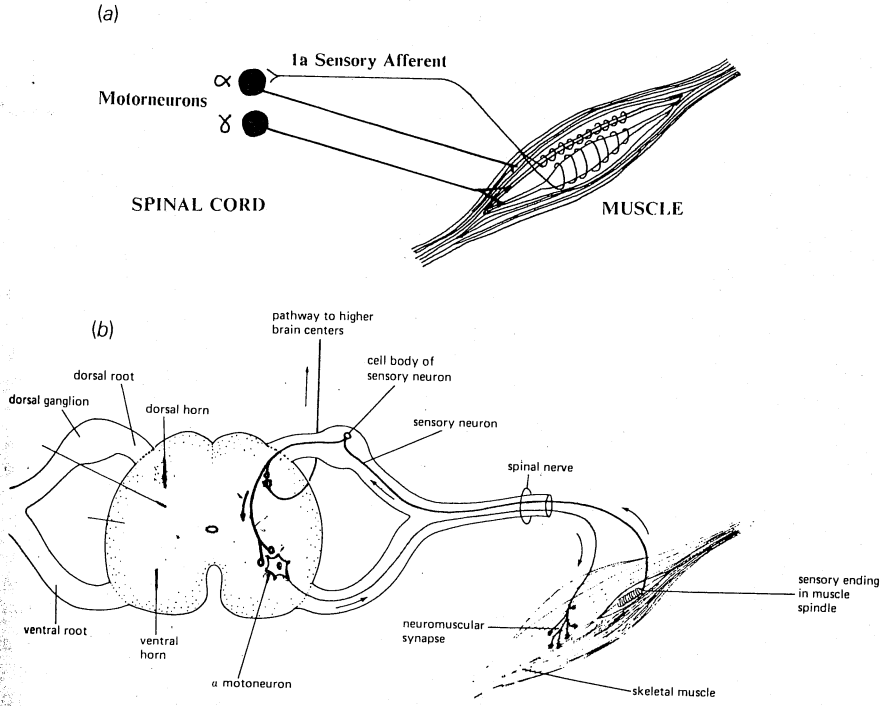

Figure 3.16. (*a*) Synaptic connections allowing for interactions between extrafusal and intrafusal muscle fibers. (*b*) Synaptic connections involved in the myotactic or stretch reflex. Stretching of a sensory ending in the muscle spindle causes the sensory neuron to fire. This activates a monosynaptic pathway that releases an excitatory transmitter onto an alpha-motoneuron. Activation of the motoneuron causes all of the muscle fibres of the motor unit to contract. Although gamma-motoneurons are also present in the spinal cord (see panel *a*), they are not mono-synaptically activated by the sensory afferents. (Panel *b* reprinted by permission of the publisher from F. L. Strand, *Physiology: A regulatory systems approach,* 2nd ed. Copyright 1983 by Macmillan.)

EMGs, may be recorded using either needle electrodes inserted near the muscle itself or surface electrodes attached to the skin (see Cacioppo, Tassinary, & Fridlund, chapter 11). Electromyograms are useful in determining whether a particular muscle is active during a task and yield useful information about the relative timing between muscle groups.

3.6.2.3 *Muscle receptors*

Muscle receptors convey information about the state of the muscles to the nervous system. They provide important feedback to the central nervous system that is used to coordinate movements. Two main types of receptors are found within muscle fibers: *Golgi tendon organs* and *muscle spindles.*

Golgi tendon organs are found near the junction of the muscle and tendon. Activation of afferents in Golgi tendon organs conveys information to the spinal cord

about the amount of force being generated by the muscle. In addition, when Golgi tendon organs are stretched, a protective reflex is activated to prevent damage to the tendon.

Muscle spindles are the second major type of muscle receptor. Muscle spindles are stretch receptors found within intrafusal muscle fibers. They signal to the spinal cord information about the length of the muscle and the rate at which the length of the muscle is changing.

3.6.2.4 *Spinal reflexes*

We have discussed autonomic reflexes and the vestibulo-ocular reflex. Now we turn to a discussion of some spinal reflexes that form the basis for more complex movements. As discussed, reflexes are modulated by higher structures, and they may be "chained" to form a more complex series of movements. The circuitry underlying all spinal reflexes involves three components: (1) a sensor such as a sensory receptor that receives input about environmental conditions, (2) a spinal neuron such as a motoneuron in the ventral horn of the spinal cord, and (3) an effector such as a muscle fiber that contracts in response to appropriate stimuli.

One important reflex based on the muscle spindle feedback to the spinal cord is the *myotatic,* or *stretch, reflex.* If the reader has ever observed the knee-jerk reflex, then he or she has observed the stretch reflex in action. The neuronal circuitry of the myotatic, or stretch, reflex is shown in Figure 3.16. Stretch of a sensory ending in the muscle spindle activates an afferent from the muscle. The afferent makes a monosynaptic *excitatory* connection with an alpha-motoneuron controlling synergist muscles (see figure) and an *inhibitory* connection via an interneuron with an alpha-motoneuron to antagonist muscles (interneuron and antagonist muscle not shown in diagram). The myotatic reflex controls load management by causing contraction of extrafusal muscles to relieve the stretch on intrafusal muscle fibers. This has the effect of maintaining a constant length (and position) under varying load. This happens quite quickly and unconsciously because only one synapse is involved. During voluntary movement *coactivation* occurs such that both the alpha- and gamma-motoneurons fire simultaneously. This serves to maintain the sensitivity of the gamma/spindle (stretch reflex) length control system.

The circuitry of the *flexor reflex* is outlined in Figure 3.17. This reflex is responsible for withdrawal from noxious stimuli. For example, when one touches a hot stove, nociceptive receptors in the skin activate neurons in the dorsal horn of the spinal cord. These sensory connections synapse onto motoneurons in the ventral horn of the spinal cord, which leads to contraction of fibers in the flexor muscle. Due to the protective nature of the flexor–withdrawal reflex, it is noteworthy that it will override any other reflex that happens to be active at the same time.

The *crossed extensor reflex* is basically the flexor reflex already described plus the contralateral half of the same reflex. The crossed reciprocal innervation that is characteristic of the crossed extensor reflex is diagrammed in Figure 3.18. Basically, the connections of the crossed reciprocal innervation are such that on one side are flexor excitation and extensor inhibition whereas on the other are extensor inhibition and flexor excitation. This combination is important for postural stability. For example, if one steps on a hot coal at a barbecue, the withdrawal of the burnt limb is accompanied by extension of the contralateral limb helping to maintain balance. Note that the reciprocal flexion–extension pattern coded in the crossed extensor

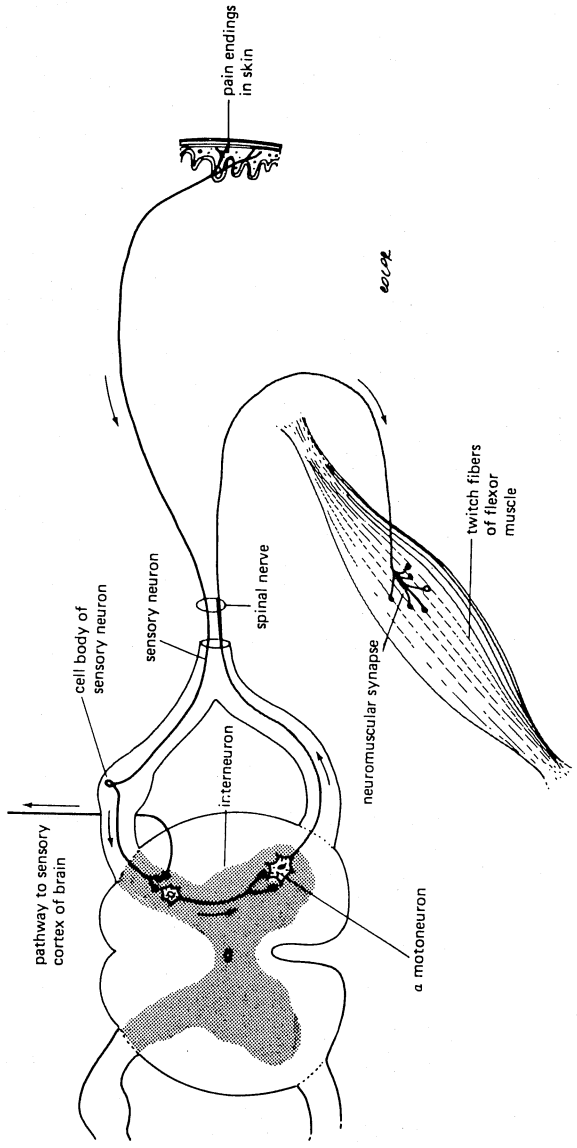

Figure 3.17. Disynaptic connections of the flexor reflex. Stimulation of pain endings in the skin activates an interneuron in the dorsal horn of the spinal cord. The interneuron then stimulates an alpha-motoneuron in the ventral horn, which produces a contraction of twitch muscle fibers. All the synapses in this pathway are excitatory. (Reprinted by permission of the publisher from F. L. Strand, *Physiology: A regulatory systems approach,* 2nd ed. Copyright 1983 by Macmillan.)

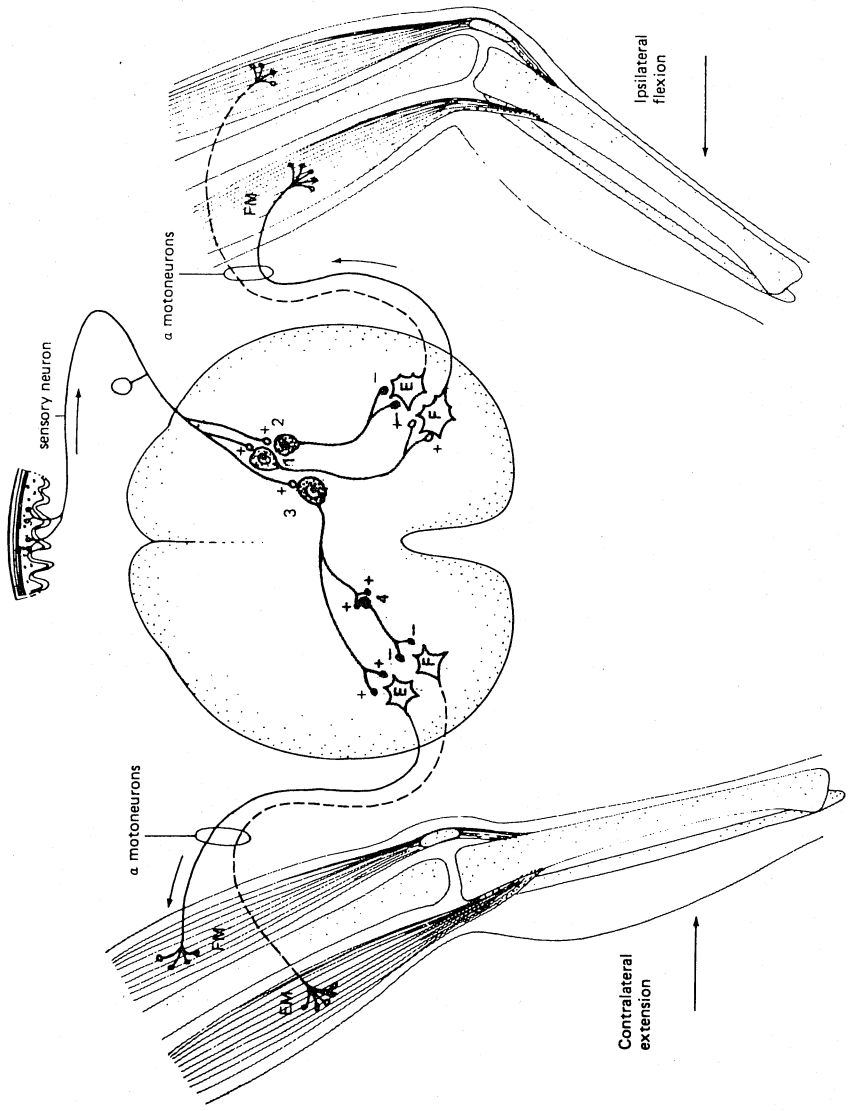

Figure 3.18. Circuitry underlying the crossed extensor reflex. When sensory endings in the skin are stimulated, the reciprocal innervation present in this reflex allows ipsilateral flexion and contralateral extension to occur simultaneously. E = extensor, F = flexor, open nerve terminals release excitatory (+) substances, closed nerve terminals release inhibitory (−) substances. (Reprinted by permission of the publisher from F. L. Strand, *Physiology: A regulatory systems approach*, [illegible])

reflex is the basic spinal pattern associated with locomotion. Thus, the crossed extensor reflex is the first reflex described thus far that clearly illustrates Sherrington's idea that complex motor acts may be built from elementary reflex actions. It is notable that spinal animals make reasonably good bilateral stepping movements, supporting the idea that much locomotor activity derives its basic patterning from spinal mechanisms.

A set of reflexes called *long spinal reflexes* is another example of how fairly complex patterns of movement can be coded at the spinal level. These reflexes involve relatively long interneuronal connections running up and down the spinal cord. The best examples of long spinal reflexes are the Magnus reflexes. These reflexes allow for postural adjustments of the body during natural head movements. For example, several patterns of postural adjustments have been described in the cat that involve receptors associated with the cervical vertebrae: (1) when the neck is extended, the hindlimbs flex and the forelimbs extend (similar to the posture of a cat looking up at a fishbowl); (2) when the neck is flexed, the forelimbs flex and the hindlimbs extend (similar to the posture of a cat looking down a hole); and (3) when the head is turned to one side, the forelimb on that side extends and the contralateral forelimb flexes.

3.6.2.5 *Cortical mechanisms of movement*

The spinal reflexes form a basis for complex movements and relieve the brain from having to carry out the most basic regulation of posture and tone of the muscles. The messages sent to the cord from higher levels may take a simpler form, serving in part to modulate reflex circuitry to produce the desired movements. We now turn to the role of various brain structures in coordinating motor control.

Many areas of the cerebral cortex are involved in the regulation of movement. Voluntary movement is preceded by increased activity in the *primary motor cortex*, a strip of cortex just anterior to the central sulcus (Evarts, 1968). This strip of cortex projects directly to alpha- and gamma-motoneurons in the spinal cord through the pyramidal tract; it also influences interneurons that are involved in reflex control. The primary motor cortex is organized topographically so that discrete regions of the cortex influence discrete body parts on the contralateral side (Foerster, 1936; Penfield & Jasper, 1954; Woolsey et al., 1950). Stimulation of the motor cortex causes movements in corresponding regions of the body; conversely, lesions to the motor cortex lead to weakness (*paresis*) or paralysis of discrete areas. Recordings of the activity of single cells in the motor cortex of awake primates suggest that neurons in the motor cortex encode the force (Evarts, 1968) and direction (Georgopoulos, Schwartz, & Kettner, 1986) of movement of a particular body part.

While the primary motor cortex has direct influences on motoneurons, the programming required for complex, goal-oriented movement is accomplished in the other areas of the cortex: the supplementary motor area, the premotor area, the primary somatosensory area, and the posterior parietal cortex. Although the precise roles of each of these cortical regions are not fully understood, certain clear divisions of functions have been identified. Stimulation of either the *premotor* or the *supplementary motor cortex* produces complex movements (Penfield & Welch, 1951; Woolsey et al., 1950). The *posterior parietal cortex* and the *primary somatosensory cortex* participate in cortical motor control, apparently by integrating sensory spatial maps with motor spatial maps (Lynch et al., 1977; Robinson et al. 1978). Lesions to

the posterior parietal cortex result in an inability to learn complex movements (apraxia) and a profound neglect of "sensory space" on the contralateral side (cf. Denny-Brown & Chambers, 1958).

Whereas the cortical control of movement is of great importance, large subcortical structures play important roles in the generation and patterning of movement. In this respect it is interesting that primary motor cortex neurons become quiescent during some types of movements, especially for movements occurring during emotional outbursts and rhythmical movements such as chewing (e.g., Fetz, Cheney, & German, 1976). These findings reflect the ability of different parts of the brain to independently control the motor system and to suppress the other circuitry that generates movement. This redundancy in the motor system, along with its hierarchical organization, appears to be a general feature of the nervous system. As Hughlings Jackson, the father of modern neurology, noted in the last century, functions are represented and re-represented in the nervous system. Nowhere is the general principle of multiple representation of function more clear than in motor systems.

3.6.2.6 *Subcortical mechanisms of movement: the basal ganglia*

The basal ganglia include several telencephalic subcortical structures (caudate, putamen, globus pallidus, and claustrum). Some investigators also include certain thalamic nuclei and the substantia nigra. These structures are highly interconnected and influence movement by direct connections to brainstem premotoneurons and the motor cortex.

Previously, the basal ganglia were thought to have generalized, diffuse effects on movement. However, it has become increasingly apparent that the basal ganglia are highly organized, both in terms of specific body loci and in terms of zones of inputs and outputs within various structures. A central role is played by the substantia nigra and the caudate. These structures are interconnected by two pathways: the nigrostriatal pathway from the substantia nigra to the caudate/putamen and a return connection, the striatonigral pathway. This core loop has been the source of considerable interest, in part because perturbations of this system profoundly disturb movement as in Parkinson's disease, Huntington's chorea, and extrapyramidal side effects of antipsychotic drugs (neuroleptics).

Many investigators view the striatum (caudate, putamen, and globus pallidus) as a receptive zone because it receives inputs from all areas of the cortex and from the substantia nigra pars compacta (the dorsal, dopaminergic part of the nigra). The striatum integrates the incoming information and relays it to so-called output structures, particularly the substantia nigra pars reticulata (the nondopaminergic, ventral aspect of the nigra) and the globus pallidus. Neurons in these output areas then synapse on *premotoneurons* (neurons that project to motoneurons). For example the neurons in the substantia nigra pars reticulata project to the superior colliculus, which gives rise to the tectospinal tract. This pathway regulates eye and head movements, especially orienting responses to novel stimuli (Hikosaka & Wurtz, 1983a,b). Regulation of movement by the basal ganglia also occurs via pathways connecting in the thalamus and thence back to the motor cortex.

Recent work (cf. Alexander, DeLong, & Strick, 1986) suggests considerable specificity in the basal ganglia. To begin with, cortical projections to the striatum are highly organized. Different areas of the caudate and putamen in primates and man receive inputs from different areas of the cortex such that inputs from motor areas of the cortex (e.g., motor cortex, supplementary motor cortex, somatosensory cortex, and arcuate premotor area) all terminate in the same region.

Alexander et al. (1986) propose a model of the basal ganglia that extends beyond simple motor functions or sensorimotor integration. They suggest that at least five parallel functionally segregated pathways form closed loops: beginning with a discrete cortical region, each pathway projects to a circumscribed area of the basal ganglia, then to a thalamic area, and then back to the cortex. Although the regions of termination of different classes of inputs overlap, a reasonable degree of topographic specificity is retained at the level of the basal ganglia. Clear motor functions are associated with at least two of these loops. However, limbic cortical areas (e.g., anterior cingulate cortex, entorhinal cortex, inferior temporal gyrus) also project to particular zones in the caudate/putamen, which are separable from the inputs from motor areas. Although the functions of this limbic input are unknown, their presence suggests that the basal ganglia subserve functions beyond those of simple motor output. These findings also reflect on the high degree of anatomical organization present within the basal ganglia.

3.6.2.7 *Subcortical mechanisms of movement: cerebellum and associated circuits*

The cerebellum regulates movement through its interactions with spinal, cortical, and brainstem structures (see Ghez & Fahn, 1985; Ito, 1984). The cerebellum is unique in its highly regular synaptic architecture and connections. Principal sources of inputs are the cortex, inferior olive, and several brainstem nuclei that are influenced by cortical and spinal inputs. Monoaminergic systems, particularly serotonergic raphe neurons and noradrenergic locus coeruleus neurons, exert inhibitory influences over wide regions of the cerebellum.

Outputs from the cerebellum all derive from one of the deep nuclei: lateral, fastigial, interpositus, and dentate. Functional segregation occurs within these nuclei so that different deep nuclei project to separate brain regions subserving either different body parts (e.g., distal vs. proximal muscles) or functions (e.g., movement initiation). Three important functional divisions of the cerebellum are the *vestibulocerebellum*, discussed previously in the section on eye movements and head position, the *spinocerebellum*, which participates in the feedback regulation of movement, and the *cerebrocerebellum*, which may help to maintain a match between planned motor acts and ongoing movements. These functional divisions correspond anatomically to different regions of the cerebellum.

Whereas traditionally regarded as a center for motor coordination, there is an increasing appreciation that cerebellar functions go beyond the coordination of movement. For example, we know that the cerebellum and related circuits such as the red nucleus play an important role in the classically conditioned nictitating membrane withdrawal response studied in rabbits (Thompson, McCormick, Lavond, Clark, Kettner, & Mauk, 1983). These studies and others (e.g., Bernston & Hughes, 1976; Berntson & Micco, 1976; Brooks & Thach, 1981) have advanced our understanding of the cerebellum beyond the original conception that it is a circuit that patterns coordinated movement, an idea that was based mostly on the effects of cerebellar disease in humans.

3.6.3 *Central integrative systems*

Most of the structures of the central nervous system are neither clearly motor nor sensory. Here, we discuss the major systems that fall in this domain. In general, these systems process interoceptive afferents, integrate this information with higher order (cognitive) processes, control autonomic functions to maintain homeostasis, and regulate emotion and memory. Although an exhaustive treatment would be impossible here, we consider the major brain structures that mediate these actions.

3.6.3.1 *Hypothalamus*

The hypothalamus is a walnut-sized collection of at least nine identifiable nuclei that lie at the base of the forebrain (see Figure 3.19). Although the hypothalamus represents only 1 percent of the total volume of the brain, it is directly involved in what sometimes seems a bewildering array of essential body functions. When it comes to packing a variety of functions into a small package, the hypothalamus has no rival.

Much of the data indicating the importance of the hypothalamus in mediating overt behavior comes from experiments in which electrical stimulation of localized regions of the hypothalamus produces changes in an animal's behavior. W. R. Hess made the original observations, for which he won the Nobel Prize in 1949. Hess (1954) observed that the behavioral changes induced by hypothalamic stimulation are not disorganized. Rather, hypothalamic stimulation produces complex species-specific behavioral patterns characteristic of particular emotional or motivational states (e.g., anger, hunger, sexual activity). In addition, there is a great deal of functional localization within the hypothalamus: Different behaviors can be elicited preferentially by stimulating different parts of the hypothalamus.

One reason for the great interest in Hess's findings is the remarkable similarity between hypothalamically induced behaviors and their naturally occurring counterparts (e.g., Bernston, Hughes, & Beattie, 1976). Some evidence indicates that stimulation of the hypothalamus elicits specific constellations of somatic and autonomic activity because the stimulation produces a motivational state. For example, animals will perform work, such as pressing a lever, in order to get access to the object of the motivated behavior (e.g., food if the animal eats in response to the stimulation; Roberts & Carey, 1965; Roberts & Kiess, 1964); Moreover, it is clear that hypothalamic stimulation [or, for that matter, stimulation in the brainstem (Berntson & Hughes, 1976)] does not simply elicit motor automatisms, as the occurrence of particular behaviors depends on the availability of an appropriate goal object as well the stimulation itself (cf. Berntson & Micco, 1976). The detailed topology of the elicited behaviors is also dependent on environmental features, emphasizing the "appropriateness" of the elicited motor sequence. Further, under natural conditions, species-typical motivated behaviors and emotional states are accompanied by changes in the autonomic and somatic motor systems as well as in the endocrine system. Hypothalamic stimulation likewise induces consistent patterns of behavioral, autonomic, and endocrine changes (Hess, 1954).

On the other hand, there is evidence of a lack of complete determinism produced by brain stimulation that is inconsistent with the notion that hypothalamic stimulation induces motivational states. Occasionally, stimulation of one site produces more than one class of responses. In such situations, the availability of suitable goal objects can alter the probability that one or the other behavior occurs

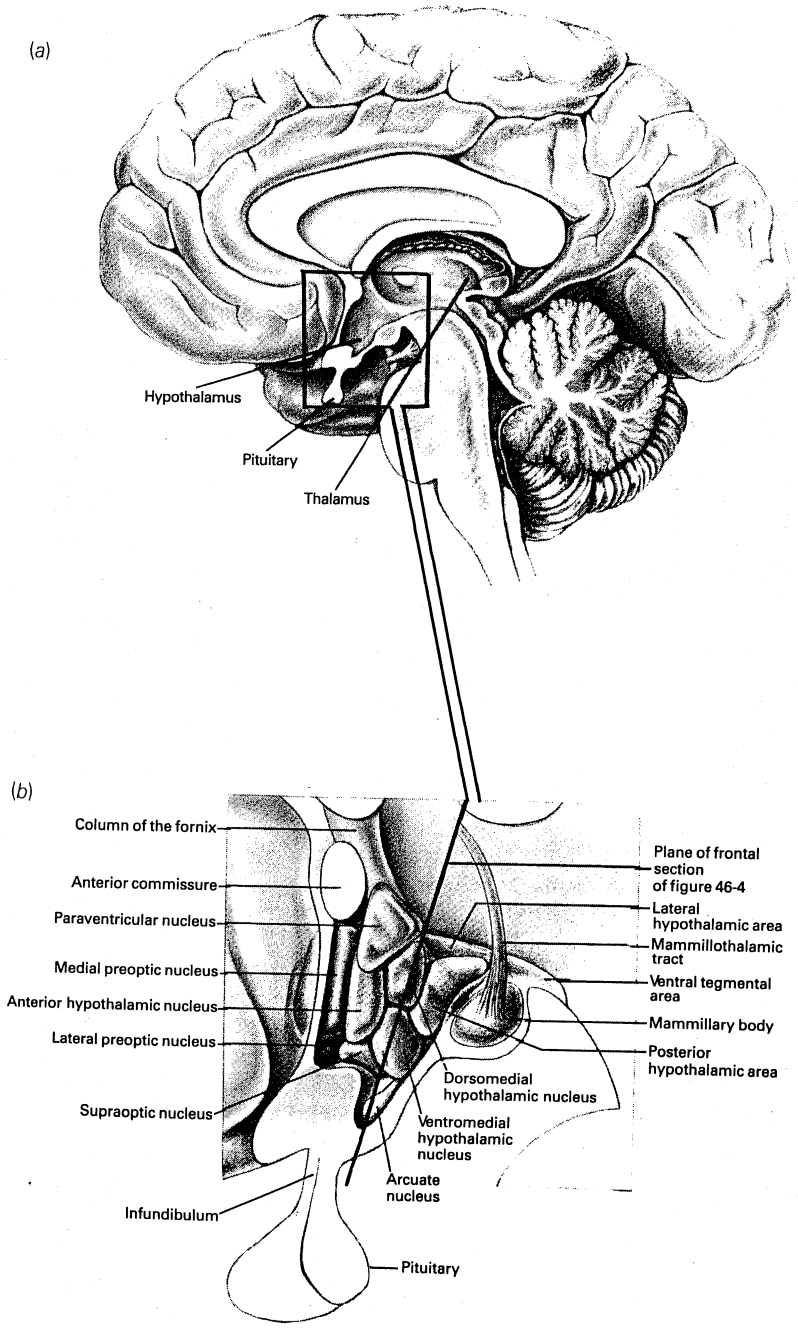

Figure 3.19. (*a*) Location of the hypothalamus within the diencephalon in relation to the pituitary gland and the thalamus. (*b*) Detail of the hypothalamus and the structures around it. (Reprinted by permission of the publisher from I. Kupfermann, Hypothalamus and limbic system I: peptidergic neurons, homeostasis, and emotional behavior, in *Principles of neural science*, E. Kandel and J. Schwartz, Eds., p. 615. Copyright 1985 by Elsevier Science.)

(Valenstein, Cox, & Kakolewski, 1970). Perhaps the best way to view the effects of hypothalamic stimulation on behavior is to suggest that the hypothalamus, through its descending connections to the brainstem, can facilitate sensorimotor reflex mechanisms that are important in the actual execution of particular classes of motivated behaviors (Flynn, Vanegas, Foote, & Edwards, 1970; Roberts, 1970). This can account for the dependence of stimulation-produced behaviors on the presence of appropriate goal objects. The occurrence of more than one type of response upon stimulation of the same hypothalamic site might be attributed to simultaneous facilitation of more than one class of reflexes, which might reasonably be expected given the number of cells influenced by brain stimulation. This suggestion has received some empirical support (Flynn et al., 1970; MacDonnell & Flynn, 1966a, b). Of course, this suggestion begs the question as to whether naturally induced hypothalamic activity can in any way be regarded as a sine qua non of motivated states.

Intertwined with its role in the organization of life-sustaining motivated behavior, the hypothalamus plays a crucial role in maintaining homeostasis by coordinating the somatic, autonomic, and endocrine systems. As one would expect, the afferent and efferent organization of the hypothalamus can be understood in these terms. Hypothalamic afferent sources are widespread and include massive indirect projections from autonomic afferents as well as inputs from interoceptors located within the hypothalamus (e.g., receptors for blood glucose and blood osmolarity). In addition, many hypothalamic neurons possess receptors for a variety of endocrine hormones, emphasizing again the growing appreciation that the brain is itself a target organ of the endocrine system. Many exteroceptive afferents also send collaterals into the hypothalamus. Perhaps the most noteworthy of these is the direct connections between the retina and the hypothalamic suprachiasmatic nucleus, a pathway involved in phase locking the circadian rhythm with the light-dark cycle (Moore & Eichler, 1972; Stephen & Zucker, 1972). Finally, many limbic structures that are intimately involved in emotional states project to the hypothalamus. Indeed, many limbic functions depend on these hypothalamic connections for their expression (e.g., Vergnes, 1976).

The efferent (output) connections of the hypothalamus exerts control over four systems: (1) the autonomic nervous system (via multisynaptic pathways within the brainstem reticular formation, described in what follows) (2) the endocrine system (both directly by secreting neuroendocrine hormones and indirectly through the pituitary gland), (3) the somatic motor system (again via multisynaptic pathways within the brainstem and spinal cord), and (4) the limbic system (described in more detail in the next section).

Hypothalamic control over the endocrine system deserves special mention. As indicated, there are two modes of control. First, neurosecretory cells in two hypothalamic nuclei (the paraventricular and supraoptic nuclei) project to the posterior pituitary where they secrete two neurohormones (oxytocin and vasopressin) directly into the bloodstream. These neurohormones are then carried via the blood supply directly to target organs. Second, a variety of hypothalamic cells release various neuropeptides into the portal vasculature of the pituitary. These peptides are carried in the blood to the anterior pituitary where they control the secretion of various hormones from pituitary cells. These pituitary hormones in turn circulate in the bloodstream and control the secretions of the other endocrine glands. This, then, represents the indirect mode of endocrine control, as it is

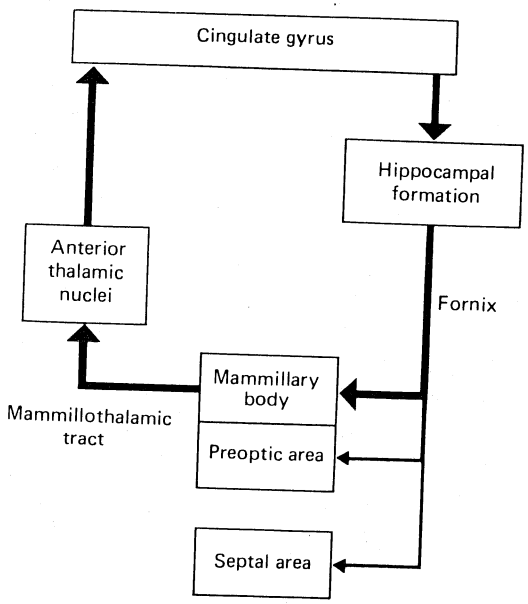

Figure 3.20. A schematic of Papez's circuit, which has been shown to be involved in the regulation of emotional states, showing the interconnections between various limbic system structures. (Reprinted by permission of the publisher from Hypothalamus and limbic system I: peptidergic neurons, homeostasis, and emotional behavior, in *Principles of neural science*, E. Kandel and J. Schwartz, Eds., p. 615. Copyright 1985 by Elsevier Science.)

mediated via intermediary *hypothalamic hormones* that regulate the secretion of anterior pituitary hormones.

3.6.3.2 *Limbic system*

The term *limbic system* refers to a highly interconnected set of subcortical structures located primarily in the forebrain (telencephalon). These structures include the cingulate gyrus of the neocortex, the hippocampus, the amygdala, the septum, and the medial nucleus of the thalamus. Many investigators would also include portions of the midbrain reticular formation due to its intimate anatomical connections with other limbic structures. Classical wisdom had it that much of the limbic system was related to the sense of smell, but this is no longer tenable. Considerable evidence now supports the idea that the limbic system subserves emotional responses.

Papez (1937) was the first to suggest that a specific circuit interconnecting various limbic structures represented the neuronal substrates of emotion (Figure 3.20). Although the details of his conceptualization are almost surely inadequate, both the connections of the limbic system and a great deal of neuropsychological work support the general proposition that the limbic system plays an important role in the modulation and expression of emotional states. Particularly important in this respect are the extensive interconnections between limbic structures and the hypothalamus. Based in part on these limbic–hypothalamic connections, the limbic

system is thought to exert modulatory influences over the hypothalamus and, consequently, over the expression of emotional states. Consistent with the suggestions derived from these anatomical considerations are the findings that damage to or stimulation of different limbic structures produces dramatic alterations in the emotional states of both humans and animals. Lesions of the septum, for example, result in extreme expressions of rage, whereas lesions of the amygdala produce a taming effect. Interestingly, the influences of both the septum and amygdala appear to be mutually antagonistic. Thus, bilateral amygdalectomy eliminates the rage response produced by lesions of the septum (Jonasson & Enloe, 1971). Many of these effects have been noted in humans as well as in animals. Electrical stimulation of these same structures has the expected complementary effects. Thus, electrical stimulation of the septum reportedly produces intensely pleasurable effects, including an increased libido (cf. Lindsley & Holmes, 1984).

Perhaps the most well-known syndrome associated with damage to the temporal lobe of the cerebrum (which includes several important limbic structures) is the *Kluver–Bucy syndrome*. The syndrome is characterized by certain forms of visual agnosia (impairments in visual recognition), dramatic reductions in fear, docility, and increased sexual activity (Kluver & Bucy, 1939). Similar symptoms have occasionally been described in the human neurological literature and result from very extensive bilateral damage to the temporal lobe, the neocortex, the amygdala, and the hippocampus. More restricted damage to the hippocampus produces another classic neuropsychological syndrome known as *anterograde amnesia*. In this form of amnesia, long-term memories formed prior to the surgery are largely unaffected; the memory loss is specific to the long-term retention and/or retrieval of postsurgical memories (Scoville, Band, & Milner, 1975).

As is the case in many conceptualizations of nervous control, emotional states can fruitfully be regarded as a hierarchy in which higher level processes influence emotional states via descending projections. The lowest level of this hierarchy is the constellation of motoric responses associated with the emotional state, which derives from activity in both the somatic and autonomic motor systems. These responses must be integrated with each other and with sensory inputs if they are to be goal directed. These later processes appear to depend on mechanisms in the brainstem and hypothalamus. Finally, the occurrence of emotional displays is influenced by situational variables that may "gate" or modulate the display via connections between the cerebral cortex and the limbic system. Note, however, that the limbic structures described previously are interconnected and linked to relevant structures such as the hypothalamus and cerebral cortex. They therefore do not conform to a hierarchical system in a literal way. Nevertheless, to think of the neural control of emotional states in hierarchical terms has had heuristic value and empirical support.

3.6.3.3 *The reticular formation*

Throughout the central core of the brainstem, extending from the midbrain rostrally to the medulla caudally, lies the reticular formation. Once thought to be both functionally and anatomically amorphous, there is now a greater appreciation for both the anatomical specificity and functional diversity of this complex region of the central nervous system.

The reticular formation contains a great variety of nuclei defined according to

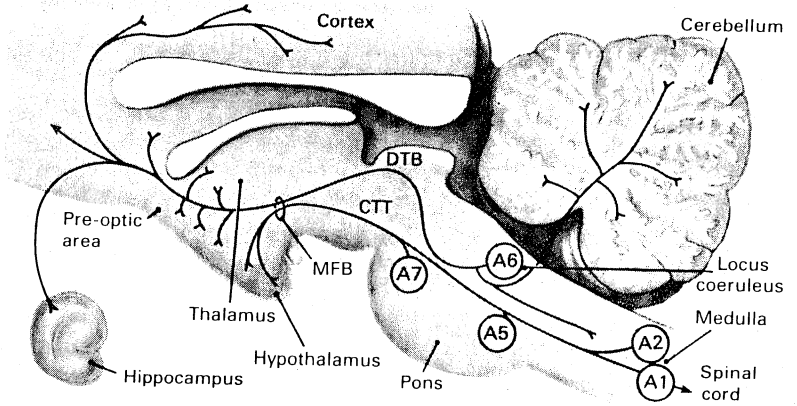

Figure 3.21. Sagittal section showing the noradrenergic pathways in the the brain. Nuclei giving rise to these neurons are labelled using the terminology of the original histochemists who mapped noradrenalin: A2, A5, A6, A7. Note that A6 corresponds to the locus coeruleus, a major source of forebrain noradrenalin. CTT = central tegmental tract, DTB = dorsal tegmental bundle, MFB = medial forebrain bundle. (Reprinted by permission of the publisher from *Physiology of Behavior* by N. R. Carlson, p. 524. Copyright 1986 by Allyn and Bacon, Needham Hts., MA.)

their cytoarchitecture and histochemistry (the distribution of neurotransmitters). Thus, the collection of serotonergic neurons that lie along the midline of the reticular formation is collectively referred to as the raphe complex. In addition, a variety of NE-containing cell groups lie within the reticular formation. The best known of these is the locus coeruleus, a small pigmented nucleus at the base of the cerebellum that is thought to have diverse and powerful effects on behavior through its widespread connections to the forebrain, cerebellum, brainstem, and spinal cord (Figure 3.21).

The reticular formation receives inputs from a diverse array of sensory modalities, including both exteroceptive and interoceptive systems. Many reticular neurons represent interneuronal links in a wide variety of reflex pathways, and much of the sensory input to the reticular formation represents the afferent limbs of these reflex pathways. These sensory inputs are also viewed as being important in controlling the level of arousal, a second major function of this region.

There are two major classes of efferent projections from the reticular core: those that ascend to the forebrain and those that descend to the spinal cord. The descending reticular projections originate in the medullary and pontine reticular formation and terminate on interneurons in the spinal cord. They are collectively referred to as the reticulo-spinal pathways. These descending projections are of two basic classes: those that modulate the tone of the proximal musculature and those that influence sensory transmission within the spinal cord. The former are involved in the regulation of posture and the control of locomotion. Much of this control is mediated via gamma-motoneurons. Some studies have shown that reticular cells increase their firing rates prior to very specific patterns of movement (e.g., turning of the head, protruding of the tongue, specific vectors of saccadic eye movements). Others have shown that electrical stimulation of a particular reticular nucleus induces

locomotion even in decerebrate animals that cannot otherwise walk on their own. This "locomotor region" appears to participate in the initiation of walking as well as in the control of velocity (Shik, Severin, & Orlofsky, 1966). The descending sensory influences of the reticular formation appear to modulate the responsiveness of spinal cord cells that respond to painful stimulation and are an important part of the analgesic effects of exogenous opiates and endogenous opioid peptides (Basbaum & Fields, 1984).

Various regions within the reticular formation project to a wide variety of forebrain structures including the thalamus, cerebral cortex, limbic system, and hypothalamus. The functions of these ascending projections are undoubtedly diverse but have often been associated with the control of sleep, wakefulness, and levels of arousal (cf. Carlson, 1988, chapter 9). Thus, the NE-containing neurons in the locus coeruleus are implicated in wakefulness, in part because many drugs that enhance arousal (e.g., amphetamine) cause the release of NE (Carlson, 1988, chapter 9). Conversely, serotonergic neurons within the raphe complex are associated with the onset of sleep because drugs that enhance serotonergic activity promote sleep.

There is also good evidence that ascending reticular projections may play a role in phasic changes in alertness and attention. Electrical stimulation of the midbrain reticular formation enhances excitability of thalamocortical projection neurons and has similar effects on the excitability of cortical cells. Singer, Tretter, and Cynader (1976) have shown that reticular stimulation increases both spontaneous discharge as well as visually induced activity in striate cortex. It is interesting to note that although the visual responses are enhanced, this is achieved at the cost of decreased selectivity in cortical responsiveness. So, for example, whereas striate cells generate enhanced responses to normally effective stimuli following reticular stimulation, they also generate responses to stimuli to which they would not normally respond at all. Thus, it is possible that reticular stimulation does not enhance signal-to-noise ratios, as many current views of attention suggest.

There is also evidence that cortical NE plays an important role in certain forms of cortical plasticity. Thus, the changes in connections between the geniculate and cortex that normally accompany monocular deprivation in developing kittens appear to require the presence of cortical NE: The application of neurotoxins specific to NE blocks the occurrence of these developmental changes (Kasamatsu & Pettigrew, 1979). The major source of NE in the cortex comes from the reticular formation.

3.7 CONCLUDING REMARKS

We have discussed many areas of neuroscience – from studies conducted in the 1800s to the present. Most importantly, we discussed concepts that have general applicability across neural systems. Some of these concepts or modes of discussion have not changed much; for example, many anatomical structures still bear the names that Vesalius assigned in 1543 in his work *De Fabrica Corporis Humani*. Perhaps more difficult are the new ways of thinking about the nervous system that have emerged; we have tried to identify trends that will continue to bear fruit. Prominent among these have been molecular processes that have proven to have considerable power in explaining basic brain functions and have enriched our understanding of synaptic transmission. Psychophysiological investigations of the systemic bodily processes involved in cognition, emotion, and behavior will

continue to provide an organismic framework necessary for the comprehensive understanding of the nervous system envisioned by the modern founders of neuroscience.

NOTE

We dedicate this chapter to Donald R. Meyer and Patricia M. Meyer, Emeritus Professors of Psychology at The Ohio State University. We acknowledge that most of the important concepts in this chapter came to us (BBW, JMW, and HCH) under their tutelage. These ideas have withstood the test of time for us, and we expect that they will for the readers as well.

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4 *Principles of bioelectrical measurement*

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4.1 INTRODUCTION

> The most significant functions of laboratory instruments are measurement and control. Since the scientist's principal activities are observations under controlled conditions, one index of the usefulness of instruments to experimenting psychologists is the extent to which they facilitate the observation, quantification and control of variables relevant to the psychological situation. (Grings, 1954, p. 2)

Parallels in the development of science and technology have been observed in both the physical and the biobehavioral sciences. Technological advances supply the scientist with progressively better tools for measurement and control. Within the physical sciences, for example, the development of the radio telescope allowed astronomers to detect and examine starlike quasars at a level beyond the range of optical imaging (Schmidt, 1963). Brown and Saucer (1958) noted several examples within the behavioral sciences in which technological advances facilitated scientific progress. For example, development of the vacuum tube oscillator greatly improved stimulus control within the study of audition, and the development of suitable amplifiers and display devices (described later in this chapter) enabled the reliable detection and quantitative description of subtle bioelectrical signals as brief as a single action potential (Erlanger & Glasser, 1937). More recently, technological advances permitting detection of weak magnetic fields led to the discovery and quantification of event-related magnetic activity in the brain (Beatty, Barth, Richer, & Johnson, 1986).

Although technological advances may permit scientists to venture into frontier areas of research, inadequate or incomplete technical knowledge may lead to serious errors of inference. For example, soon after the discovery of X-rays, numerous scientists employing the technology for observing the effects of X-rays reported a related phenomenon called *N*-rays (Rostron, 1960, cited in Barber, 1976). The effects misattributed to *N*-rays were later shown to be the result of difficulties involved in estimating by eye the brightness of faint objects (Wood, 1904). In addition, soon after the birth of experimental psychology, the reaction times being measured in Wilhelm Wundt's laboratory at the University of Leipzig were discovered by James Cattell to be in error because of asymmetries in the time required for the magnet in the chronoscope to attract and release the armature (Boring, Davis, & Merzbach, 1976). More recently, Jonides (1982) reported a surprising effect involving temporal integration of a sequence of two very briefly presented visual patterns. It was later determined that the method for presentation of the visual patterns failed to properly account for the decay time of the phosphor on the