13th Edition

DUKES' PHYSIOLOGY OF DOMESTIC ANIMALS

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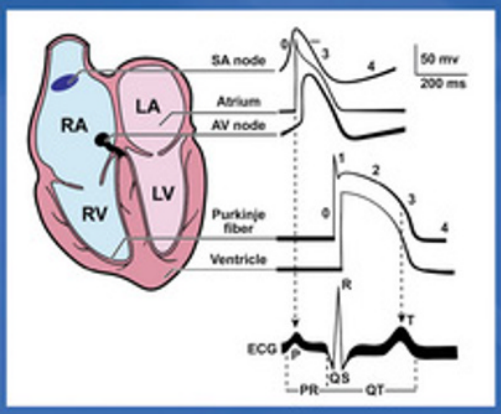
William O. Reece

Associate Editors
Howard H. Erickson
Jesse P. Goff
Etsuro E. Uemura



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Dukes' Physiology of Domestic Animals

This book is dedicated to my wife Shirley Ann Bruckner Reece, born 12/03/1932, died 09/29/1999.

Thanks to God for the gift of Shirley for the 46 years of our marriage and for the seven children (Mary Kay, Kathy Ann, Barbara Jean, Sara Lucinda, Anna Marie, Susan Theresa, and William Omar II) we were privileged to bring forth. Shirley was raised in Chicago, and received her BS in Foods and Nutrition at Iowa State University. We were united in marriage prior to receiving our degrees in 1954.

Shirley was a model wife and mother. At every age, she had wisdom beyond her years and was admired by all who knew her. She personified joy, received by grace through God, enjoyed life and loved Ames. Because of her example, support for my vocation, and enthusiasm for family, church, community, and the veterinary profession, I have been encouraged to continue with *Dukes' Physiology of Domestic Animals* and thereby give honor for her presence throughout much of my life.

W.O.R.

Dukes' Physiology of Domestic Animals

Thirteenth Edition

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Preface

We are pleased to continue the legacy established in 1933 by Dr H. Hugh Dukes when the lithoprinted first edition of *The Physiology of Domestic Animals* was published by Edwards Brothers, Inc., Ann Arbor, Michigan. The preface by H.H. Dukes included the following opening statement:

> This book was written mainly at Iowa State College; it was completed at Cornell University. Based on nearly fifteen years of experience in the field of animal physiology, it represents an attempt to provide students of veterinary medicine with a suitable textbook for their course in physiology. I believe also, on the basis of experience, that much of the book will be useful to students of animal husbandry. Furthermore, I venture the opinion that practitioners of veterinary medicine who wish to keep up with the trend in physiology will find the book helpful.

The first two lithoprinted editions were followed by the third revised edition in 1935 with an improved format, printed from type, by Comstock Publishing Company, Inc., Ithaca and New York. The seventh edition, the last edition authored by Dr Dukes, was published in 1955. It was the first to be published by Comstock Publishing Associates, a Division of Cornell University Press, Ithaca and London, who continued as publishers for the 8th, 9th, 10th, 11th, and 12th editions, which published in 2004.

The 8th edition was the first to be multiauthored and was begun by Dr Melvin J. Swenson as editor. Dr Swenson continued as editor for the 9th and 10th editions and coedited with Dr William O. Reece for the 11th edition. Dr Reece edited the 12th edition, the last one to be published by Cornell University Press. Publishing rights were licensed by Cornell University Press to John Wiley & Sons, Inc. for the 13th multiauthored book with William O. Reece, Editor, and Howard H. Erickson, Jesse P. Goff, and Etsuro E. Uemura, Associate Editors.

The vision of Dr Dukes for his textbook *The Physiology of Domestic Animals*, which was to provide students of veterinary medicine with a suitable textbook for their courses in physiology, and to be useful to students in animal husbandry and practitioners of veterinary medicine, has been a goal throughout all the years since the first edition and is being continued with the 13th edition.

Many features of the previous edition will be continued that include the following for each chapter.

1. The text content is preceded by an outline listing the first- and second-order headings.
2. A brief introduction.
3. A list of questions that precede each first-order heading that alert students to important information that follows. Answers to the questions will be found in the text that follows.
4. Key words are in bold color on first use.
5. Meaningful self-evaluation exercises are provided at the end of each chapter that feature important facts or concepts.
6. Answers, explanations, or solutions are provided for each self-evaluation exercise.

Conscientious use of the above features provide not only an organized study when first used, but also a quick review when needed for future use.

Our effort to identify the 13th edition as an all-new work is apparent in many ways. The chapters within several sections have a single author and their number reduced in other sections. This permits greater consistency of presentation and content overlap is minimized.

An important change was made for the renal and respiratory chapters. Previously the entire topic of each was presented in a single chapter. Now, the one single chapter has been divided into several chapters where emphasis can be focused on a single concept. This will facilitate lecture organization and selective referral.

A notable addition to this edition is the provision of full color throughout. The use of color not only enhances the attractiveness but also provides a means for contrast within the text and figures.

Other features include a downloaded version of the 13th edition available online. All figures and tables will be on PowerPoint to facilitate lecture presentations. An effort has been made to reduce pagination of the volume while at the same time providing increasing font size and space for figures and tables. Overall, the 13th edition of *Dukes' Physiology of Domestic Animals* will continue with its classic stature as a comprehensive resource, not only stressing basic physiology with application to animals, but also with updated features to assist teaching effectiveness.

William O. Reece

Acknowledgments

We are grateful for the efforts of Erica Judisch, Commissioning Editor, Veterinary Medicine, Wiley Blackwell, Heidi Lovette, Science Editor, Cornell University Press, and Tonya Cook, Rights Manager, Cornell University Press, for successfully negotiating the transfer of rights from Cornell University Press to Wiley Blackwell. Their professionalism and patience throughout a complex process is appreciated.

Cornell University Press has been as important to the success of the book as the legacy of *The Physiology of Domestic Animals*, that began with Dr Dukes, whose publishing career was spanned at Ithaca. The continued integrity and cooperation of Cornell University Press as publisher during my tenure was always apparent. My appreciation and thanks are extended to all directors, science editors and staff throughout the years for their efforts.

A project of this complexity requires participation by many individuals. My indebtedness and thanks are extended to these very nice people.

The authors and section editors, in addition to their teaching, research, service, and administrative duties, devoted their talents to this project.

Much of my time during the preliminary phases and preparation of manuscripts involved the Veterinary Medical Library, Iowa State University. Kristi Schaaf, Director, was a friendly, knowledgeable resource for location of reference material and other information as needed. Also helpful was Lana Greve, Library Assistant.

Dr Anumantha Kanthasamy, Professor and Chair, Department of Biomedical Sciences, College of Veterinary Medicine, Iowa State University, provided office resources and services, assisted by Linda Erickson, Administrative Specialist, William Robertson, Laboratory Supervisor, and Kim Adams. Paige Behrens, Office Assistant and Iowa State University student in Graphic Design, assisted by Megan Demoss, transformed my manuscripts and all other essential items to computer documents.

Drs Howard Erickson, Jesse Goff, and Etsuro Uemura, Associate Editors for this volume, helped in the planning and its execution. Their advice, enthusiasm, and hard work have never wavered, and their innovations have provided a new freshness. In addition, Dr Howard Erickson provided faithful support and planning for the 12th edition.

Mal Rooks Hoover, Certified Medical Illustrator, College of Veterinary Medicine, Kansas State University, generously provided her expertise to enhance the effectiveness, for many of the figures, including color, that appear in the chapters authored by Dr Reece, Dr Erickson, and several other authors in the cardiovascular section. We are grateful for her effort on our behalf.

Dr Darrell Trampel sadly passed away during the production of this book. He will be greatly missed by colleagues and friends.

Nancy Turner, Senior Development Editor, Wiley Blackwell, provided timely information and guidance from the very beginning of the project. Her knowledge, experience, professionalism, and assistance in all phases were extremely helpful. This effort was continued by the expertise of Catriona Cooper, Senior Project Editor, Wiley Blackwell, in finalizing the manuscript and the associated details required for submission to the copy editor. Our thanks are extended to Nancy and Catriona on behalf of all the authors, for their patient and friendly assistance and attention to details. Extended thanks to Kathy Syplywczak, Project Manager, and Jolyon Philips, copy editor, for their expertise and attention to detail that was needed in making this edition a volume for which we can all be proud.

Above all, I thank God for this community of people and for His answer to my many prayers for this project.

William O. Reece

Tributes to Drs H. Hugh Dukes and Melvin J. Swenson

Veterinary educators, researchers, authors, and administrators

Dr H. Hugh Dukes (1895–1987)

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About the companion website

This book is accompanied by a companion website:

www.wiley.com/go/reece/physiology

The website includes:

- Review questions and self-evaluation exercises from the book
- Powerpoints of all figures from the book for downloading
- PDFs of all tables from the book for downloading

SECTION I

Neurophysiology

Section Editor: Etsuro E. Uemura

1 Nervous Tissue

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The nervous system has two categories of cells, neurons (Greek *neuron*, nerve) and neuroglia (Greek *glia*, glue). Their names reflect the fact that neurons give rise to nerves, while neuroglia are thought of as cells simply holding neurons together. Neurons and neuroglia are far more complex in their shape than cells in any other tissue. Their morphological heterogeneity reflects the functional complexity of the nervous system. Neurons and neuroglia play different roles in the nervous tissue. Neurons are specialized in information processing. Specialized contact areas called synapses mediate signals from one neuron to others. Synapses are the basis of complex neuronal networks designed for information processing. Neurons stop dividing within a few months after birth. Therefore, if nerve damage involves cell bodies in the adult animal, resulting neuronal death will permanently change the structure and functions of the affected areas. Unlike neurons, neuroglia continue to divide. This glial capacity to divide is essential for their structural and functional support of neurons. Neurons and glial cells require a chemically stable environment. Endothelial cells of the central nervous system and the choroid plexus help maintain such an environment by regulating molecules secreted into the interstitial fluid and cerebrospinal fluid (CSF).

Division of the nervous system

1 Differentiate between the central nervous system and the peripheral nervous system.
2 What is the relationship between the autonomic and the central nervous systems?

The nervous system can be classified into three systems: the central nervous system, peripheral nervous system and autonomic nervous system. The **central nervous system (CNS)** is composed of the cerebrum, cerebellum, brainstem, and spinal cord. It is the central processing unit of the entire nervous system. All nervous tissue other than the cerebrum, brainstem, cerebellum, and spinal cord is referred to as the **peripheral nervous system (PNS)**. The PNS comprises the nerves, ganglia (spinal, cranial, sympathetic trunk, collateral, terminal), and sensory receptors. The PNS conveys (i) sensory signals about the external and internal environment of the body to the CNS and (ii) motor signals from the CNS to the peripheral effectors (skeletal muscle, cardiac muscle, smooth muscle, secretory glands). Certain neural components of the CNS and PNS regulate the visceral organs, smooth muscles (e.g., vascular, pupillary dilator, pupillary sphincter, ciliary, orbital, arrector pili), and glands (salivary, lacrimal, nasal, adrenal). These neural components of the CNS and PNS are collectively referred to as the **autonomic nervous system (ANS)**. The ANS is, in general, not under voluntary control, but rather its action is controlled by the hypothalamus. The ANS consists of many specialized neural components (e.g., nuclei, ganglia, nerves, tracts and visceral plexus). For example, the increased heart rate in the "fight or flight" response involves the hypothalamus (i.e., CNS), intermediolateral nucleus in the spinal cord (i.e., CNS), ganglia (i.e., PNS) and peripheral nerves (i.e., PNS).

Cells of the nervous system

1 What are three different types of neurons?
2 What are the functions of an axon and a dendrite?
3 What is the axon hillock? What is its functional significance?
4 What are the structural and functional differences between myelinated and nonmyelinated axons?
5 Name the neuroglia of the CNS and PNS, and explain their functions.
6 How do Schwann cells differ from oligodendrocytes?
7 What are the bases of classifying peripheral nerve fibers?

Dukes' Physiology of Domestic Animals, Thirteenth Edition. Edited by William O. Reece, Howard H. Erickson, Jesse P. Goff and Etsuro E. Uemura.

Companion website: www.wiley.com/go/reece/physiology

Neurons and neuroglia are the two categories of cells of the nervous system. **Neurons** share certain universal cellular features with all other cells in the body; however, neurons have certain unique features that separate them from other cells. For example, they have distinctive cell shapes with a membrane capable of generating electrical impulses. They transfer impulses from one neuron to the next via synapses (Greek *synapsis*, a connection), the specialized contact areas between two neurons. Although transmission of impulses is a basic biological function performed by all neurons, their electrical property alone does not explain the diverse roles they play in a complex neural network. **Neuroglia** are the most abundant cells in nervous tissue (over 90%), filling essentially all the space in the nervous system not occupied by neurons and blood vessels. They provide structural, metabolic, and protective support for neurons.

Neurons

The most obvious difference between neurons and other cells in the body lies in their great variety of shapes and sizes. Neurons have highly irregular shapes with one or more cellular processes extending from the cell body (Figure 1.1). The **neuronal cell body** (also referred to as the **soma** or **perikaryon**) contains the same organelles found in other cells. However, the rough endoplasmic reticulum and polysomes (collectively referred to as **Nissl substance**) are especially abundant in perikarya. Each neuron has a single axon. The area of the cell body where an axon originates is the **axon hillock**. The axon hillock is also referred to as the trigger zone, as action potentials are generated here. Just distal to the axon hillock is the **initial segment** of the axon.

Axons frequently branch at a distance from the cell body, forming synapses with other neurons, muscle cells, or glands. The remaining neuronal processes are **dendrites** (Greek *dendron*, tree) that resemble trees (Figure 1.1). Dendrites and perikarya are the primary receptive sites of impulses from other neurons. The number of dendrites varies depending on the type of neuron (Figure 1.2). Action potentials are generated at the axon hillock. An action potential travels along the axon at a speed that varies from 0.5 to 120 m/s. Larger axons, over 1 μm in diameter, are myelinated in both the CNS and PNS, while axons less than 1 μm in diameter are not myelinated. Myelinated axons conduct impulses much faster than nonmyelinated axons. There is a constant relationship between axon diameter, internodal length (i.e., length of each myelin sheath), and conduction velocity. Larger axons have longer internodes and faster conduction velocities. Neurons are contiguous not continuous and they communicate with each other via synapses. If a neuron is linked to more than one recipient neuron, its axon branches to make synaptic connections with all the recipient neurons. Neurons, like muscle cells, do not divide once they reach maturity. Therefore, any physical injury that leads to neuronal death will permanently change the structure and functions of the affected areas.

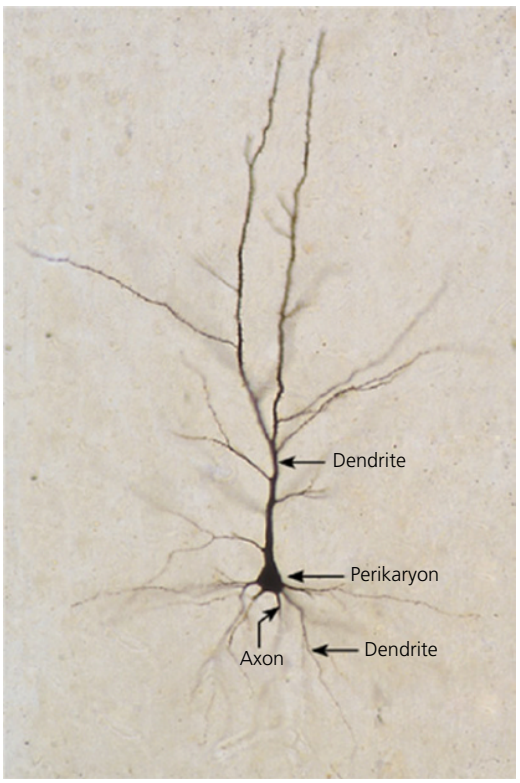


Figure 1.1 A cortical multipolar neuron stained with the Golgi silver impregnation method showing the perikaryon, axon, and dendrites. Only one axon emerges from the perikaryon. All other neuronal processes are dendrites.

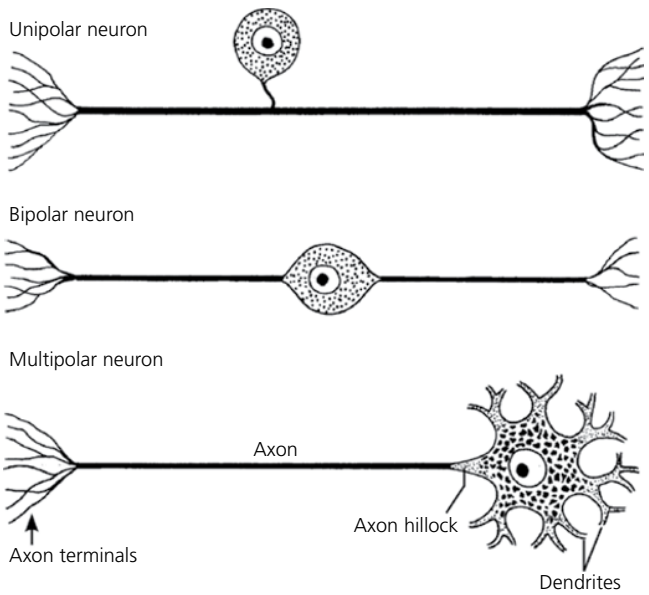


Figure 1.2 The classification of neurons is based on the number of cell processes emerging from the cell body. Cell bodies of unipolar neurons are present in the spinal and cranial ganglia. Cell bodies of bipolar neurons are present in the retina of the eye, spiral ganglia of the auditory nerve, vestibular ganglia of the vestibular nerve, and olfactory epithelium. The majority of neurons are multipolar neurons.

The color of fresh nervous tissue reflects neuronal cell bodies and axons. Areas with a high population of perikarya (e.g., cerebral cortex) appear gray and are referred to as the **gray matter**. In contrast, areas mainly made of myelinated axons appear white because of the presence of lipid in myelin. The name **white matter** is used to indicate such areas.

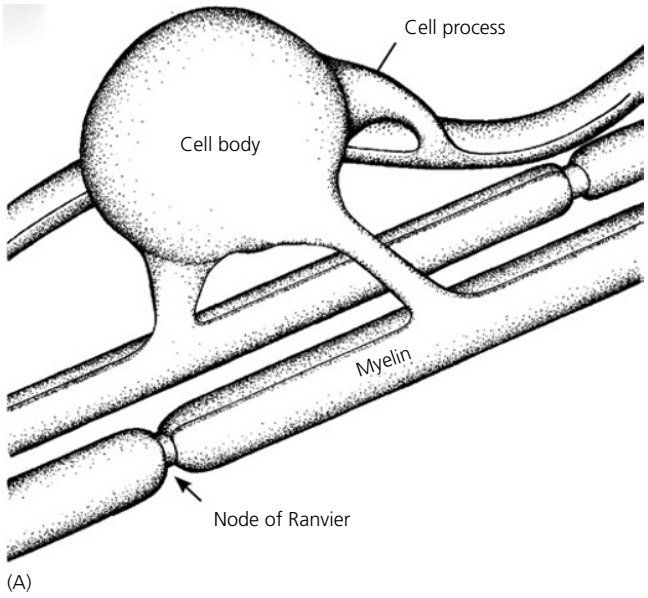
Classification of neurons

Neurons are classified into three types (unipolar, bipolar, and multipolar) based on the number of cellular processes extending from the cell body (Figure 1.2). **Unipolar neurons** have a single stem process that bifurcates to form two processes, the peripheral and central. Unipolar neurons innervate peripheral tissues, bringing somatic and visceral sensory information to the CNS. Thus they are also referred to as primary sensory neurons. **Bipolar neurons** have two processes. Bipolar neurons are located in the retina of the eye (see Figure 7.4), spiral ganglion of the cochlea (see Figure 6.2B), vestibular ganglion of the vestibular organ (see Figure 9.1), and olfactory epithelium (see Figure 5.2). Bipolar neurons are sensory neurons. Their peripheral processes innervate sensory receptors, bringing sensory signals to the CNS. An exception to this rule is the olfactory cells. A terminal branch of the olfactory cell forms a dendritic bulb and its cilia act as receptors detecting the chemical environment in nasal air. **Multipolar neurons** are the most prevalent type. As the name "multipolar" suggests, each neuron has numerous cell processes (one axon and many dendrites). The length and arrangement of neuronal processes vary considerably.

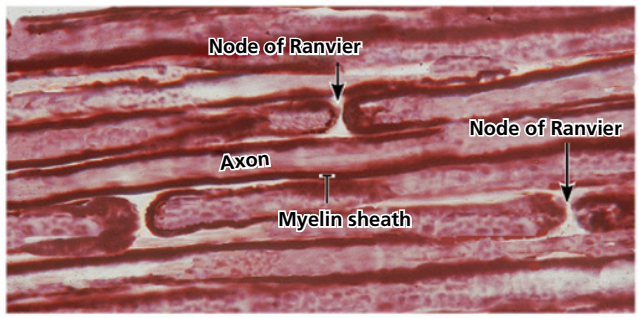
Neuroglia

Neuroglia are generally small in size and outnumber neurons by as much as 10 : 1 to 50 : 1. Their small size is such that only their nuclei are clearly seen in routine histological preparations. The nuclei range in diameter from 3 to 10 μm, which is about the size of the smallest neurons. Unlike neurons, neuroglia have the capacity to divide. Schwann cells are the only neuroglia of the PNS. Neuroglia of the CNS are oligodendrocytes, ependymal cells, microglia, and astrocytes.

Schwann cells (also referred to as neurolemmocytes) support axons of the PNS, depending on the size of the axon, in two ways. Schwann cells associated with most axons over 1 μm in diameter form myelin sheaths by concentrically wrapping their plasma membrane around the axon (up to 50 or more layers) (Figure 1.3C). Schwann cells are arranged side by side along the axon. Each Schwann cell forms an **internode** of the myelin sheath of various lengths (25–1000 μm). The larger axons have longer internodes and faster conduction speed. The junction between each internode is the **node of Ranvier** (Figure 1.3B). Schwann cells are also associated with most axons less than 1 μm in diameter. Schwann cells associated with smaller axons do not form a myelin sheath, but they hold many smaller axons in their processes. **Oligodendrocytes** (Greek *oligos*, little; *dendron*, dendrite) are small neuroglia of the CNS. They are present



(A)



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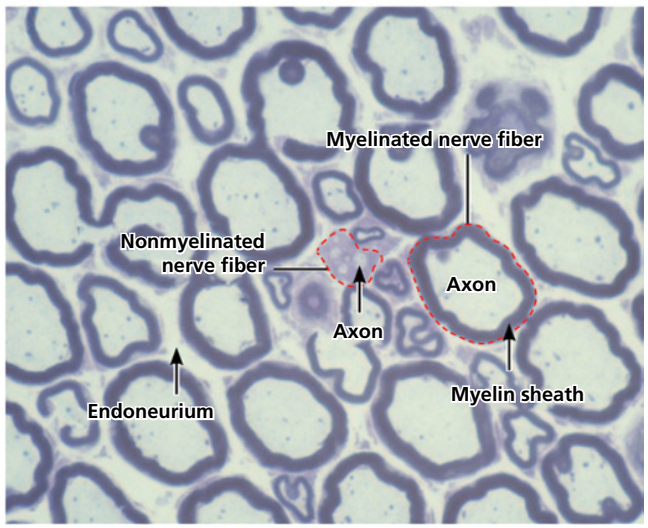

(C)

Figure 1.3 (A) Oligodendrocytes myelinate most axons about 1 μm and over in diameter. Each oligodendrocyte contributes segments of myelin sheath (i.e., internodes) for many axons. (B) Longitudinal section of a peripheral nerve showing axons and their darkly stained myelin sheath, and nodes of Ranvier. (C) Electron micrograph of nonmyelinated and myelinated axons. Nonmyelinated axons are much smaller in size than myelinated ones. Each axon is surrounded by endoneurium.

in both the white and gray matter. Oligodendrocytes have numerous cell processes that extend to adjacent axons to form myelin sheaths (Figure 1.3A). Generally, oligodendrocytes myelinate most axons over 1 μm in diameter to speed conduction velocity (Tables 1.1 and 1.2).

Table 1.1 Classification of peripheral nerve fibers by the letter system.

Type	Diameter (μm)	Conduction velocity (m/s)	Function
Aα	12–22	70–120	Somatic motor, proprioception
Aβ	5–12	30–70	Touch, pressure
Aγ	3–8	15–30	Motor to muscle spindle
Aδ	1–5	12–30	Fast pain and temperature
B	1–3	3–15	Visceral motor (preganglionic)
C	0.3–1.5	0.3–1.5	Visceral motor (postganglionic), slow pain and temperature

Table 1.2 Classification of peripheral sensory nerve fibers by the numerical system.

Type	Letter equivalent	Diameter (μm)	Origin
Ia	Aα	12–22	Muscle spindle (primary)
Ib	Aα	10–15	Golgi tendon organ
II	Aβ, Aγ	5–12	Muscle spindle (secondary), touch, pressure
III	Aδ	1–5	Fast pain and temperature
IV	C	0.3–1.5	Slow pain and temperature

An axon and myelin sheath (if present) together form a **nerve fiber**. Peripheral nerve fibers vary in diameter, ranging from 0.3 to 22 μm. Nerve fibers are classified according to their fiber diameter, speed of conduction, and functions. The largest nerve fibers are classified as Aα and the smallest ones as C (Table 1.1). Since the conduction velocity reflects myelination and the axonal diameter, Aα nerve fibers that innervate the skeletal muscle are heavily myelinated and have the fastest conduction velocity. Other type A (β, γ, δ) and B nerve fibers are progressively smaller and poorly myelinated. Most nerve fibers classified as C are not myelinated and have a slow conduction velocity. A numerical system (I, II, III, IV) is used to classify sensory nerve fibers (Table 1.2). The largest sensory fibers are classified as Ia and the smallest ones as IV. Type IV sensory fibers are mostly nonmyelinated.

Microglia comprise 10–20% of all neuroglia. Microglia are the macrophages of the CNS and act as the first line of defense against tissue injury or infection. Once activated, microglia proliferate and assume a phagocytic role by developing into round, often large cells. They clear debris from the injured area. However, phagocytosis is not the only means of destroying foreign invaders. For example, microglia are also known to release nitric oxide, which prevents viral replication.

Astrocytes (Greek *astron*, star) are star-shaped cells with numerous long cell processes (Figure 1.4). However, they appear as cells with pale ovoid nuclei with routine staining. Astrocytes represent approximately 50% of the glial cell population in the CNS. They provide structural and metabolic support for neurons. For example, astrocytes seal the outer and inner surfaces of the CNS by forming the outer and

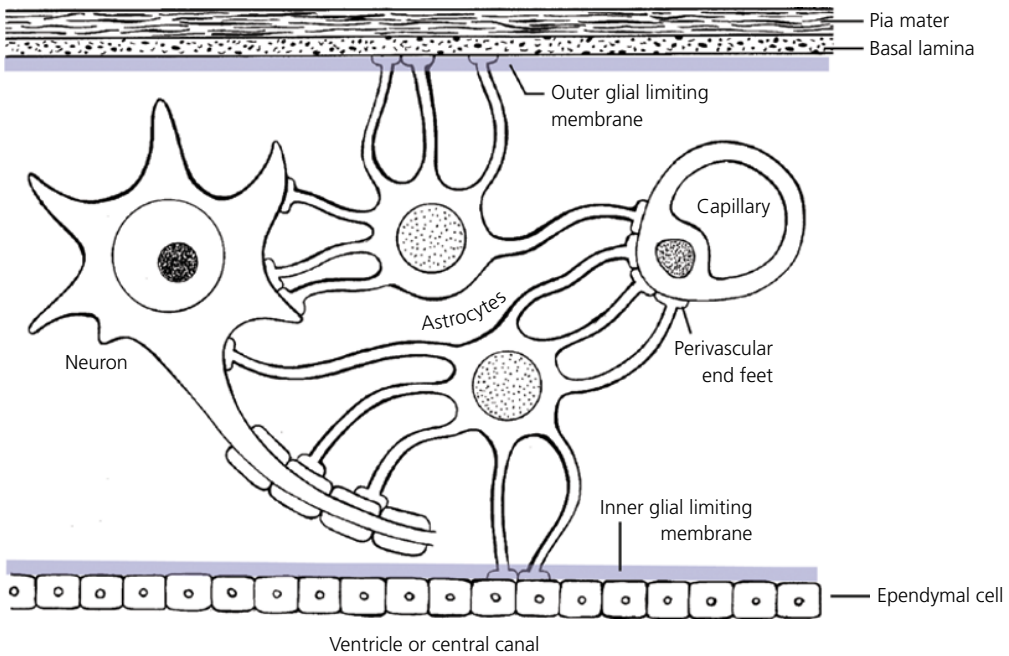

Figure 1.4 Relationship of astrocytes to other cellular and structural components of the central nervous system. Astrocytic processes surround neurons, individual or groups of synapses, capillaries and internodal areas between myelin sheaths. They also form a plexus beneath the pia mater (outer glial limiting membrane) and ependyma (inner glial limiting membrane).

inner glial limiting membranes, respectively. Astrocytes release **neurotrophic factors** (e.g., nerve growth factor), which are important for neuronal survival. Elongation of axons and dendrites requires not only the physical presence of astrocytes, but also **extracellular adhesion molecules** (e.g., laminin, fibronectin) released from astrocytes. Astrocytic processes cover the greater part of neurons, synaptic sites, internodal areas, and capillaries. Astrocytic covering of synaptic sites and internodal areas may prevent signal interference from nearby synapses and axons.

The astrocytic processes that cover capillaries are the **perivascular end feet**. Experimental studies suggest that such close contact between astrocytes and the capillary endothelium is important for glucose transport, regulation of extracellular environment (pH, ion concentration, osmolarity), glutamate metabolism, and maintenance of the endothelial blood–brain barrier. Astrocytes maintain the optimal extracellular environment for neurons and neuroglia. For example, astrocytes are equipped with ionic channels for potassium (K^+), sodium (Na^+), chloride (Cl^-), bicarbonate (HCO_3^-) and calcium (Ca^{2+}). Therefore, they are capable of exchanging these ions with neighboring cells, including neurons. Excitation of neurons accompanies a marked flux of K^+ into the extracellular space. However, an increase in K^+ concentration is prevented by astrocytes, which take up K^+ and relocate it to areas with low neuronal activities or release it to the blood and CSF. Astrocytes also prevent the build-up of potentially neurotoxic substances. Glutamate, for example, is a neurotransmitter that excites postsynaptic neurons (see Figure 3.2B). It is also neurotoxic if accumulated beyond a certain concentration. Astrocytes prevent excess accumulation of extracellular glutamate by metabolizing glutamate into glutamine. Glutamine from astrocytes is used by neurons for synthesis of new glutamate, which is repackaged into synaptic vesicles to be used as a neurotransmitter.

Astrocytes participate in the repair process following tissue injury. Under slowly degenerative conditions, astrocytes retain their small size. Thus only special stains can observe their reactive cytoplasm and cell processes. However, typical astrocytic reactions to pathological conditions are cellular swelling and hyperplasia (Greek *hyper*, above; *plasis*, formation; a condition characterized by an increase in the number of cells). Astrocytic swelling is often induced by injuries from hypoxia (a condition where oxygen levels are below normal), trauma, and hypoglycemia (Greek *hypo*, under; *glykys*, sweet; *haima*, blood; the presence of low sugar levels in the blood). Swelling usually reflects changes in extracellular ionic concentrations (e.g., increase in K^+, decrease in Na^+ and Cl^-, accumulation of glutamate). Destructive lesions of the CNS, especially those caused by trauma, promote astrocytic hyperplasia. In a cerebral infarct, i.e., an area of necrosis (Greek *nekrosis*, deadness; death of tissue) resulting from insufficient blood supply, astrocytes proliferate along the edge of the necrotic area, often sealing off the lesioned area.

Ependymal cells (Greek *ependyma*, upper garment) cover the ventricles and central canal of the CNS (Figure 1.5). They also line the choroid plexus. The ependymal cells of the ventricles and central canal form a selective barrier between the nervous tissue and **CSF**. Junctional complexes are present between adjacent ependymal cells, enabling them to modify the CSF by secretory or absorptive processes. The choroid plexus secretes CSF (Table 1.3). However, it is not the only source of CSF. CSF is also released from the brain through (i) the ependymal lining of the ventricles and central canal and (ii) the pia–outer glial limiting membrane that covers the external surface of the CNS.

The CSF leaves the ventricular system via a small opening, the lateral aperture of the fourth ventricle, to enter the subarachnoid space. It also enters the central canal of the caudal medulla oblongata and spinal cord. The CSF in the subarachnoid

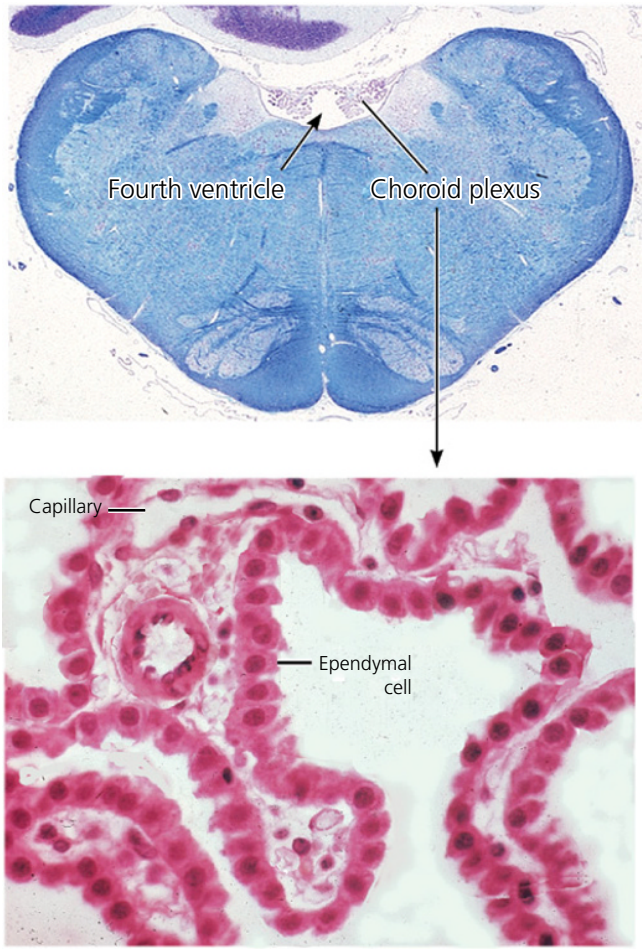

Figure 1.5 The choroid plexus in the fourth ventricle of the medulla oblongata. The choroid plexus is composed of vascular connective tissue lined with ependymal cells on the ventricular surface.

Table 1.3 Normal CSF values.

Color: clear
Cells: <5/mm^3
Protein: <25 mg/dL
Glucose: 2.7–4.2 mmol/L
Pressure: <170 mmH_2O

space is drained into the dorsal sagittal sinus, which also receives numerous tributary veins from the cerebral hemispheres and passes blood to the maxillary, internal jugular and vertebral veins and to the vertebral venous plexuses. The CSF in the subarachnoid space of the meninges not only protects the brain and spinal cord from trauma, but also reduces the effective weight of the brain significantly by providing a buoyancy effect.

Extracellular environment of the CNS

1 What are the blood–CSF and blood–brain barriers? Where are they located?
2 What transport mechanisms are involved in production of the CSF by the choroid plexus?
3 Explain the formation, circulation, and function of the CSF.
4 What structure represents the blood–brain barrier?
5 What transport mechanisms are involved in the blood–brain barrier?
6 List the areas of the brain where the blood–brain barrier is absent and explain the reason.

Neurons and neuroglia require a chemically stable environment. Thus, the brain receives only the essential materials from the blood and CSF. Two structures acting as gatekeepers to the brain's interior are (i) the **choroid epithelium** of the choroid plexus that acts as the blood–CSF barrier and (ii) the **capillaries** of the nervous tissue that act as the blood–brain barrier.

Blood–CSF barrier

The choroid plexus is present in the lateral, third and fourth ventricles (Figure 1.6). It is formed by invagination of the pia mater covered with choroid epithelial cells on the surface facing the ventricle. Vasculature of the pia mater follows the choroid plexus, providing rich capillary networks. The choroid epithelial cells are modified ependymal cells (they have microvilli instead of cilia on the apical surface). The capillary endothelium of the choroid plexus has many fenestrations in its wall, allowing passage of many small molecules. In contrast, choroid epithelial cells are sealed together by a tight junction that prevents the passage of water-soluble molecules into the CSF. Tight junctions are the anatomical basis of the **blood–CSF barrier** (Figure 1.7) Thus, **choroid epithelial cells** play a key role in regulating what can enter and leave the CNS tissue, maintaining an optimal environment for neurons and neuroglia. The choroid plexus relies on carrier proteins to transport essential molecules. Carrier proteins are located on the basal surface of the choroid epithelial cells. Essential molecules are released into the ventricle through the apical surface of the choroid epithelial cells, probably by facilitated diffusion. The CSF is also important for removing waste products from the CNS. Waste products removed from the CNS are drained into the dorsal sagittal sinus via the arachnoid villi.

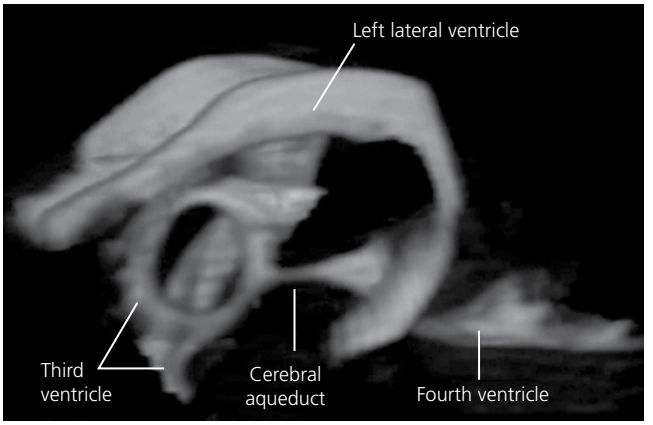

Figure 1.6 MRI reconstruction of the ventricles of a dog showing the lateral ventricles, third ventricle, cerebral aqueduct, and fourth ventricle. Dr A. Zur Linden, Iowa State University College of Veterinary Medicine. Reproduced with permission from Dr A. Zur Linden.

Clinical correlations

Certain antibiotics (e.g., penicillin and most cephalosporin antibiotics) are actively removed from the CSF. Thus, the concentration of penicillin in CSF is about 1% of that in the blood. Interestingly, the choroid plexus under inflammatory conditions (e.g., meningitis) becomes leaky, resulting in a partial breakdown of the blood–CSF barrier. Consequently, the concentration of penicillin in CSF increases to 20% or more of that in the blood, preventing further bacterial growth or even killing bacteria. As inflammation subsides, the choroid plexus regains the function of the blood–CSF barrier and resumes removal of penicillin from CSF, allowing the possibility of a relapse of bacterial growth. Therefore, use of antibiotics that are not actively removed from the CSF (e.g., ceftriaxone with broad-spectrum activity against Gram-positive and Gram-negative bacteria) must be considered for treating many types of meningitis.

Cerebrospinal fluid is 99% water, which the choroid plexus secretes into the ventricles by creating ion gradients on both apical and basal surfaces of choroid epithelial cells (Figure 1.7). Water in the choroid epithelial cells dissociates into hydrogen (H^+) and hydroxyl (OH^-) ions. OH^- combines with intracellular CO_2 produced by cell metabolism to form bicarbonate ions (HCO_3^-). At the basal surface of the cells, H^+ is exchanged for extracellular sodium ions (Na^+) from the blood. Na^+ is pumped out through the apical surface into the ventricles. The flux of Na^+ results in an excess positive charge in the ventricles. To neutralize this excess positive charge, chloride ions (Cl^-) and HCO_3^- move into the ventricles. Water also diffuses into the ventricles to maintain osmotic balance. These processes maintain water and concentration of ions in the CSF appropriate for the brain and spinal cord. Water and ions are not the only substances that the CNS must obtain from the blood. The majority of micronutrients

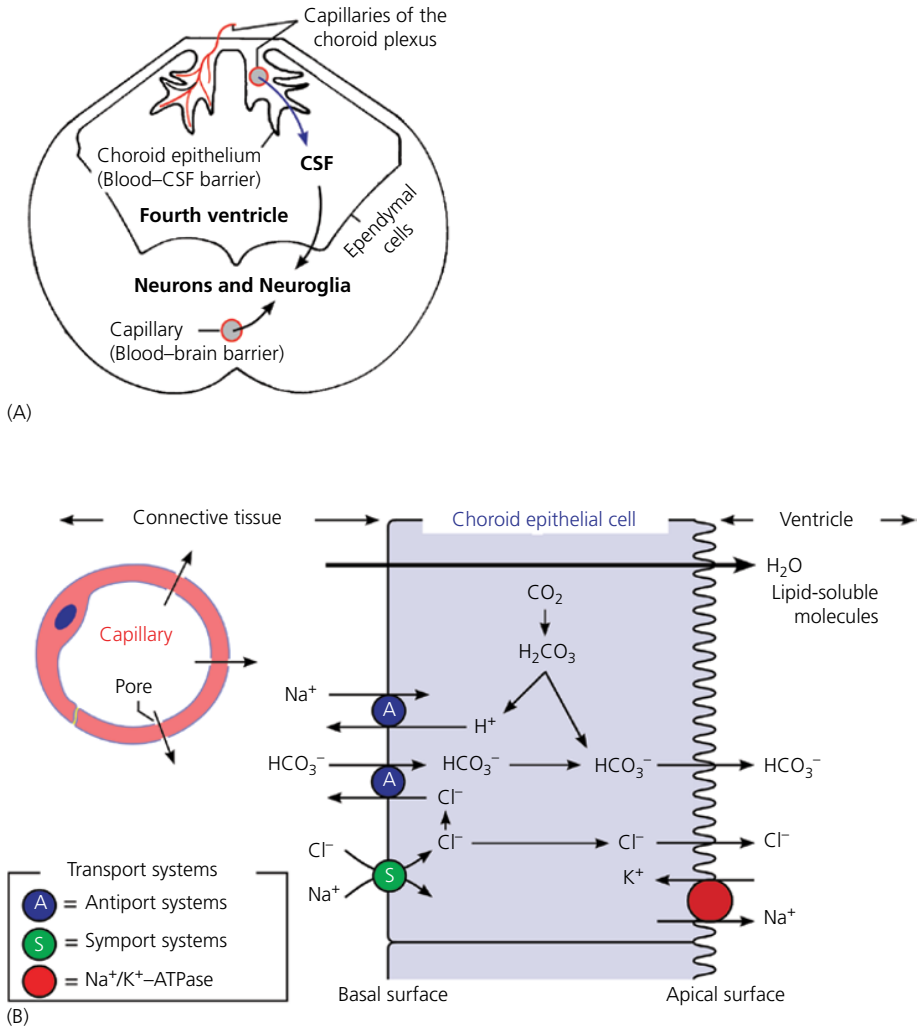

Figure 1.7 (A) Neurons and neuroglial cells receive essential materials via two routes. Capillaries in the choroid plexus provide micronutrients, whereas interstitial capillaries provide oxygen and substances that the CNS consumes rapidly and in large amounts. The fourth ventricle is exaggerated here and not proportional to the size of the medulla oblongata. (B) The capillaries in the choroid plexus do not act as the blood–CSF barrier, as they are fenestrated (i.e., many pores) and intercellular gaps between endothelial cells are not tight as those found in capillaries of the CNS. As a result, molecules easily cross the capillary endothelial cell of the choroid plexus. The blood–CSF barrier is provided by the choroid epithelial cells, which are joined together by tight junctions. Microvilli of the choroid epithelial cells are present on the ventricular side of the epithelium. The choroid plexus produces CSF by diffusion, facilitated diffusion, and active transport systems. The choroid plexus epithelium also transports metabolites from CSF to blood (not shown).

(substances that are essential to the brain but only needed in relatively small amounts) come from the CSF. Micronutrients include vitamin B_6 (pyridoxine), folates (members of vitamin B-complex class) and vitamin C. In contrast, nutrients (glucose, amino acids, lactate) that the CNS requires in large amounts are delivered directly into the interstitial fluid by the capillary endothelium. This process depends on a facilitated-diffusion system.

Blood–brain barrier

It is known that a dye such as trypan blue, injected intravenously, stains all tissues of the body except the brain and spinal cord. Animals do not show any adverse effects from this procedure. However, when the dye is injected into the ventricle, the whole brain is diffusely stained and animals suffer from neurological problems. Clearly, the central nervous tissue has some barrier against the passage of a circulating dye, and this barrier is referred to as the blood–brain barrier (Figure 1.8). The site of the blood–brain barrier was shown by use of a tracer, horseradish peroxidase (HRP). HRP injected into the ventricle easily enters the extracellular spaces of the brain by crossing the ependymal cells. Although HRP in the brain passes through the capillary basement membrane, it is prevented from crossing the capillary wall into the lumen. However, there are a few specialized areas in the brain that allow entry of dyes or HRP. These nonbarrier regions include the choroid plexus, hypophysis,

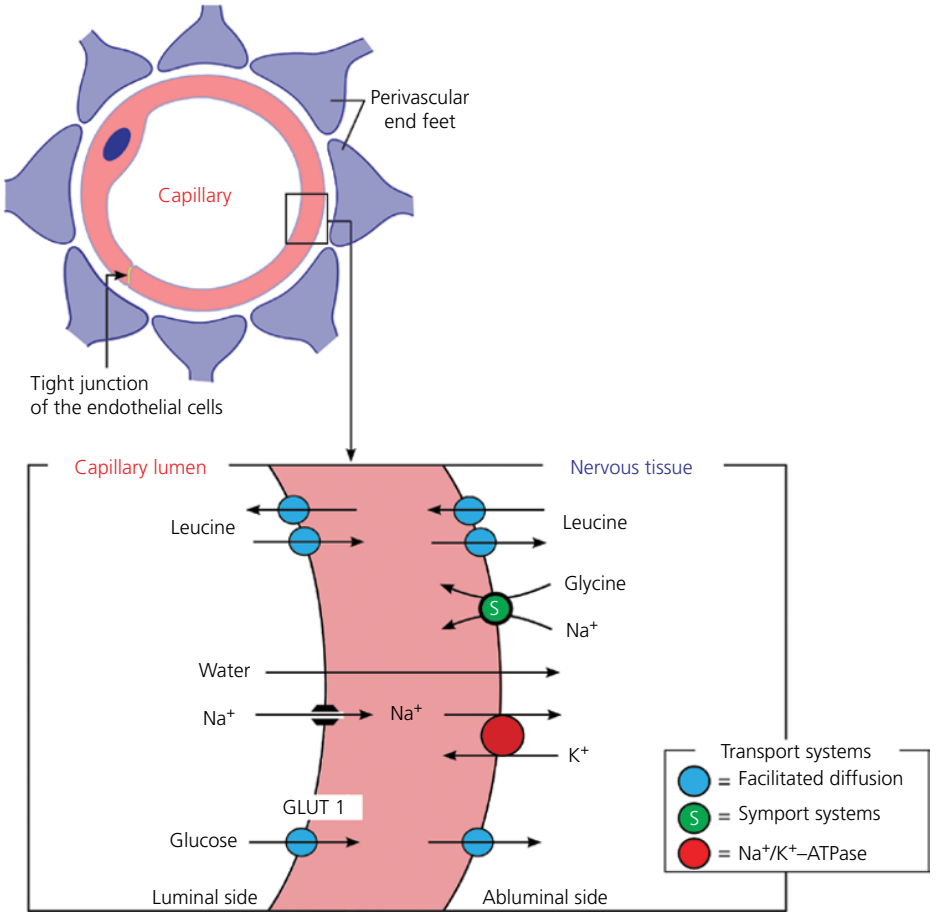

Figure 1.8 Transport of molecules across capillaries of the CNS. Continuous tight junctions of endothelial cells restrict the diffusion of large and small solutes across the endothelial cells. The perivascular end feet encircle the capillary. Transport carriers for essential amino acids and glucose facilitate their movement into the CNS. Active transport systems moves small nonessential amino acids from brain to blood. Na^+ is transported from blood to the CNS by Na^+ transporters on the luminal membrane and Na^+/K^+-ATPase on the abluminal membrane. This Na^+ movement drives transport of water into the CNS.

median eminence, pineal gland, and area postrema. Capillaries in these areas are fenestrated, which is essential for these areas to carry out their function (e.g., release of hormones into the circulation, monitoring circulating molecules). Thus, capillaries are the factor that restricts what can enter the brain from the blood.

The morphological basis of the blood–brain barrier is established by the electron microscope. Capillaries of the CNS are associated with three unique features: (i) continuous **tight junctions** that seal neighboring endothelial cells, (ii) absence of **fenestrations** and (iii) only a small number of **pinocytotic vesicles**. Although capillary endothelium is the structural basis of the blood–brain barrier, such a property appears to be maintained by astrocytes that form perivascular end feet around the entire outer surface of the capillary endothelium (Figure 1.8). This association suggests that the interaction between astrocytes and endothelial cells is important for the maintenance of the blood–brain barrier. Thus, it is not surprising to see the absence of normal astrocyte–endothelial cell relationships in the nonbarrier regions of the brain mentioned above and in brain tumors. The transcellular transport is the only way for any substance in the blood to enter the CNS. The plasma membrane is made of a lipid bilayer. It is not permeable to charged molecules and most polar molecules such as sugars and amino acids. Anions in water are attracted electrostatically to the hydrogen atom of water, whereas cations are attracted to the oxygen atom of water. Such attraction of ions to water molecules imposes a barrier for ions to pass through the hydrophobic lipid bilayer of membrane. Thus, lipophilic substances (e.g., nicotine and ethanol) are very permeable and their transport through the endothelial cells is only limited by blood flow. Gases (e.g., CO_2, O_2, N_2O) diffuse rapidly into brain. Water also crosses freely in either direction through the membrane by diffusion as the osmolality of the plasma changes.

The brain needs certain water-soluble nutrients, such as glucose or certain essential amino acids. However, water-soluble compounds are restricted from passing through the blood–brain barrier into the brain. Glucose is a vital source of energy in the brain and its transport depends on a specific glucose carrier (GLUT 1) in the capillary endothelial cells. GLUT 1 is a facilitative transporter located at both the luminal and the abluminal side of the endothelial membrane. Facilitated diffusion carried out by the carriers does not consume energy. Facilitated diffusion moves molecules in both directions across the membrane, but the net flow is from the side of higher concentration to that of lower concentration. Since glucose is rapidly consumed in the CNS, the glucose concentration in interstitial fluid is normally lower than in blood plasma. As a result, the net flow of glucose across the blood–brain barrier is from blood to interstitial fluid. Specific carriers have substrate specificity. Thus, the carriers that transport D-glucose do not transport the L-enantiomer.

Large neutral amino acids (e.g., phenylalanine, leucine, tyrosine, isoleucine, valine, tryptophan, methionine histidine, and L-dopa) are transported by facilitated diffusion both on the luminal and abluminal sides of the endothelial cells. Some of them, for example tryptophan, are precursors for neurotransmitters (serotonin, melatonin) synthesized in the CNS. Serotonin is involved in mood and sleep and melatonin regulates the sleep–wake cycle (circadian rhythm). Smaller neutral amino acids such as glycine, alanine, serine, cysteine, proline, and γ-aminobutyric acid (GABA) are synthesized in the CNS. These amino acids are also transported primarily from the brain to the circulation. Their transport requires an energy-dependent and Na^+-dependent symport carrier located at the abluminal side of the endothelial cell membrane. Na^+/K^+-ATPase located on the abluminal endothelial membrane provides the energy to drive the Na^+ and amino acid symport carrier by maintaining high extracellular Na^+ concentration in the CNS. Ion channels are also present in the luminal endothelial membrane. These ion channels and Na^+/K^+-ATPase work together to remove K^+ from the interstitial fluid of the CNS in order to maintain a constant K^+ concentration.

It appears that essential amino acids which are precursors for catecholamines (epinephrine and norepinephrine synthesized from tryosine) and indolamine (e.g., serotonin and melatonin synthesized from tryptophan) are transported into the CNS. On the other hand, amino acids that are synthesized in the CNS and which function as neurotransmitters are not just restricted from crossing the blood–brain barrier into the CNS, but are transported out of the CNS. This lopsided transport across the blood–brain barrier may ensure that neurotransmitters will not accumulate in the brain, preventing the potential neurotoxic glutamate effect and unwanted inhibition of neurons by glycine and GABA.

Clinical correlations

Water crosses the membrane freely in either direction by diffusion. This property of water across the membrane can be clinically useful in osmotherapy. For example, mannitol, $C_6H_8(OH)_6$, is poorly permeable and intravenous administration of mannitol osmotically dehydrates the brain. Thus, mannitol can be used to reduce dangerously elevated intracranial pressure (e.g., after head trauma). Mannitol is also used experimentally to deliver drugs to the CNS by temporarily opening the blood–brain barrier. This osmotic disruption approach uses a concentrated dose of mannitol to remove fluid from the brain's endothelial cells, which causes endothelial cells to shrink and the tight junctions to open. However, the temporary opening of the blood–brain barrier is only applicable in disorders that do not require long-term treatment.

The blood–brain barrier is essential for maintaining stable functions of the CNS. The barrier imposed by the capillary endothelium ensures that any changes in nutrients, ions, and hormones do not directly influence synaptic functions. Unfortunately, the strict criteria set by the barrier applies equally to therapeutic drugs. The lipophilic antibiotic chloramphenicol crosses the blood–brain barrier without problems, but the highly hydrophilic penicillin is prevented from crossing the barrier. A high proportion (over 95%) of large-molecule drugs do not cross the blood–brain barrier, which includes all the products of biotechnology, recombinant proteins, and monoclonal antibodies. Thus, most drugs that are effective in the treatment of systemic diseases are not effective for treating CNS diseases. It is highly desirable that drugs are developed which can either directly or indirectly bypass the blood–brain barrier. Fortunately, inflammation associated with certain diseases affects the blood–brain barrier by increasing the permeability of endothelial membranes to certain antibiotics, allowing drugs to enter the CNS. As the inflammation decreases, entrance of the antibiotic also decreases, lowering the effectiveness of treatment.

Self-evaluation

Answers can be found at the end of the chapter.

1 Dendrites of neurons receive signals from other neurons.
- **A** True
- **B** False

2 Neurons that have one axon and numerous dendrites are classified as:
- **A** Bipolar neuron
- **B** Multipolar neuron
- **C** Unipolar neuron

3 Axon hillock is a site that generates action potentials.
- **A** True
- **B** False

4 Neuroglia that is part of the choroid plexus comprises:
- **A** Astrocytes
- **B** Ependymal cells
- **C** Microglia
- **D** Oligodendrocytes

5 Which statement about astrocytes are not correct?
- **A** Astrocytes form the choroid plexus
- **B** Astrocytes transport glucose from capillaries to neurons
- **C** Astrocytes form perivascular end feet
- **D** Astrocytes continue dividing after birth
- **E** Astrocytes prevent intercellular accumulation of the neurotransmitter glutamate

6 The myelin sheath:
- **A** Is made by oligodendrocytes in the PNS
- **B** Is made by Schwann cells in the CNS
- **C** Slows the nerve impulse traveling along axons
- **D** Enables faster conduction velocity

7 A nerve fiber is made of:
- **A** An axon only
- **B** An axon and Schwann cells.
- **C** An axon and endoneurium
- **D** An axon and epineurium

8 Leucine is transported by facilitated diffusion at the blood–brain barrier.
- **A** True
- **B** False

9 What structure represents the blood–brain barrier?
- **A** Choroid plexus
- **B** Microglia
- **C** Endothelial cells
- **D** Astrocytes
- **E** Meninges

10 Nerve fibers classified as Aα are larger in diameter and faster in conduction than those fibers classified as C fibers.
- **A** True
- **B** False

11 Axons in the CNS are myelinated by:
- **A** Astrocytes
- **B** Schwann cells
- **C** Ependymal cells
- **D** Oligodendrocytes

12 Na^+/K^+-ATPase is located on which membrane of endothelial cells?
- **A** Luminal
- **B** Abluminal

13 Glucose in the CNS is transported by:
- **A** Simple diffusion
- **B** GLUT 1
- **C** Facilitated diffusion
- **D** Na^+-dependent symport carrier
- **E** Na^+/K^+-ATPase

14 The choroid plexus produces the CSF.
- **A** True
- **B** False

15 The CSF in the third ventricle enters the fourth ventricles via cerebral aqueduct.
- **A** True
- **B** False

16 What represents the blood–CSF barrier?
- **A** Meninges
- **B** Capillary endothelium of the choroid plexus
- **C** Perivascular end feet
- **D** Choroid epithelium
- **E** Astrocytes

17 The blood–brain barrier is absent in the:
- **A** Spinal cord
- **B** Cerebellum
- **C** Choroid plexus
- **D** Area postrema
- **E** Two of the above

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Answers

1 A
2 B
3 A
4 B
5 A
6 D
7 B
8 A
9 C
10 A
11 D
12 B
13 B
14 A
15 A
16 D
17 E

2 Electrochemical Basis of Neuronal Function

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Neurons function by establishing communication mediated by electrical and chemical means. Thus the excitability of neurons and their ability to propagate electrical signals are one of the most prominent features of the nervous system. The relatively static membrane potential of inactive cells is the **resting membrane potential**. It reflects selective ionic permeability of the plasma membrane, maintained at the expense of continuous basal metabolism. The resting membrane potential plays a central role in the excitability of nerves. When a neuron receives excitatory or inhibitory signals, the neuronal membrane generates excitatory or inhibitory graded membrane potentials (i.e., transient changes in the resting membrane potential). Once the electrical stimulus fulfills specific criteria, the neuronal membrane undergoes dynamic reversal of membrane potential, known as an action potential. In this chapter, four basic physiologic properties of neurons (resting membrane potential, graded potential, action potential, and propagation of action potential) are discussed for a better understanding of neuronal functions.

Distribution of intracellular and extracellular ions

1. Name five major intracellular and extracellular ions and indicate which ions are more highly concentrated inside neurons relative to outside.
2. What two energy gradients drive the movement of ions across the membrane?
3. What is the equilibrium potential?
4. What happens to the membrane potential if an ion is allowed to selectively cross the membrane?
5. What are the properties and functions of Na^+/K^+-ATPase?

The neuronal membrane, like other cell membranes, is made of a lipid bilayer. It is not permeable to charged molecules and most polar molecules such as sugars and amino acids. Anions in water are attracted electrostatically to the hydrogen atom of water and cations to the oxygen atom. Attraction of ions to water molecules acts as a barrier for passage of ions across the hydrophobic lipid bilayer of the membrane. This property is the basis for the unique distribution of inorganic ions (e.g., Na^+, K^+, Cl^-) across the neuronal membrane. The proteins present in the membrane are receptors, transporters, and enzymes. The selective permeability of the neuronal membrane reflects the presence of ion channels. These ion channels allow some ions to pass through the membrane in the direction of their concentration and electrostatic gradients. The neuron has four main types of selective ion channels: Na^+, K^+, Ca^{2+}, and Cl^- channels. These ion channels are either in an open state (also referred to as nongated or leak channels) or have gates that may open or close in response to specific stimuli (e.g., voltage or chemicals). Nongated channels play a role in maintaining the intracellular and extracellular ion concentrations. Voltage-gated ion channels are important for generation of action potentials and their propagation along axons. Chemically gated ion channels play a role in synaptic transmission by opening ion channels when they bind with a variety of ligands, such as a neurotransmitter or intracellular signaling molecules. Channel proteins mediate **passive transport** of molecules across the membrane and metabolic energy is not necessary. Uncharged molecules are passively transported across the membrane according to the concentration gradient of the solute. Uncharged molecules diffuse through the membrane from the side of higher concentration to the side of lower concentration. Charged molecules cross the membrane according to the electrochemical gradient (i.e., the combination of the concentration and electrical

Dukes' Physiology of Domestic Animals, Thirteenth Edition. Edited by William O. Reece, Howard H. Erickson, Jesse P. Goff and Etsuro E. Uemura.

Companion website: www.wiley.com/go/reece/physiology

gradients). **Active transport** requires specific carrier proteins and metabolic energy, such as hydrolysis of ATP.

In the resting state of neurons, the electrolyte content differs greatly from that of the extracellular fluid (Table 2.1). The concentration of Na^+ ions is approximately 10 times greater in the extracellular fluid (150 mmol/L) than in the intracellular fluid (15 mmol/L). Similarly, the concentration of Cl^- ions is much greater in the extracellular fluid (150 mmol/L) than in the intracellular fluid (13 mmol/L). In contrast, the concentration of intracellular K^+ (100 mmol/L) is approximately 20 times higher than in the extracellular fluid (5 mmol/L). There are many negatively charged intracellular organic molecules (e.g., proteins, nucleic acids, carboxylic groups, and metabolites carrying phosphate). Since the organic anions are too large to pass through the membrane, they are called **fixed anions**. They drive the electrical charge of cytoplasm facing the plasma membrane towards negative relative to the outside of the membrane.

Table 2.1 Intracellular and extracellular distribution of ions across the neuronal membrane.

Ion	Extracellular concentration (mmol/L)	Intracellular concentration (mmol/L)
Na^+	150	15
K^+	5	100
Ca^{2+}	2	0.0002
Cl^-	150	13
Fixed anions	—	385

The selective permeability of the membrane is key for maintaining the separation of charges across the membrane (Figure 2.1). If the neuronal membrane is selectively permeable only to K^+, the high **concentration gradient** of K^+ should drive them from inside the cell to outside through K^+ nongated channels. However, intracellular fixed anions prevent an efflux of K^+ ions. At the same time, extracellular positive charges drive K^+ into the neuron due to **electrostatic forces**. However, the distribution of K^+ remains stable as the movement of ions in one direction under the influence of the concentration gradient is precisely balanced by the movement of ions in the opposite direction due to the **electrochemical gradient**. When the two opposing forces (concentration gradient, electrostatic forces) are equal, intracellular and extracellular K^+ concentrations are in equilibrium. The membrane potential derived at the equilibrium of K^+ is called the K^+ equilibrium potential (approxi-

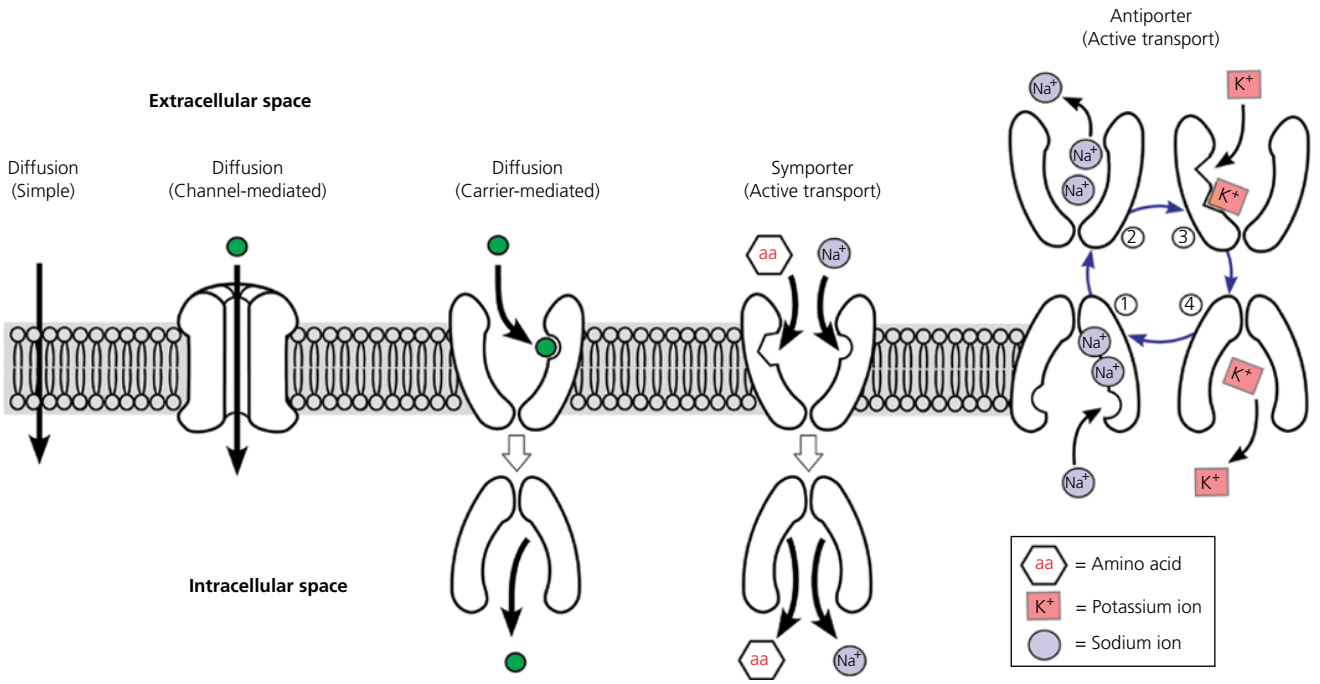

Figure 2.1 Transport of solute across the neuronal membrane. *Simple diffusion*: the molecules move according to their concentration gradient. Simple diffusion does not require input of energy and net movement of the molecules stops after reaching equilibrium. *Channel-mediated diffusion*: when the channel is in the open state, certain charged ions (e.g., Na^+ and K^+) are able to pass through the pore to reach the other side of the plasma membrane. *Carrier-mediated diffusion*: movement of substances across cell membranes with the aid of a carrier protein (e.g., GLUT transporter that move hexoses such as glucose, galactose, mannose, and fructose). *Symporter*: a carrier protein cotransports two or more molecules in the same direction across the cell membrane. Examples include Na^+–glucose, Na^+–amino acid, Na^+–neurotransmitter uptake. *Antiporter*: exchange of molecules takes place in opposite directions, i.e., one enters the cell as the other exits the cell. An example is Na^+/K^+-ATPase that maintains the concentration gradients of Na^+ and K^+ across the cell membrane. The following steps are involved in moving molecules against their concentration gradient. (1) An ATP molecule binds to the ATPase. This step creates binding sites for three Na^+ ions on the intracellular side of the carrier. (2) The energy released by hydrolysis of the high-energy bond changes the conformation of the carrier protein so that the channel opens to the extracellular side. At the same time, the binding affinity for Na^+ decreases and the Na^+ ions are released into the extracellular side. (3) After the loss of Na^+, the phosphate group detaches, creating high-affinity binding sites for K^+ on the extracellular side of the carrier channel. Two K^+ ions from the extracellular fluid attach to the carrier protein. (4) A new ATP molecule binds to the ATPase, changing the conformation. Subsequent opening of the channel to the cytoplasmic side releases K^+ into the cytoplasm.

Table 2.2 Nernst equation to determine equilibrium potential of ions.

The Nernst equation for calculating the equilibrium potential of an ion present on both sides of the cell membrane is as follows:

$$E_{ion} = 2.303\frac{RT}{zF}\log\frac{[ion]_o}{[ion]_i}$$

where:
E_{ion} = ionic equilibrium potential
R = gas constant (8.314 J mol^{-1} K^{-1})
T = temperature of Kelvin scale (273.15 + temperature in °C)
z = valence of the ion
F = Faraday constant (96 485 C mol^{-1})
$[ion]_o$ = ionic concentration outside the cell
$[ion]_i$ = ionic concentration inside the cell

The equilibrium potential calculated by the Nernst equation:
$E_K = 61.5\,mV \log 5/100 = -80\,mV$
$E_{Na} = 61.5\,mV \log 150/15 = +62\,mV$
$E_{Cl} = 61.5\,mV \log 150/13 = -65\,mV$

mately –80 mV) (Table 2.2). Similarly, if the membrane is selectively permeable only to Na^+, the electrochemical gradient drives Na^+ into the neuron to establish the equilibrium. The membrane potential derived from the equilibrium of Na^+ is the Na^+ equilibrium potential (approximately +62 mV). The Cl^- equilibrium potential is very similar to the K^+ equilibrium potential.

Resting membrane potential

1. Explain the ionic mechanisms contributing to the resting membrane potential and approximate voltage in most mammalian neurons.
2. What is the relationship between ionic driving forces, ion channels, and the membrane potential?
3. What role does the Na^+/K^+-ATPase play in maintaining the resting membrane potential?

The potential difference across the membrane of resting neurons is referred to as the resting membrane potential. It is about –65 mV (i.e., the inside of the neuron is about 65 mV less than the outside). The resting membrane potential reflects asymmetric distribution of certain ions (K^+, Na^+, Cl^-, fixed anions) across the neuronal membrane. The resting membrane potential of a neuron is far from the equilibrium potential for K^+ (–80 mV) or Na^+ (+62 mV). This is because the membrane of resting neurons is selectively permeable to K^+ due to the presence of high numbers of nongated K^+ channels. Na^+ ions are driven inwards across the membrane by the electrochemical gradient. However, the Na^+ conductance is extremely small due to limited Na^+ nongated channels available. This significantly limits Na^+ influx despite their large electrochemical gradient. Thus the resting potential reflects the unequal distribution of ions across the neuronal membrane.

The asymmetric distribution of K^+ and Na^+ across the membrane is maintained by the Na^+/K^+-ATPase (Na^+/K^+ pump) in the membrane (Figure 2.1). The Na^+/K^+-ATPase moves Na^+ and K^+ against their electrochemical gradient, removing Na^+ and bringing K^+ into the neuron. The pumping of Na^+ and K^+ can be turned off reversibly by the use of metabolic inhibitors (e.g., dinitrophenol, azide, cyanide), while intracellular injection of ATP can reverse such an inhibitory effect. The Na^+/K^+ pump works continuously, regardless of the state of electrical activity of a neuron, maintaining the large ionic concentration gradients across the membrane.

Graded potential

1. What are the two types of postsynaptic potentials and how do they generate membrane depolarization or hyperpolarization?
2. Where is the axon hillock located in a neuron and what role does it play in postsynaptic membrane potentials?
3. What are the two mechanisms that modify membrane potentials at the axon hillock?

A neuron receives hundreds of inputs from other neurons primarily via axodendritic and axosomatic synapses. In response to neurotransmitters from presynaptic neurons, brief local changes in postsynaptic membranes are generated at each synaptic site. These local membrane potentials are referred to as **graded potentials**, as their amplitude is directly proportional to the intensity of the stimulus applied at synaptic sites. Each synaptic site generates graded potentials, so that thousands of graded potentials occur at cell bodies and dendrites. Graded potentials generated by synaptic sites at dendrites and cell bodies travel to reach the axon hillock (also referred to as the **trigger zone**) of a neuron (see Figure 1.2). The axon hillock is where graded potentials are integrated to generate action potentials. In unipolar and bipolar neurons, the trigger zone is at a terminal area of a neuronal process that is equivalent to a dendrite. The trigger zone is most sensitive to the depolarizing action of the local currents and is a crucial region of neurons that generates action potentials in response to incoming graded potentials. Graded potentials reaching the trigger zone must be strong enough to depolarize the membrane to the level known as the **threshold potential** (or voltage), about –55 mV. Once the sum of graded potentials exceeds the threshold, the trigger zone triggers action potentials that propagate along the axon. If the depolarization does not reach the threshold, an action potential is not generated and the graded potentials decay.

Excitatory and inhibitory postsynaptic potentials

Graded potentials modulate the postsynaptic neuron by shifting the resting membrane potential toward or away from the threshold potential. Shifting the membrane potential toward more positive is called **depolarization** (Figure 2.2) and a depolarizing graded potential is referred to as an **excitatory postsynaptic potential (EPSP)** (Figure 2.3A). For example, acetylcholine and glutamate induce depolarizing graded potentials by opening ligand-gated Na^+ channels, triggering an influx of Na^+. Synapses that induce EPSPs are called **excitatory synapses**, as they drive the postsynaptic membrane potential toward the threshold. In contrast, neurotransmitters such as γ-aminobutyric acid (GABA) and glycine bind to ligand-gated Cl^- channels

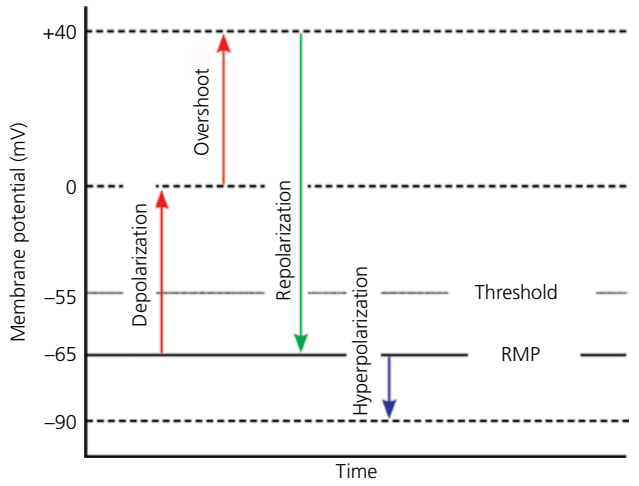

Figure 2.2 Terminology related to membrane potential of neurons. *Depolarization*: decrease in the potential difference across the plasma membrane, going to more positive. *Overshoot*: a portion of depolarization that causes the inside of the cell to be positively charged with respect to the outside. *Repolarization*: change in potential that returns the membrane potential to a negative value after the depolarization phase of an action potential. Repolarization returns the membrane potential to the resting membrane potential (RMP) (–65 mV). *Hyperpolarization*: increase in the potential difference across the membrane to more negative, away from the RMP. *Threshold*: critical membrane voltage (–55 mV) to which the membrane potential must be depolarized in order to generate an action potential. When the graded potential reaches the threshold potential, there is about a 50% chance of generating an action potential. The membrane potential must exceed the threshold to generate an action potential.

that trigger influx of Cl^-. Subsequent shifting of the membrane potential toward more negative is called **hyperpolarization** (Figure 2.2). A hyperpolarizing graded potential is called an **inhibitory postsynaptic potential (IPSP)** and synapses that induce IPSPs are called **inhibitory synapses** (Figure 2.3B). Thus, the postsynaptic membrane can be stimulated or inhibited, depending on the transmitter involved and the subsequent change in ion permeability that alters membrane excitability.

Summation of graded potentials

Numerous presynaptic axons converge on a postsynaptic neuron, generating thousands of EPSPs and IPSPs. The axon hillock is able to process all graded potentials by algebraic processing, i.e., adding or subtracting potential changes. The axon hillock continues to process graded potentials as long as (i) the sum of all graded potentials stays under the threshold potential and (ii) the presynaptic changes occur faster than the decay rate of the graded potential in the postsynaptic neuron. Thus, when a synapse triggers a small depolarization (EPSP), a simultaneous depolarization at another synapse located at a different site on the same cell body or dendrites is summated to induce a larger depolarization. However, simultaneous hyperpolarization (IPSP) at another synapse located elsewhere on the same cell body or dendrites results in a smaller membrane depolarization.

There are two modes of summation, spatial and temporal (Figure 2.4). In **spatial summation**, graded potentials induced by

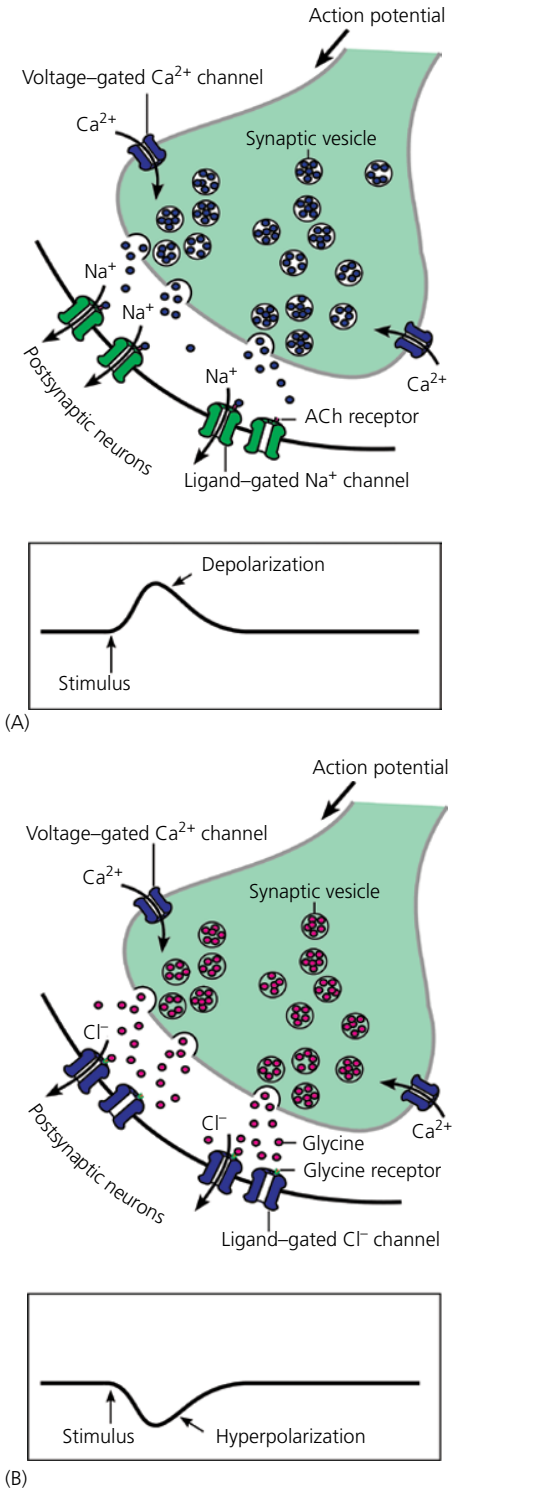

Figure 2.3 Postsynaptic potentials generated at the postsynaptic cell body and dendrites. (A) Neurotransmitters, for example acetylcholine (ACh) and glutamate, induce excitatory postsynaptic potentials (EPSPs) by opening ligand-gated Na^+ channels, triggering an influx of Na^+. EPSPs drive the membrane potential toward threshold voltage. (B) The neurotransmitters glycine and GABA induce inhibitory postsynaptic potentials (IPSPs) by binding to ligand-gated Cl^- channels that trigger an influx of Cl^- ions. IPSPs drive the membrane potential away from threshold voltage.