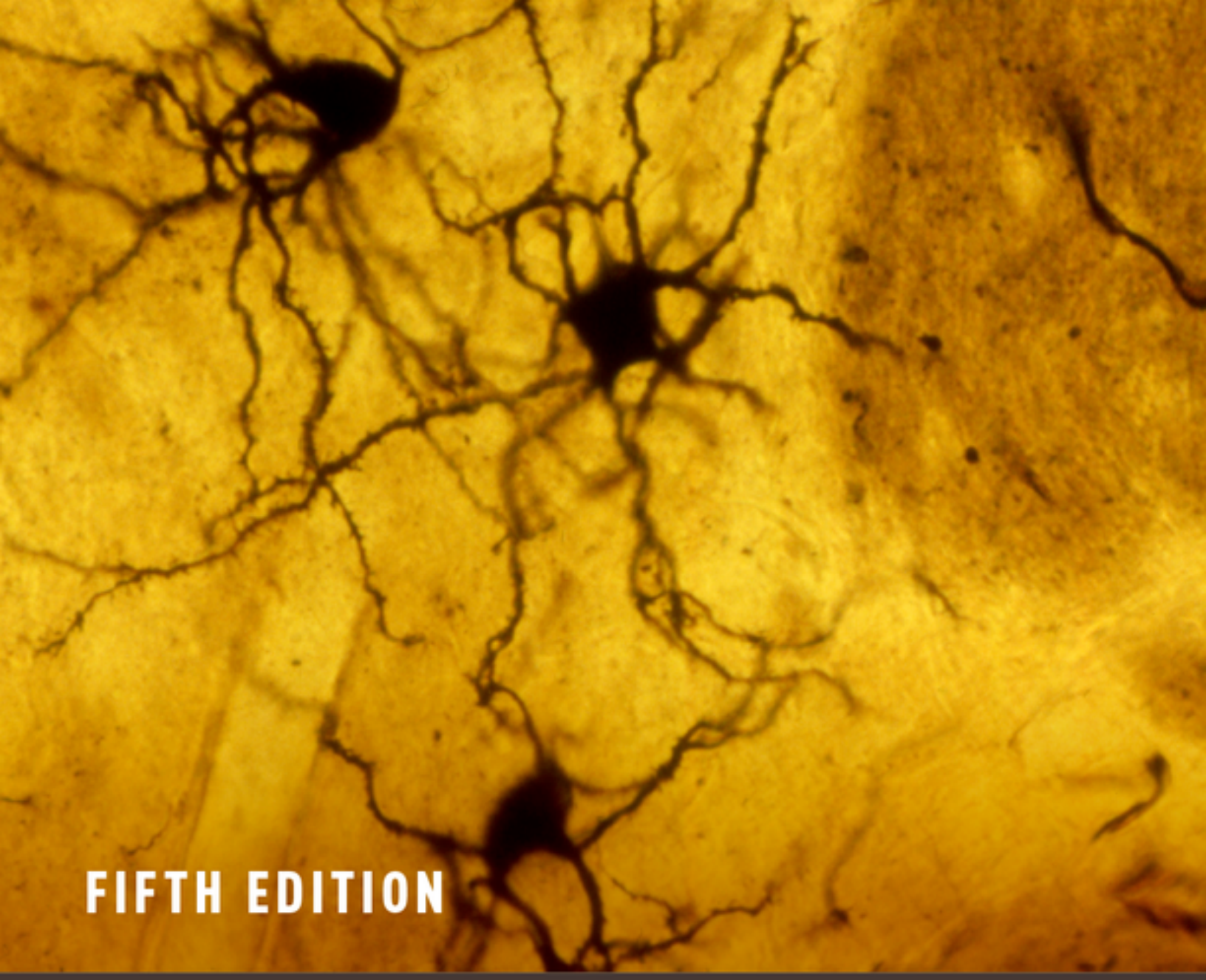

FIFTH EDITION

The Central Nervous System

PER BRODAL

OXFORD

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Oslo, Norway

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Contents

Preface

This book is intended primarily for use by students of medicine, physical therapy, and psychology—that is, for use in neuroscience or neuroanatomy courses by students who need knowledge of the nervous system as a basis for later clinical study and practice. This fifth edition has been thoroughly updated to incorporate salient new data and insights without expanding the scope or reducing the accessibility of the text. Several chapters have been reorganized to improve coherence and readability.

My intentions remain the same as those of my father, Alf Brodal, when he wrote the Norwegian forerunner of this book 70 years ago: to stimulate understanding rather than memorization of isolated facts, while at the same time fostering a realistic attitude toward our ability to explain the marvels of the human brain.

The book aims to present the difficult subject of neuroscience so that those approaching it for the first time can understand it. Therefore, many details are left out that might be of great interest to the specialist but would merely obscure the essentials for the beginner. Everyday experiences and clinical examples are integrated throughout the text to help students link the new material with their prior knowledge and future profession. The nervous system, however, is exceedingly complex, both structurally and functionally, and much remains to be learned before we can answer many fundamental questions. Thus, while an undergraduate course can provide only partial insights, no one is served by a presentation that avoids controversial issues and areas of ignorance. Indeed, pointing out what we do not know is sometimes better than presenting an oversimplified version. For this reason I have also discussed how the data were obtained and the limitations inherent in the various methods.

The main challenge—for both the student and the scientist—is to understand how the nervous system solves its multifarious tasks. This requires an integrated approach, drawing on data from all fields of neurobiology, as well as from psychology and clinical research. Textbooks sharing this goal nevertheless differ markedly in how they present the material and where they put the emphasis. Perhaps because my own field of research is the wiring patterns of the brain, I strongly feel that knowledge of how the nervous system is built—in particular, how the various parts are interconnected to form functional systems—is a prerequisite for proper understanding of data from other fields. A fair knowledge of brain anatomy is especially important for sound interpretations of the symptoms of brain disease. Textbooks of neuroanatomy often overwhelm the reader with details that are not strictly relevant for either functional analysis or clinical thinking. Neither does a strong emphasis on cellular mechanisms at the expense of the properties of neural systems seem the right choice if the aim is to help readers understand how the brain performs its tasks and how the site of a disease process relates to a patient's symptoms. Therefore, neither anatomical nor cellular and molecular details are included in this book if they cannot in some way be related to function. My hope is that the book presents a balance of cellular and neural systems material that is right for students.

In-depth sections and more advanced clinical material are clearly marked so that they do not disturb reading of the main text. Because readers' needs differ, however, they are encouraged to read selectively and pick the material they find most relevant and interesting from their perspective, regardless of whether it is placed in the main text or in boxes. The frequent subheadings should facilitate such selective reading.

I have received help from several colleagues, for which I am truly grateful. Jan Bjaalie, Niels Christian Danbolt, Paul Heggelund, Jan Jansen, Harald Kryvi, Kirsten Osen, Ole Petter Ottersen, Eric Rinvik, and Jon Storm-Mathisen have all provided constructive criticism and advice. I also gratefully acknowledge the expert help of Gunnar Lothe and Carina Knudsen, who produced the photographic work.

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Oslo, Norway

Introduction

A BIRD'S EYE VIEW OF THE NERVOUS SYSTEM

What are the main tasks of the nervous system? This question is not easily answered—our brains are necessary for most of what we associate with being a human. At a superior level, we need the brain to create our reality: it makes it possible for us to select, sort, and interpret the overwhelming amount of information we receive from our bodies and the environment. The brain furthermore enables our control of behavior in accordance with our interpretations of reality. This control concerns behavior in a wide sense: one aspect is control and maintenance of the body and its inner milieu; another is our interaction with our surroundings and other human beings through actions and speech. A third aspect is our inner, subjective, mental reality that others can only partially know. In early childhood, plastic changes of brain circuits form the basis of our ability to create order and predictability, without which we would be unable to relate successfully to our environment and ourselves.

The essential building block of the nervous system is the **neuron** (nerve cell), specialized for rapid conveyance of signals over long distances and in a very precise manner. Together, billions of neurons in the brain form complicated and highly organized networks for **communication** and **information processing**.

The nervous system receives a wealth of information from an individual's surroundings and body. From all this information, it extracts the essentials, stores what may be needed later, and emits a command to muscles or glands if an answer is appropriate. Sometimes the answer comes within milliseconds, as a **reflex** or automatic response. At other times it may take considerably longer, requiring cooperation among many parts of the brain and involving **conscious processes**. In any case, the main task of the nervous system is to ensure that the organism adapts optimally to the environment.

The nervous system is equipped with sense organs, **receptors** that react to various forms of sensory information or stimuli. Regardless of the mode of stimulation (the form of energy), the receptors "translate" the energy of the stimulus to the language spoken by the nervous system, that is, **nerve impulses**. These are tiny electric discharges rapidly conducted along the nerve processes. In this way signals are conveyed from the receptors to the regions of the nervous system where information processing takes place.

The nervous system can elicit an external response only by acting on **effectors**, which are either muscles or glands. The response is either **movement** or **secretion**. Obviously, muscle contraction can have various expressions, from communication through speech, facial expression, and bodily posture to walking and running, respiratory movements, and changes of blood pressure. But one should bear in mind that the nervous system can only act on muscles and glands to express its "will." Conversely, if we are to judge the activity going on in the brain of another being, we have only the expressions produced by muscle contraction and secretion to go by.

On an anatomic basis we can divide the nervous system into the **central nervous system** (CNS), consisting of the brain and the spinal cord, and the **peripheral nervous system** (PNS), which connects the CNS with the receptors and the effectors. Although without sharp transitions, the PNS and the CNS can be subdivided into parts that are concerned primarily with the regulation of visceral organs and the internal milieu and parts that are concerned mainly with the more or less conscious adaptation to the external world. The first division is called the **autonomic** or **visceral nervous system**; the second is usually called the **somatic nervous system**. The second division, also called the cerebrospinal nervous system, receives information from sense organs capturing events in our surroundings (vision, hearing, receptors in the skin) and controls the activity of voluntary muscles (made up of cross-striated skeletal muscle cells). In contrast, the autonomic nervous system controls the activity of involuntary muscles (smooth-muscle and heart muscle cells) and gland cells. The autonomic system may be further subdivided into the **sympathetic system**, which is mainly concerned with mobilizing the resources of the body when demands

are increased (as in emergencies), and the **parasympathetic system**, which is devoted more to the daily maintenance of the body.

The **behavior** of a vertebrate with a small and—comparatively speaking—simple brain (such as a frog) is dominated by fairly fixed relationships between a stimulus and its response. Thus, a stimulus, produced for example by a small object in the visual field, elicits a stereotyped pattern of goal-directed movements. Few neurons are intercalated between the sense organ and the effector, with correspondingly limited scope of response adaptation. Much of the behavior of the animal is therefore instinctive and automatic, and not subject to significant change by learning. In mammals with relatively small brains compared with their body weights (such as rodents), a large part of their brain is devoted to fairly direct sensorimotor transformations. In primates, the relative brain weight has increased dramatically during some million years of evolution. This increase is most marked in humans with relative brain weight double that of the chimpanzee. In humans, there are few fixed relationships between sensations and behavior (apart from a number of vital reflexes). Thus, a certain stimulus may cause different responses depending on its context and the antecedents. Consequently, we often can choose among several responses, and the response can be changed on the basis of experience. Such flexibility requires, however, increased "computational power" in terms of number of neurons available for specific tasks. The more an animal organizes its activities on the basis of previous experience, and the more it is freed from the dominance of immediate sensations, the more complex the processes that are required of the central nervous system. The behavior of humans cannot be understood merely on the basis of what happened immediately before. The British neuropsychologist Larry Weiskrantz (1992) puts it this way: "We are controlled by predicted consequences of our behavior as much as by the immediate antecedents. We are goal-directed creatures" (p. 8).

The higher processes of integration and association—that is, what we call **mental processes**—are first and foremost functions of the **cerebral cortex**. The vast number of neurons in this part of the brain primarily explains the unique adaptability and learning capacity of human beings. Indeed, the human brain not only permits adaptation to extremely varied environments; it also enables us to change our environment to suit our needs. This entails enormous possibilities but also dangers, because we produce changes that are favorable in the short run but in the long run might threaten the existence of our species.

STUDYING THE STRUCTURE AND FUNCTION OF THE NERVOUS SYSTEM

Some of the many methods used for the study of the nervous system are described in the following chapters—that is, in conjunction with discussion of results produced by the methods. Here we limit ourselves to some general features of neurobiological research.

Many approaches have been used to study the structure and function of the nervous system, from straightforward observations of its macroscopic appearance to determination of the function of single molecules. In recent years we have witnessed a tremendous development of methods, so that today problems can be approached that were formerly only a matter of speculation. The number of neuroscientists has also increased almost exponentially, and they are engaged in problems ranging from molecular genetics to behavior. Although the mass of knowledge in the field of neurobiology has increased accordingly, more important, the understanding of how our brains work has improved considerably. Nevertheless, the steadily expanding amount of information makes it difficult for the scientist to have a fair knowledge outside his or her specialty. It follows that the scientist may not be able to put findings into the proper context, with the danger of drawing erroneous conclusions

Traditionally, methods used for neurobiological research were grouped into those dealing with **structure** (neuroanatomy) and those aiming at disclosing the **function** of the structures (neurophysiology, neuropsychology). The borders are far from sharp, however, and it is typical of modern neuroscience that anatomic, physiologic, biochemical, pharmacological, psychological, and other methods are combined. Cell biological methods especially are being applied with great success. Furthermore, the introduction of modern computer-based imaging techniques has opened exciting possibilities for studying the relation between structure and function in the living human brain. More and more of the methods originally developed in cell biology and immunology are being applied to the nervous system, and we now realize that neurons are not so different from other cells as was once assumed.

Animal Experiments Are Crucial for Progress

Only a minor part of our present knowledge of the nervous system is based on observations in humans; most has been obtained in experimental animals. In humans we are usually limited to a comparison of symptoms that are caused by naturally occurring diseases, with the findings made at postmortem examination of the brain. Two cases are seldom identical, and the structural derangement of the brain is often too extensive to enable unequivocal conclusions.

In animals, however, the experimental conditions can be controlled, and the experiments may be repeated, to reach reliable conclusions. The properties of the elements of neural tissue can be examined directly—for example, the activity of single neurons can be correlated with the behavior of the animal. Parts of the nervous system can also be studied in isolation—for example, by using tissue slices that can be kept viable in a dish (*in vitro*) for hours. This enables recordings and experimental manipulations, with subsequent structural analysis of the tissue. Studies in invertebrates with a simple nervous system have made it possible to discover the fundamental mechanisms that underlie synaptic function and the functioning of simple neuronal networks.

When addressing questions about functions specific to the most highly developed nervous systems, however, experiments must be performed in higher mammals, such as cats and monkeys, with a well-developed cerebral cortex. Even from such experiments, inferences about the human nervous system must be drawn with great caution. Thus, even though the nervous systems in all higher mammals show striking similarities with regard to their basic principles of organization, there are important differences in the relative development of the various parts. Such anatomic differences indicate that there are functional differences as well. Thus, results based on the study of humans, as in clinical neurology, psychiatry, and psychology, must have the final word when it comes to functions of the human brain. But because clinicians can seldom experiment, they must often build their conclusions on observations made in experimental animals and then decide whether findings from patients or normal volunteers can be explained on such a basis. If this is not possible, the clinical findings may raise new problems that require studies in experimental animals to be solved. Basically, however, the methods used to study the human brain are the same as those used in the study of experimental animals.

Ethics and Animal Experiments

Experiments on animals are often criticized from an ethical point of view. But the question of whether such experiments are acceptable cannot be entirely separated from the broader question of whether humans have the right to determine the lives of animals by using them for food, by taking over their territories, and so forth. With regard to using animals for scientific purposes, one has to realize that a better understanding of human beings as thinkers, feelers, and actors requires, among other things, further animal experiments. Even though cell cultures and computer models may replace some of them, in the foreseeable future we will still need animal experiments. Computer-based models of the neuronal interactions taking place in the cerebral cortex, for example, usually require further animal experiments to test their tenability.

Improved knowledge and understanding of the human brain is also mandatory if we want to improve the prospects for treatment of the many diseases that affect the nervous system. Until today, these diseases—most often leading to severe suffering and disability—have only occasionally been amenable to effective treatment. Modern neurobiological research nevertheless gives hope, and many promising results have appeared in the past few years. Again, this would not have been possible without animal experiments.

Yet there are obviously limits to what can be defended ethically, even when the purpose is to alleviate human suffering. Government authorities and the scientific community itself have enacted strict rules to ensure that only properly trained persons perform animal experiments and that the experiments are conducted so that discomfort and pain are kept at a minimum. Most international neuroscience journals require that the experiments they publish have been conducted in accordance with such rules.

All Methods Have Sources of Error

Even though we do not treat systematically the sources of error inherent in the various methods discussed in this book, certainly all methods have their limitations. It often requires intimate, personal experience with a method to fully realize its limitations and sources of error. Unfortunately, when scientific results are cited and interpreted by others after their first publication, limitations and uncertainties tend to disappear, ending up with general "truths" that are perpetuated by uncritical reading and citations. One source of error when conducting animal experiments is to draw premature

conclusions about conditions in humans. This problem is evident in a book like this: while the aim is to describe and understand the human brain, most of the data on neurons and their circuits derive from animal experiments.

Purely anatomic methods also have their sources of error and have led to many faulty conclusions in the past about connections between neuronal groups. In turn, such errors may lead to misinterpretations of physiologic and psychological data. The study of humans also entails sources of error—for example, of a psychological nature. Thus, the answers and information given by a patient or a volunteer are not always reliable; for example, the patient may want to please the doctor and answer accordingly. Further, the context of brain scanning (confined in a narrow tube with instructions to not move) is highly artificial and obviously influences how the person feels and responds.

Reductionism and the "Mereological Fallacy"

Scientific experiments aim at isolating structures and processes so that they can be observed in isolation (e.g., taking neurons out the brain to eliminate the number of influencing factors). However necessary such a **reductionistic** approach may be, it also means that phenomena are studied out of their natural context. Conclusions with regard to how the parts function in an intact animal in conjunction with all other parts must therefore be speculative. Arguably, **disciplinary bias** (seeing only one's own topic of research) and **reductionism** pose serious obstacles to a deeper understanding of the complex phenomena related to human beings and their brains.

As a consequence of uncritical reductionism, all too often neuroscientists ascribe attributes (psychological or behavioral) to the brain or part of the brain that can logically apply only to the whole animal. This mistake is called the **mereological fallacy** by Bennett and Hacker (2003, p. 73).[1] They point out the obvious truth that although we cannot perceive (or perform) anything without a properly functioning brain, it is not our brains that see and feel—these are concepts that make sense only in relation to a person. An analogy would be that an airplane needs an engine to fly, but we say that the airplane, not its engine, takes off from the runway.

1. **Mereology** is the logic of the relations between parts and the whole.

Revising Scientific "Truths" from Time to Time

That our methods have sources of error and that our interpretations of data are not always tenable are witnessed by the fact that our concepts of the nervous system must be revised regularly. Reinterpretations of old data and changing concepts are often made necessary by the introduction of new methods. As in all areas of science, conclusions based on the available data should not be regarded as final truths but as more or less probable and preliminary interpretations. Natural science is basically concerned with posing questions to nature. How understandable and unequivocal the answers are depends on the precision of our questions and how relevant they are to the problem we are studying: stupid questions receive stupid answers. It is furthermore fundamental to science—although not always easy for the individual scientist to live up to—that conclusions and interpretations be made without any bias and solely on the strength of the facts and the arguments. It should be irrelevant whether the scientist is a young student or a Nobel laureate.

Neuroethics

Due mainly to technological developments, knowledge of the human brain has increased tremendously in the past decades. Neuroscientists now approach questions about human nature that formerly were the domain of philosophy and the social sciences. Furthermore, it is now possible to interfere directly with the workings of the normal brain in ways that were unthinkable some years ago, and imaging techniques promise to reveal information about a person's personality, intentions, feelings, dispositions, and so forth. Correlations are sought between brain measures (e.g., as recorded with functional magnetic resonance imaging [fMRI]) and future outcomes in education, criminality, health-related behavior, and so forth. Numerous "neuroscience-based" educational and learning programs constitute a whole industry (often with a misconceived neuroscientific background and scant empiric support).

The surge in powerful neuroscientific methods has raised concerns that their widespread use may challenge core humanistic values. Indeed, a new field—**neuroethics**—is concerned with the growing realization that neuroscientific knowledge can be misused to legitimate value-based actions and beliefs—matters in which

neuroscience can provide only indirect arguments. It is a matter of concern, for example, that psychological phenomena are commonly "explained" by referring to a part of the brain or a neurotransmitter. Further, it has become a popular, although controversial,[2] notion that brain scans can reveal a person's character, intentions, truthfulness, mental aberrations, and so forth. Indeed, neuroscientific evidence is increasingly being offered in court cases; neuroeconomics is a new field of research; insurance companies show interest in neuroscientific evidence to aid their decisions; and so forth. Such use, other than the fact that it may be scientifically flawed, needs critical evaluation in a broad and long-term perspective, including ethical, social, and legal implications.

2. It is one thing is to find an association between a certain brain activity and a mental state (e.g., the feeling of pain) in an experimental situation but quite another to conclude that a person who shows this brain activity is in this particular mental state (this is called the **problem of reverse inference**). Indeed, we know that similar patterns of brain activity may be associated with different mental states, and a particular mental state may be associated with different patterns of activity.

The Central Nervous System

PART ONE

Main Features of Structure and Function

General information about the structure and function of the nervous system forms a necessary basis for treatment of the specific systems described in subsequent parts of this book. **Chapters 1** and **2** describe the structure of nervous tissue and some basic features of how neurons are interconnected, while **Chapters 3**, **4**, and **5** deal with the functional properties of neurons as a basis for understanding communication between nerve cells. **Chapter 6** provides an overview of the macroscopic (and, to some extent, the microscopic) structure of the nervous system with brief descriptions of functions. **Chapter 7** treats the membranes covering the central nervous system, the cavities within the brain, and the cerebrospinal fluid produced in these. Finally, **Chapter 8** describes the blood supply of the brain and the spinal cord.

Structure of the Neuron and Organization of Nervous Tissue

1

OVERVIEW

The nervous system is built up of nerve cells, **neurons**, and special kinds of supporting cells, **glial cells** (discussed in Chapter 2). The nerve cells are responsible for the functions that are unique to the nervous system, whereas the glial cells are non-neuronal cells that primarily support and protect the neurons. Neurons are composed of a cell body called the **soma** (plural somata) and several processes. Multiple short **dendrites** extend the receiving surface of the neuron, while a single **axon** conducts nerve impulses to other neurons or to muscle cells. Neurons are characterized by their ability to respond to stimuli with an electrical discharge, a **nerve impulse**, and, further, by their fast **conduction** of the nerve impulse over long distances. In this way, signals can be transmitted in milliseconds from one place to another, either within the central nervous system (CNS) or between it and organs in other systems of the body. When the nerve impulse reaches the **synapse**, which is the site of contact between the axon and the next neuron, a substance called a **neurotransmitter** is released from the **axon terminal** that conveys a chemical signal from one neuron to the next.

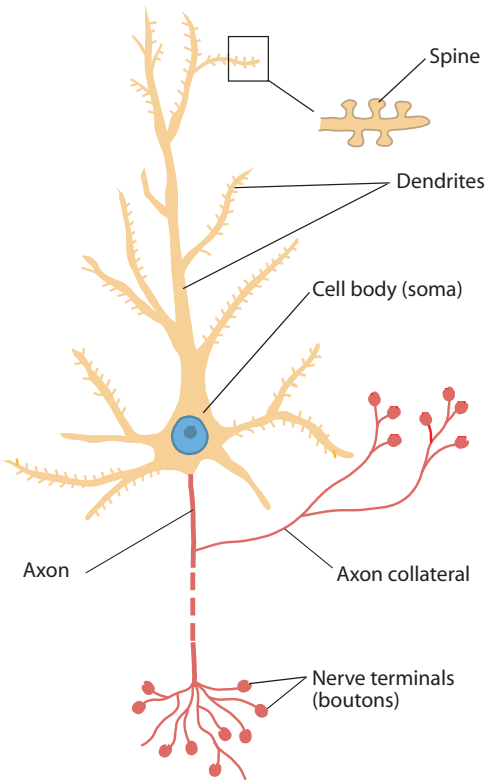
Neurons are classified into two broad groups: **projection neurons** that transmit signals over long distances and **interneurons** that mediate cooperation among neurons that lie grouped together. Many axons are surrounded with a **myelin sheath** to increase the speed of impulse propagation. Nervous tissue contains some areas that look gray—**gray matter**—and others that look whitish—**white matter**. White matter consists of axons and no neuronal somata, and the color is due to the whitish color of myelin. Gray matter consists mainly of somata and dendrites, which have a gray color. Neuronal somata are collected in groups sharing connections and functional characteristics. In the CNS, such a group is called a **nucleus** and, in the peripheral nervous system (PNS), a **ganglion**. A bundle of axons that interconnect nuclei is called a **tract**. A **nerve** connects the CNS with peripheral organs. Groups of neurons that are interconnected form complex **neuronal networks** that are responsible for performing the tasks of the CNS. A fundamental principle of the CNS is that each neuron influences many others (**divergence**) and receives synaptic contacts from many others (**convergence**). A neuron contains a **cytoskeleton** consisting of various kinds of neurofibrils. They are instrumental in forming the neuronal processes and in transport of substances along them. By **axonal transport**, building materials and signal substances can be brought from the cell soma to the nerve terminals (anterograde transport), and signal substances are carried from the nerve terminal to the soma (retrograde transport).

NEURONS AND THEIR PROCESSES

Neurons Have Long Processes

Like other cells, a neuron has a **cell body** with a nucleus surrounded by cytoplasm containing various organelles. The nerve cell body is also called the **perikaryon** or **soma** (Figs. 1.1, 1.2 and 1.3). Long processes extend from the cell body. The numbers and lengths of the processes can vary, but they are of two main kinds: **dendrites** and **axons** (Fig. 1.1). The dendrites usually branch and form dendritic "trees" with large surfaces that receive signals from other nerve cells. Each neuron may have multiple dendrites but has only one axon, which is specially built to conduct the nerve impulse from the cell body to other cells. The axon may have many ramifications, enabling its parent cell to influence many other cells. Side branches sent off from the parent axon are termed **axon collaterals** (Fig. 1.1). The term **nerve fiber** is used synonymously with "axon." The axons vary, from those that ramify and end close to the cell body to those that extend for more than 1 m (Fig. 1.10; see also Figs. 33.6 and 33.7). These structural differences are closely connected to functional differences.

Figure 1.1



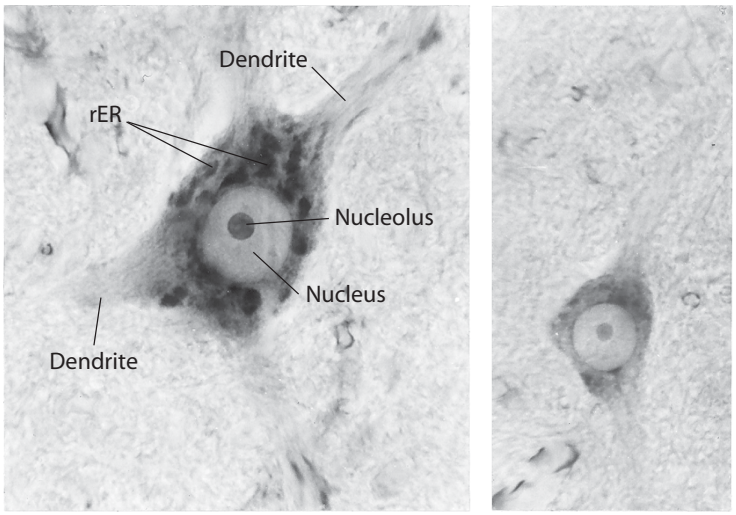
A neuron. Half-schematic to illustrate the neuron's main parts. The axon is red.

Neurons Are Rich in Organelles for Oxidative Metabolism and Protein Synthesis

When seen in a microscopic section, the nucleus of a neuron is characterized by its large size and light staining (i.e., the chromatin is extended, indicating that much of the genome is in use). There is also a prominent nucleolus (Figs. 1.2 and 1.3). These features make it easy to distinguish a neuron from other cells (such as glial cells), even in sections in which only the nuclei are clearly stained. The many **mitochondria** in the neuronal cytoplasm are an indication of the high metabolic activity of nerve cells. The mitochondria depend entirely on aerobic **adenosine triphosphate (ATP)** production and, unlike those in most other cell types, cannot utilize anaerobic ATP synthesis. **Glucose** is the substrate for ATP production in the mitochondria of nerve cells, which cannot, unlike in muscle cells, for example, use fat.

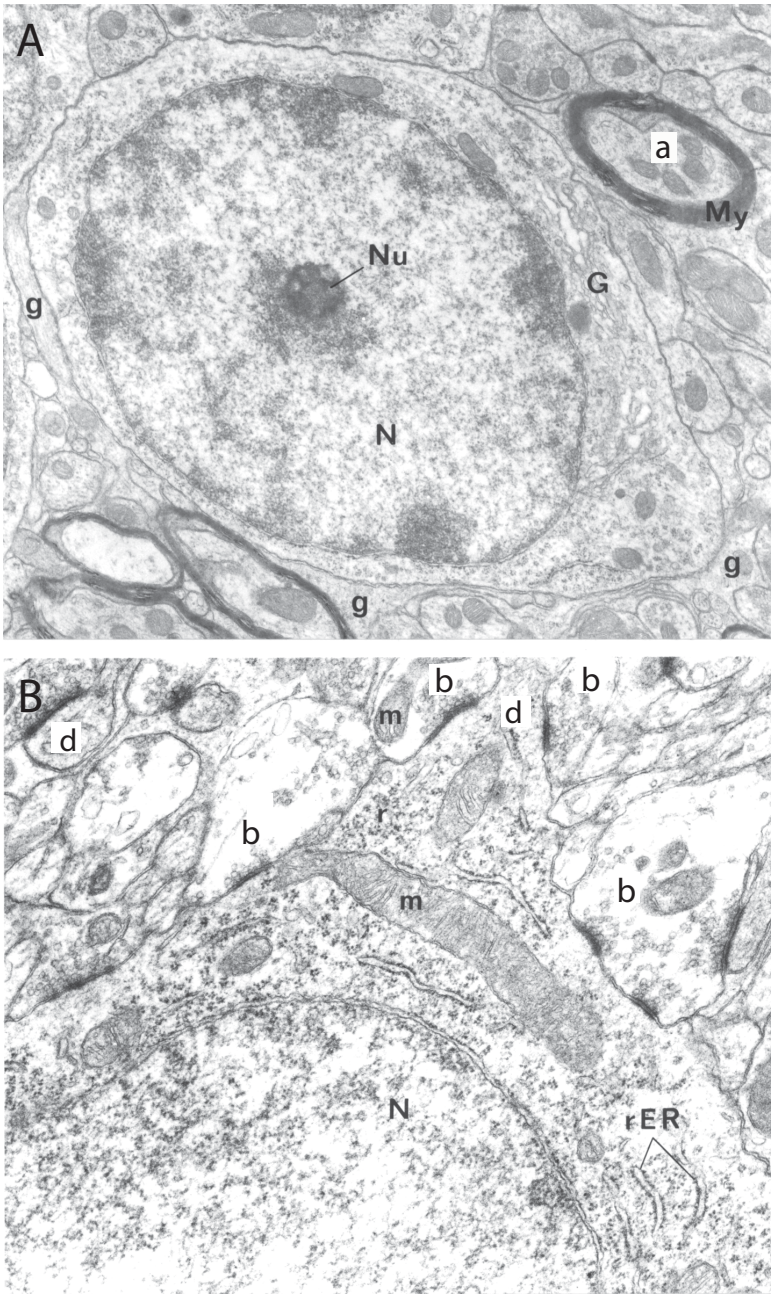
Neuronal somata also contain conspicuous amounts of free ribosomes and **rough endoplasmic reticulum** (rER) for synthesis of proteins. Large clumps of rER are seen via light microscopy in the cytoplasm of neurons greater than a certain size (Figs. 1.2 and 1.3). These were called tigroid granules or **Nissl bodies** long before their true nature was known. There are also as a rule several Golgi complexes, which modify proteins before they are exported or inserted in membranes. The large neuronal production of proteins probably reflects the enormous neuronal surface membrane, which contains many protein molecules that must be constantly renewed. Membrane proteins, forming, for example, ion channels and receptors (binding sites) for neurotransmitters, are constantly being recycled.

Figure 1.2



Neuronal somata (cell bodies). Two motor neurons, one small and one large, are shown. The large, pale nucleus has a distinct nucleolus. Only the cell body and the proximal parts of the dendrites are visible with the staining method used here. The stain (thionine) binds primarily to nucleic acids (DNA in the nucleus and RNA in the cytoplasm and nucleolus). The deeply stained clumps in the cytoplasm represent aggregates of rough endoplasmic reticulum (rER). Photomicrographs taken with a light microscope of a 20-μm-thick section of the spinal cord. Magnification, ×800.

Figure 1.3

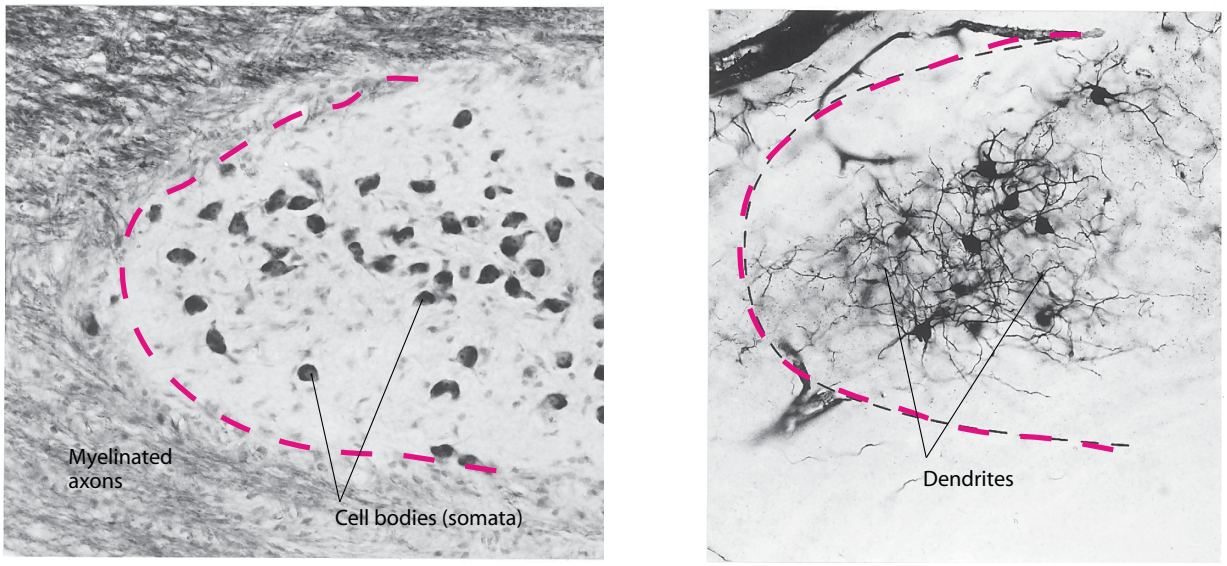


Ultrastructure of the neuron. Electron micrograph showing the cell body of a small neuron (**A**) and parts of a larger neuron (**B**). The nucleus (N) is light, due to extended chromatin, and contains a nucleolus (Nu). The cytoplasm contains rough endoplasmic reticulum (rER) and a Golgi complex (G)—that is, organelles involved in protein synthesis. The presence of many mitochondria (m) reflects the high oxidative metabolism of neurons. Nerve terminals, or boutons (b), forming axosomatic and axodendritic synapses are also seen. Glial processes (g) follow closely the surface of the cell body and the dendrites (d). a, axon; My, myelin. Magnifications, ×9,000 (top) and ×15,000 (bottom).

Dendrites Are Equipped with Spines

To study the elements of nervous tissue, it is necessary to use thin sections that can be examined microscopically. Different staining methods make it possible to distinguish the whole neuron or parts of it from the surrounding elements (Figs. 1.2 and 1.4). It then becomes evident that the morphology of neurons varies, with regard to both the size of the cell body and the number, length, and branching of the dendrites (Fig. 1.2; see also Figs. 33.6 and 33.7). The size

Figure 1.4



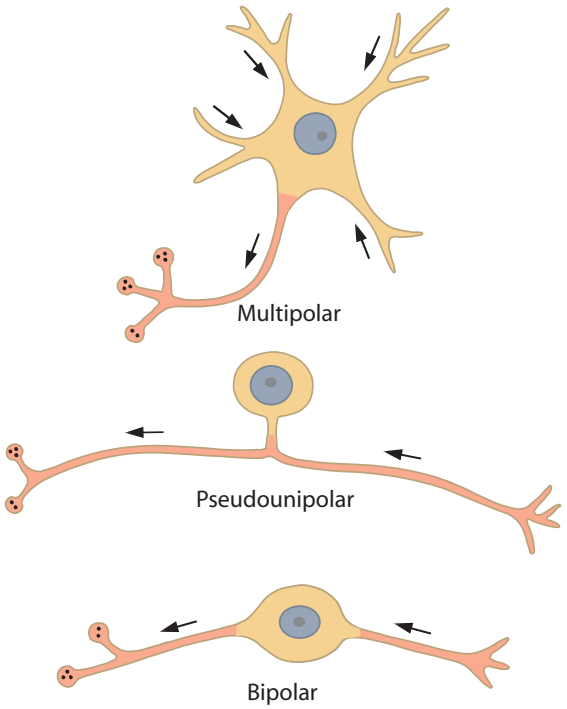
Neurons. Photomicrographs of sections stained with two different methods. **Left:** Only the cell bodies (somata) of a group of neurons are stained and visible in the section. The dark region surrounding the group of neurons contains myelinated fibers that are also stained. **Right:** The same cell group but treated via the Golgi method so that the dendrites and the cell bodies are visualized. Magnification, ×150.

of the dendritic tree is related to the number of contacts the cell can receive from other nerve cells. Dendrites often have small spikes, **spinae** (sing. spina) or **spines**, which are sites of contact with other neurons (Figs. 1.1, 1.7 and 1.9).

Most Neurons Are Multipolar

Most neurons have several processes and are therefore called **multipolar** (Fig. 1.5A). Special kinds of neurons, however, may have a different structure. Thus, neurons that conduct sensory signals from the receptors to the CNS have only one process that divides close to the cell body. One branch conducts signals (impulses) from the receptor toward the cell soma; the other conducts signals toward and into the CNS. Such neurons are called **pseudounipolar** (Fig. 1.5B). In accordance with the usual definition, the process conducting signals toward the cell body should be termed a dendrite. In terms of both structure and function, however, this process must be regarded as an axon. Some neurons have two processes, one conducting toward the cell body and the other away from it (Fig. 1.5C). Such neurons, present in the retina (see Fig. 16.4) and the inner ear (see Fig. 17.6B), are called **bipolar**. Also in these neurons both processes function as axons.

Figure 1.5



Neurons exemplifying three different arrangements of processes. Arrows show the direction of impulse conduction.

Communication between Nerve Cells Occurs at Synapses

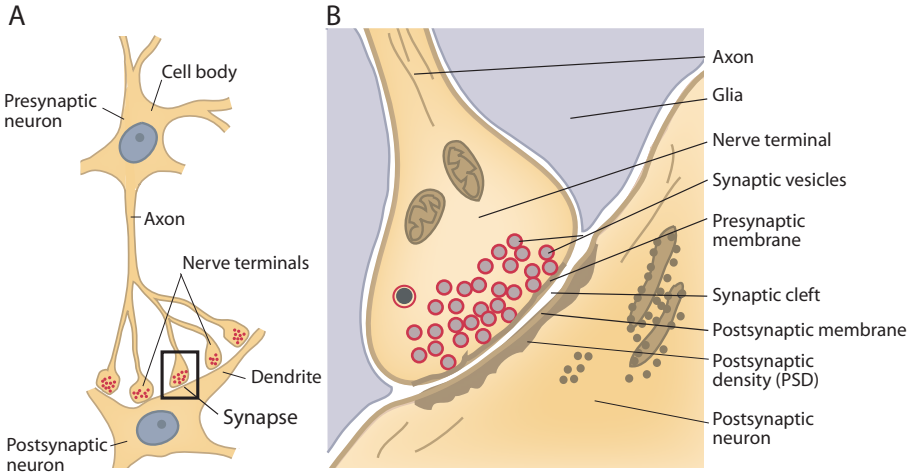
The terminal branches of an axon have club-shaped enlargements called **boutons** (Figs. 1.1, 1.3, and 1.6). The term **terminal bouton** is used when the bouton sits at the end of an axon branch, and we also use the term **nerve terminal**. In other instances, the bouton is only a thickening along the course of the axon, with several such **en passage boutons** along one terminal branch (Fig. 1.9A). In any case, the bouton lies close to the surface membrane of another cell, usually on the dendrites or the cell body. Such a site of close contact between a bouton and another cell is called a **synapse** (Fig. 1.6). In the PNS, synapses are also formed between boutons and muscle cells (see Figs. 21.4 and 21.5).

The synapse is where information is transmitted from one neuron to another. This transmission does not occur by direct propagation of the nerve impulse from one cell (neuron) to another but by liberation of signal molecules that subsequently influence the other cell. Such a signal molecule is called a **neurotransmitter** or, for short, a **transmitter** (the term "transmitter substance" is also used). The neurotransmitter is at least partly located in small vesicles in the bouton called **synaptic vesicles** (Figs. 1.6 and 1.7). How the synapse and the transmitters work is discussed in Chapters 4 and 5. Here we restrict ourselves to the structure of the synapse.

The membrane of the nerve terminal is separated from the membrane of the other nerve cell by a narrow cleft approximately 20 nm wide (i.e., 2/100,000 mm). This **synaptic cleft** cannot be observed under a light microscope. Only when electron microscopy of nervous tissue became feasible in the 1950s could it be demonstrated that neurons are indeed anatomically separate entities. In the electron microscope, one can observe that the membranes facing the synaptic cleft are thickened (Figs. 1.6 and 1.7), due to accumulation of specific proteins that are of crucial importance for transmission of the synaptic signal. Many of these protein molecules are **receptors** for neurotransmitters; others form **channels** for passage of charged particles (ions). The membrane of the bouton facing the cleft is called the **presynaptic membrane**, and the membrane of the cell that is contacted is called the **postsynaptic membrane** (Fig. 1.6). We also use the terms pre- and postsynaptic neurons.

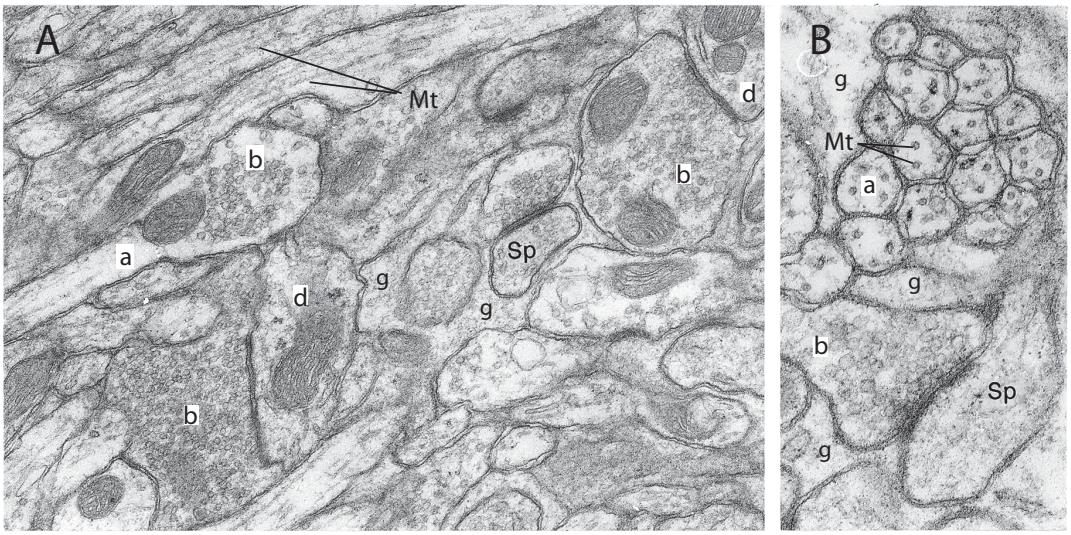
The **postsynaptic density** (Fig. 1.6) connects to the cytoskeleton with actin filaments and other proteins. This connection probably anchors the postsynaptic receptors to the site of neurotransmitter release. In addition, certain proteins in the postsynaptic density, such as **cadherins**, bind to corresponding proteins in the presynaptic membrane to keep the nerve terminal in place (cadherins are present also in many other cell-to-cell contacts, e.g., in adherence contacts between epithelial cells). Other proteins in the postsynaptic density have modulatory actions on synaptic function, for example, by changing receptor properties. Synaptic modifications associated with learning involve structural and functional changes of the postsynaptic density.

Figure 1.6



The synapse. **A:** Schematic overview of pre- and postsynaptic neurons. **B:** The main structural elements of a typical synapse. Based on electron micrographs. Compare with Figs. 1.3 and 1.7.

Figure 1.7



Synapses. **A, B:** Electron micrographs showing boutons (b) in synaptic contacts with dendrites (d), and dendritic spines (Sp). Note how processes of glia (g) cover the dendrites and nerve terminals except at the site of synaptic contact. Note bundle of unmyelinated axons (a) in **B**. Microtubules (Mt) are responsible for axonal transport. Magnifications, ×20,000 (**A**) and ×40,000 (**B**).

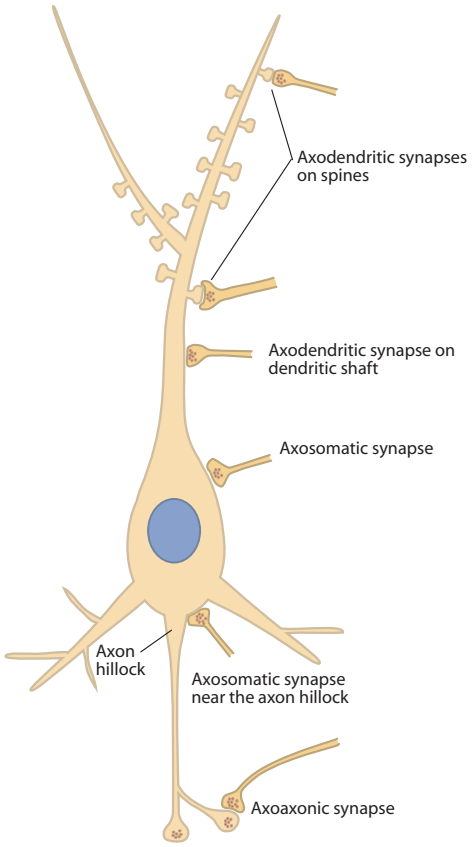
Placement of Synapses Has Functional Significance

The functional significance of a synapse depends, among other factors, on its position on the postsynaptic neuron (Fig. 1.8). In general, the closer the synapse is to the **axon hillock** (the initial part of the axon), the stronger is its effect. A synapse located far out on a dendrite has a relatively weak effect. Accordingly, many such synapses must as a rule be active simultaneously to exert a decisive influence.

Synapses formed on the cell soma are called **axosomatic**, while synapses on dendrites are called **axodendritic** (Fig. 1.8). Where dendrites are equipped with spines, one or two **axospinous** synapses are always formed with the spine head (1.7B, Figs. 1.8, and 1.9A). Interestingly, both the form and number of spines change in association with learning. Nerve terminals may also form a synapse with an axon (usually close to a terminal bouton of that axon), and such synapses are called **axoaxonic** (Fig. 1.8 and 1.9B). This enables selective control of one terminal only without influencing the other terminals of the parent axon. Axoaxonic synapses thus increase the precision of the signal transmission.

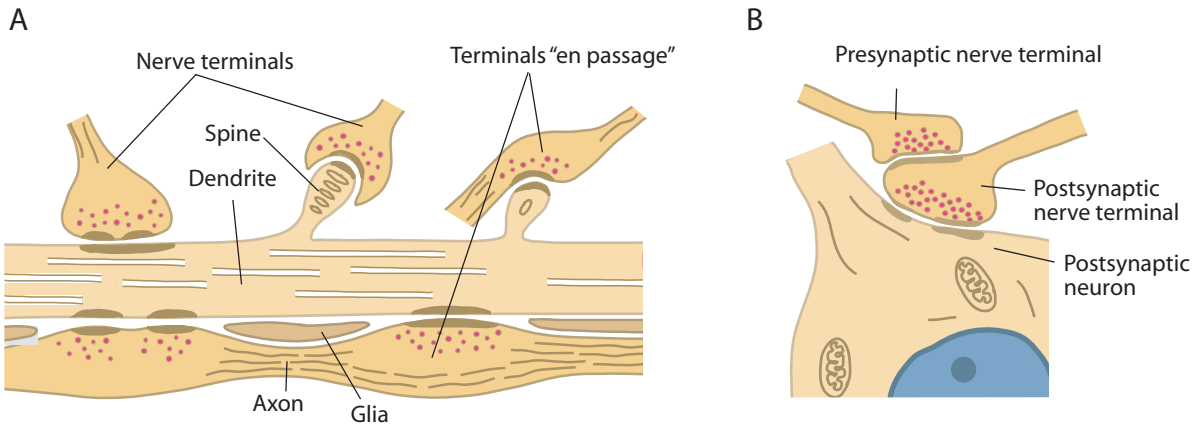
There are many more axodendritic than axosomatic synapses because the dendritic surface is so much larger. Every neuron has many thousands of synapses on its surface, and the sum of their influences determines how active the postsynaptic neuron will be at any moment.

Figure 1.8



The placement of synapses. The position of a synapse determines (together with other factors) its effect on the postsynaptic neuron.

Figure 1.9



A: *Axodendritic synapses*. A nerve terminal (bouton) may form a synapse directly on the shaft of the dendrite or on a spine. The axon may also have several boutons en passage. **B:** *Axoaxonic synapse*. The presynaptic nerve terminal influences—by usually inhibiting—the release of neurotransmitter from the postsynaptic nerve terminal.

Two Main Kinds of Nerve Cell: Projection Neurons and Interneurons

Some neurons influence cells that are at a great distance, and their axons are correspondingly long (more than a meter for the longest). They are called **projection neurons**, or **Golgi type 1** (Fig. 1.10). Neurons that convey signals from the spinal cord to the muscles are examples of projection neurons; other examples are neurons in the cerebral cortex with axons that contact cells in the brain stem and the spinal cord (see Fig. 33.6). As a rule, the axons of projection neurons send out branches, or **collaterals**, in their course (Figs. 1.1 and 1.11). Thus, one projection neuron may send signals to neurons in various other parts of the nervous system.

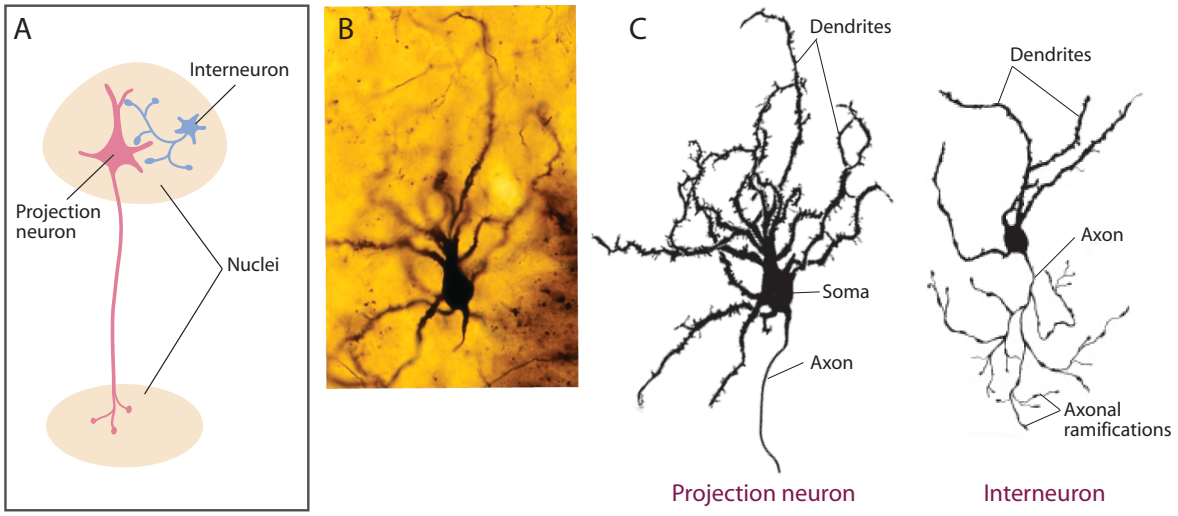
The other main type of neuron is the **interneuron**, or **Golgi type 2** (Fig. 1.10, see also Fig. 33.7), characterized by a short axon that branches extensively in the vicinity of the cell body. Its name implies that an interneuron is intercalated between two other neurons (Fig. 1.12). Even though, strictly speaking, all neurons with axons that do not leave the CNS are thus interneurons, the term is usually restricted to neurons with short axons that do not leave one particular neuronal group. The interneurons thus mediate communication between neurons within one group. Because interneurons may be switched on and off, the possible number of interrelations among the neurons within one group increases dramatically. The number of interneurons is particularly high in the cerebral cortex, and it is the number of interneurons that is so much higher in the human brain than in that of any other animal. The number of typical projection neurons interconnecting the various parts of the nervous system, and linking the nervous system with the rest of the body, as a rule varies more with the size of the body than with the stage of development.

The distinction between projection neurons and interneurons is not always very clear, however. Many neurons previously regarded as giving off only local branches have been shown via modern methods also to give off long axonal branches to more distant cell groups. Thus, they function as both projection neurons and interneurons. For example, many of the "classical" projection neurons in the cerebral cortex (see Fig. 33.6) give off collaterals that end within the cell group in which the cell body is located.

Tasks of Interneurons

Figure 1.12 shows how an interneuron (b) is intercalated in an impulse pathway. One might perhaps think that the simpler direct pathway shown below from neuron A to neuron C would be preferable. After all, the interneuron leads to a delay in the propagation of the signal from A to C, and this would be a disadvantage. Most important, however, is that the interneuron provides added **flexibility**. Thus, whether the signal is transmitted from a to c can be controlled by other synaptic

Figure 1.10

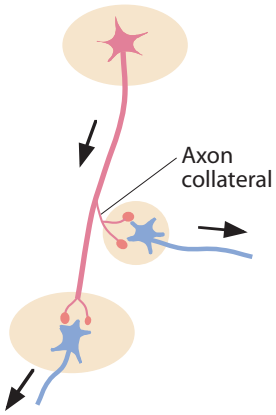


Projection neurons and interneurons. **A:** A projection neuron sends its axon to neurons in other nuclei (cell groups), often at a long distance. The axon of an interneuron ramifies and makes synaptic contacts in its vicinity (within the same nucleus). Schematic. **B:** Photomicrograph from a section treated with the Golgi method, showing a projection neuron (from the brain stem of the monkey). With this method the whole neuron is impregnated with silver salts, rendering it black. The depth of field is only a fraction of the thickness of the section (100 μm). Therefore, only part of the neuron is clearly visible in the photomicrograph. **C:** Drawing of the projection neuron shown in **B**, and an interneuron from the same material.

inputs to interneuron b. Identical synaptic inputs to neuron a may be propagated further by neuron c in one situation but not in another, depending on the state of interneuron b. This kind of arrangement may partly explain why, for example, identical stimuli may cause pain of very different intensity: interneurons along the pathways conveying sensory signals are under the influence of other parts of the brain (e.g., neurons analyzing the meaning of the sensory stimulus).

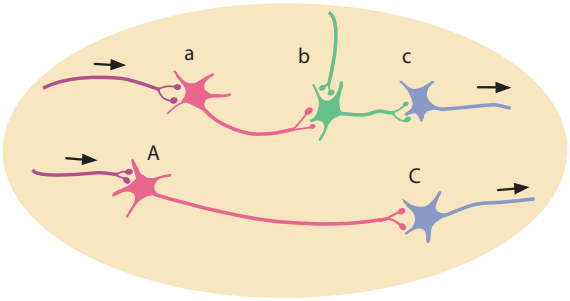
Figure 1.13 illustrates another important task performed by interneurons. Interneuron B enables neuron A to act back on itself and reduce its own firing of impulses. The arrangement acts to prevent neuron A from becoming excessively active. Thus, the negative **feedback** provided by the interneuron would stop the firing of neuron A. Such an arrangement is present, for example, among motor neurons that control striated muscle contraction (see Fig. 21.14).

Figure 1.11



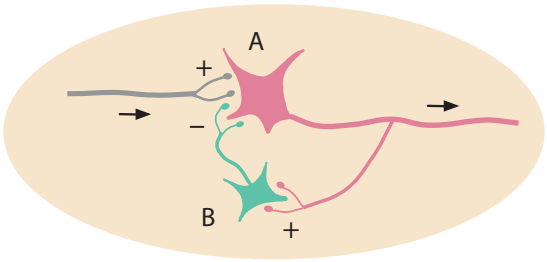
Collateral of a projection neuron. By sending off collaterals, a projection neuron may establish synapses in different cell groups (nuclei). Arrows show the direction of impulse conduction.

Figure 1.12



An interneuron (b) intercalated in a pathway from neuron a to neuron c. This arrangement increases the flexibility, as compared with the direct pathway from neuron A to C shown below. Arrows show the direction of impulse conduction.

Figure 1.13



An interneuron (B) mediates negative feedback to the projection neuron (A). Arrows show the direction of impulse conduction.

Many Axons Are Isolated to Increase the Speed of Impulse Propagation

The velocity with which the nerve impulse travels depends on the diameter of the axon, among other factors. In addition, how well the axon is insulated is of crucial importance. Many axons have an extra layer of insulation (in addition to the axonal membrane) called a **myelin sheath**. Such axons are therefore called **myelinated**, to distinguish them from those without a myelin sheath, which are called **unmyelinated** (see Figs. 2.6 and 2.7).

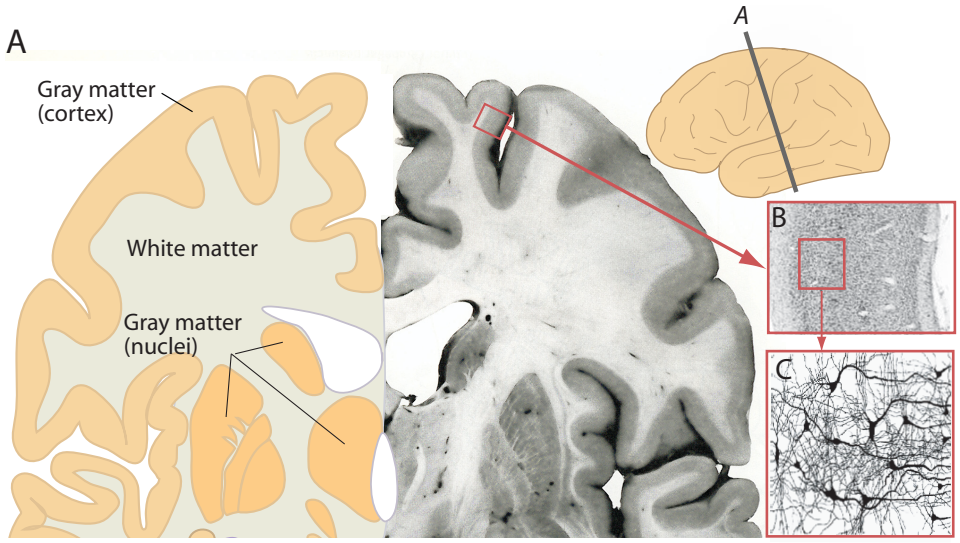
Many of the tasks performed by the nervous system require very rapid conduction of signals. If unmyelinated axons were to do this, they would have to be extremely thick. Nerves bringing signals to the muscles of the hand, for example, would be impossibly thick, and the brain would also have to be much larger. Insulation is thus a very efficient way of saving space and expensive building materials. Efficient insulation of axons is, in fact, a prerequisite for the dramatic development of the nervous system that has taken place in vertebrates as compared with that in invertebrates.

Myelin and how it is formed is discussed in Chapter 2, while the conduction of nerve impulses is discussed Chapter 3.

White and Gray Matter

The surfaces made by cutting nervous tissue contain some areas that are whitish and others that have a gray color (Fig. 1.14). The whitish areas consist mainly of myelinated axons, and the myelin is responsible for the color; such regions are called **white matter**. The gray regions, called **gray matter**, contain mainly cell bodies and dendrites (and, of course, axons passing to and from the neurons). The neurons themselves are grayish in color. Owing to this difference in color, one can macroscopically identify regions containing cell bodies and regions that contain only nerve fibers in brain specimens.

Figure 1.14



Gray and white matter. **A:** Drawing and photograph of an unstained frontal section through the human brain. The white matter consists only of axons and glial cells, whereas the gray matter contains the cell bodies, dendrites, and nerve terminals. **B:** Low-power photomicrograph of a section through the cerebral cortex (frame in **A**) stained so that only neuronal somata are visible (as small dots). **C:** Drawing of neurons in a section through the cerebral cortex (Golgi method). Only a small fraction of the neurons present in the section are shown.

Neurons Are Collected in Nuclei and Ganglia

When examining sections from the CNS under the microscope, one sees that the neuronal cell bodies are not diffusely spread out but are collected in groups. Such a group is called a **nucleus** (Figs. 1.14, 1.15, and 1.16). Neurons collected in this manner share connections with other nuclei and constitute in certain respects a **functional unit**; thus, the neurons in a nucleus receive the same kind of information and act on the same (or similar) target. In the PNS, a corresponding collection of cell bodies is called a **ganglion**.

Axons that end in a nucleus are termed **afferent**, whereas axons that leave the nucleus are **efferent**. We also use the terms afferent and efferent for axons conducting toward and away from the CNS, respectively. Thus, sensory axons conveying information from sense organs are afferent, while the motor axons innervating muscles are efferent.

Axons Form Tracts and Nerves

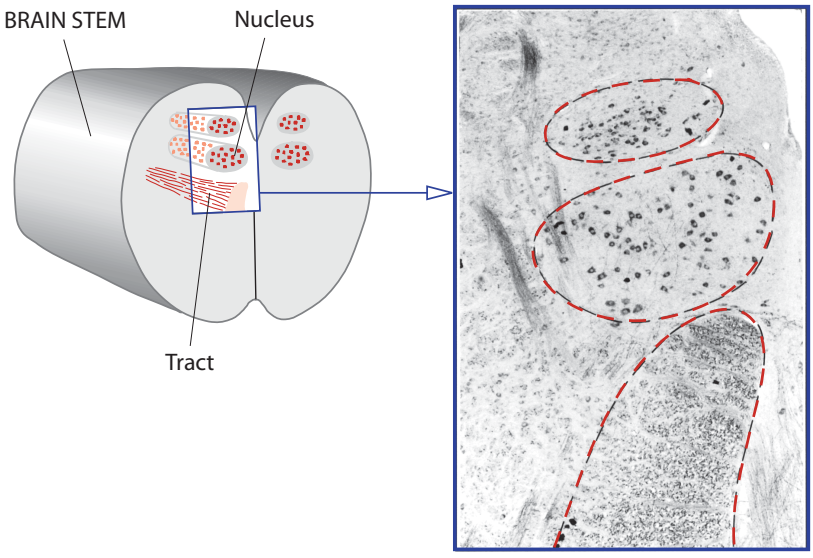
Axons from the neurons of one nucleus usually have common targets and therefore run together, forming bundles. Such a bundle of axons connecting one nucleus with another is called a **tract** (tractus; Figs. 1.15 and 1.16). In the PNS, a collection of axons is called a **nerve** (nervus; Fig. 1.16, see also Fig. 21.2). We also use the term **peripheral nerve** to emphasize that a nerve is part of the PNS. Tracts form white matter of the CNS, and, likewise, peripheral nerves containing myelinated axons are whitish.

Schematically, the large tracts of the nervous system are the main routes for nerve impulses—to some extent, they are comparable to highways connecting big cities. In addition, there are numerous smaller pathways often running parallel to the highways, and many smaller bundles of axons leave the big tracts to terminate in nuclei along the course. The number of smaller "footpaths" interconnecting nuclei is enormous, making possible, at least theoretically, the spread of impulses from one nucleus to almost any part of the nervous system. Normally, the spread of impulses is far from random but, rather, is highly ordered and patterned. As a rule, the larger tracts have more significant roles than the smaller ones in the main tasks of the nervous system. Consequently, diseases affecting such tracts usually produce marked symptoms that can be understood only if one has a fair knowledge of the main features of the wiring patterns of the brain.

COUPLING OF NEURONS: PATHWAYS FOR SIGNALS

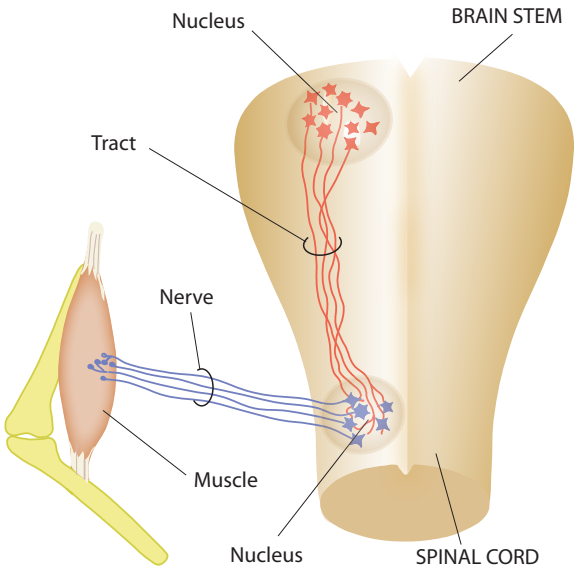
In addition to the properties of synapses, which determine the transfer of signals among neurons, the function

Figure 1.15



Nucleus and tract. **Left:** Schematic of part of the brain stem, showing the three-dimensional shape of two nuclei and a tract. **Right:** Photomicrograph showing the same structures in a section stained to visualize somata and myelinated axons. Magnification, ×75.

Figure 1.16



Nucleus, tract, and nerve. Three-dimensional schematic of parts of the brain stem, spinal cord, and a muscle in the upper arm. Axons from a nucleus in the brain stem form a tract destined for a nucleus in the spinal cord. The axons of the neurons in the spinal nucleus leave the CNS and form a nerve passing to the muscle.

of the nervous system depends on how the various neuronal groups (nuclei) are interconnected (often called the wiring pattern of the brain). This pattern determines the pathways that signals may take and the possibilities for cooperation among neuronal groups. Thus, although each neuron is to some extent a functional unit, it is only by proper cooperation that neurons can fulfill their tasks. We describe here some typical examples of how neurons are interconnected, as such general knowledge is important for understanding the specific examples of connections dealt with in later chapters.

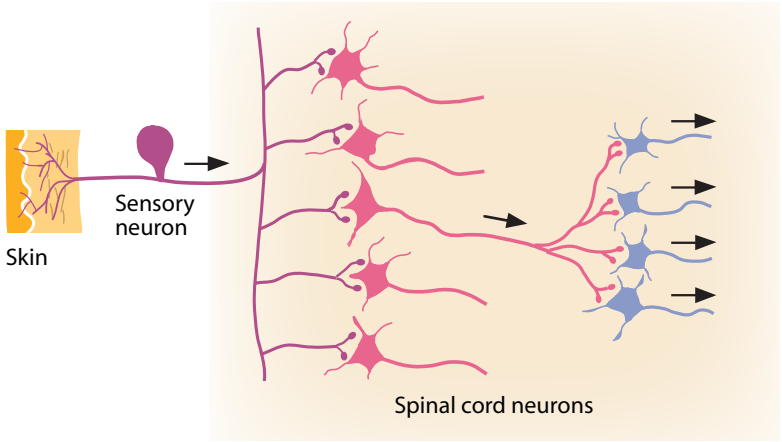
Divergence and Convergence

A fundamental feature of the CNS is that each neuron influences many—perhaps thousands—of others; that is, information from one source is spread out. This phenomenon is called **divergence** of connections. Figure 1.17 shows schematically how a sensory signal (e.g., from a fingertip) is conducted by a sensory neuron to the spinal cord and from there diverges to many spinal neurons. Each of the spinal neurons acts on many neurons at higher levels.

Another equally ubiquitous feature, **convergence** of connections, is shown schematically in Fig. 1.18. This means that each neuron receives synaptic contacts from many other neurons. The motor neuron shown in Fig. 1.18 controls the contraction of a number of striated muscle cells (but could have been almost any neuron in the CNS). The motor neuron receives synaptic contacts from many sources (peripheral sense organs, motor neurons in the cerebral cortex that initiate voluntary movements, and so forth). In this case, the motor neuron represents the **final common pathway** of all the neurons acting on it.

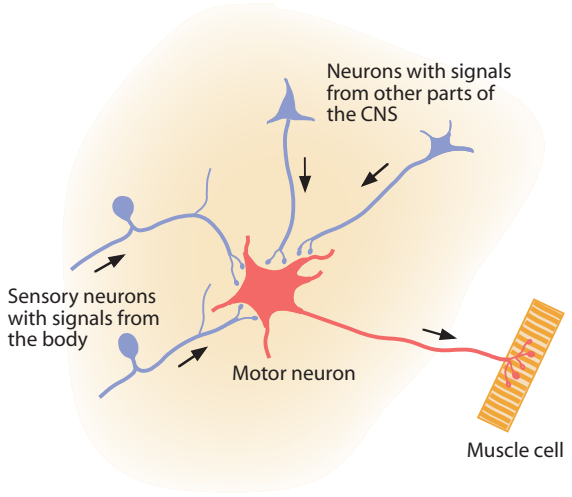
The nerve impulses may not necessarily follow all the available pathways shown in Figs. 1.17 and 1.18 because,

Figure 1.17



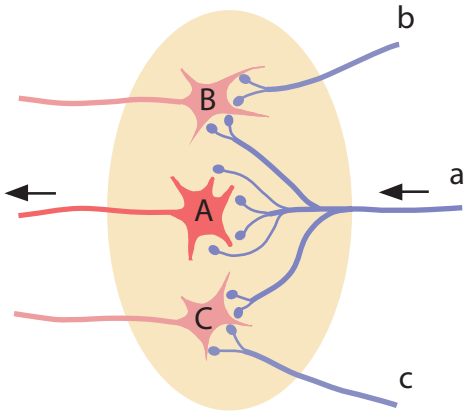
Divergence of neural connections. Highly simplified diagram. The axon collaterals of one sensory neuron contact many neurons in the spinal cord (red). Each of the spinal neurons contacts many other neurons (blue) in the cord or in the brain stem. In this way, the signal spreads from one neuron to many others. Arrows show the direction of impulse conduction.

Figure 1.18



Convergence of neural connections. Synaptic inputs from many neurons (blue) converge onto one neuron (red). In this example, the red neuron is motor and sends its axon to striated muscle cells. The sum of all converging synaptic inputs determines the frequency of impulses sent from the motor neuron to the muscle cells—and thus their strength of contraction. Arrows show the direction of impulse conduction.

Figure 1.19



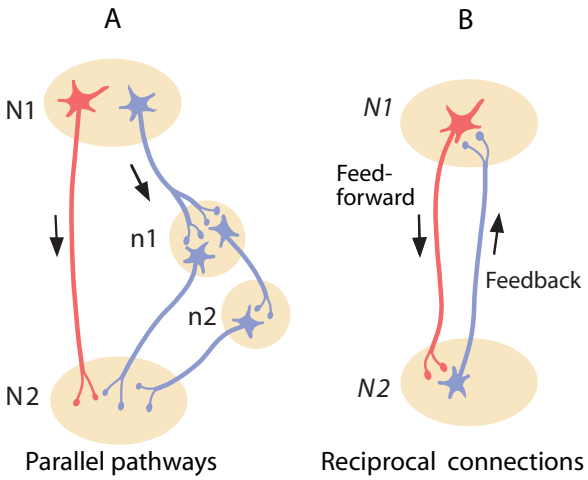
Summation. Many synapses must act on a neuron at the same time to make it fire impulses. Axon a makes many synaptic contacts with neuron A, and their effects summate so that neuron A fires impulses. In contrast, axon a forms only few synapses with neurons B and C and is not able on its own to fire these neurons. If, however, axons b and c also send impulses at the same time as axon a, summation ensures that neurons B and C fire impulses. Arrows show the direction of impulse conduction.

as a rule, many synapses must be active almost simultaneously to make a neuron fire impulses. Thus, more than one of the blue neurons in Fig. 1.18 must be active at the same time to bring the motor neuron to fire impulses and make the muscle contract. This phenomenon is termed **summation** and is exemplified further in Fig. 1.19. The many synapses axon a makes on neuron A brings the latter to fire a series of nerve impulses whenever axon a is active. But because of fewer synapses, the impact of axon a on neurons B and C is too weak to make them fire impulses. If, however, axons b and c are active simultaneously with a, their effects are summated so that neurons B and C may fire impulses. Summation is discussed further in Chapter 4.

Parallel Pathways and Reciprocal Connections

Figure 1.20 illustrates common types of connections among neuronal groups (nuclei). Figure 1.20A shows the principle of **parallel pathways**. There is one direct pathway from nucleus N1 to N2 and one indirect pathway that is synaptically interrupted in other nuclei (n1 and n2). Thus, some of the information reaching N2 is a direct consequence of the activity in N1, whereas information passing through n1 and n2 is modified by other connections acting on these nuclei (not shown). The abundance of such parallel pathways in the human

Figure 1.20



Examples of organization of neuronal pathways. Arrows show the direction of impulse conduction; N1, N2, n1, and n2 are nuclei in different parts of the CNS.

cerebral cortex is one of the factors that explains its enormous flexibility and capacity for information processing (Fig. 1.23). Parallel pathways may, further, be of practical importance after partial **brain injury**. If, for example, the direct pathway between N1and N2 is interrupted, the indirect one may at least partly take over the tasks formerly performed by the direct one (examples of this are discussed in Chapter 11).

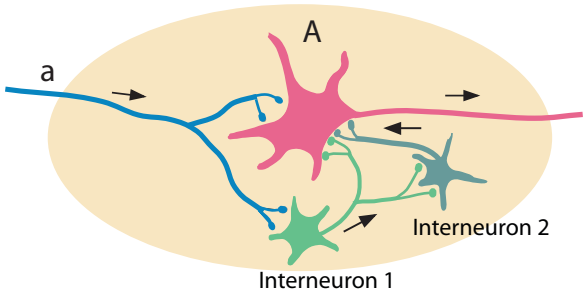
Reciprocal connections represent another common arrangement, in which a nucleus receives connections from the nuclei to which it sends axons (Fig. 1.20B). In many cases, such back-projections serve as **feedback**, whereby the first nucleus is informed of the outcome of the impulses emitted to the second one. If the influence is too strong, the feedback may serve to reduce activity, and vice versa if the influence is too weak. Among other actions, such feedback connections serve to stabilize the functioning of the nervous system. Thus, many of the symptoms appearing in neurological diseases are due to the failure of feedback mechanisms. Often, however, it is not obvious which one should be regarded as a feedback connection and which one as a **feed-forward** connection. Presumably, a single pathway may serve both purposes.

Couplings Contributing to Continuous Neuronal Activity

There is always electric activity in the CNS, because numerous neurons are firing impulses at any given time. In the cerebral cortex, for example, even during sleep there is considerable neuronal activity. How is this activity sustained, even in the absence of sensory inputs? In early embryonic life, groups of neurons become **spontaneously active**—that is, they fire impulses without any external influence (this is caused by development of special membrane properties). As the nervous system matures, neuronal behavior is governed more and more by synaptic connections with other neurons; nevertheless, some neurons remain spontaneously active. Another feature contributing to continuous activity is that, when activated, most neurons fire a train of impulses, not just one. Further, interneurons contribute to prolongation of activity, as schematically exemplified in Fig. 1.21.

Impulses in axon a make neuron A fire impulses, propagated along its axon. At the same time, axon a makes interneuron 1 fire impulses, which act on neuron A and interneuron 2. The latter acts on neuron A to produce impulses. Owing to a delay of a few milliseconds at each synapse and the time for conducting the impulse in the axons, neuron A receives synaptic inputs over a prolonged period. This kind of coupling (in reality far more elaborate than shown in Fig. 1.21) can translate a brief synaptic input to long-lasting neuronal firing in a neuronal network. Working memory—that is, the ability to keep task-relevant information in mind for a while—depends on neurons that continue firing after a stimulus has stopped.

Figure 1.21

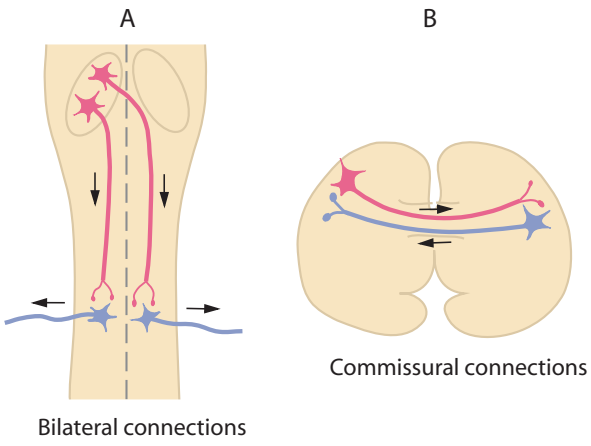


Interneurons that prolong the activity of a projection neuron (A) when activated by impulses in axon a. Arrows show the direction of impulse conduction.

Connections between the Two Halves of the Central Nervous System

Another important general feature of the CNS is that many nuclei have connections with both sides of the brain—so-called **bilateral connections** (Fig. 1.22A). Some tracts supply both sides with approximately the same number of axons (i.e., equal numbers of crossed and uncrossed axons), whereas other tracts are predominantly crossed (contralateral), with only a few axons supplying the same (ipsilateral) side. Although the functional significance of such bilateral connections may not always be clear, they can contribute to recovery of function after partial brain damage.

Figure 1.22



Examples of organization of neuronal pathways. Arrows show the direction of impulse conduction.

That the two sides of the CNS cooperate extensively is witnessed by the vast number of **commissural connections**—that is, direct connections between corresponding parts in the two brain halves (Fig. 1.22B). Such connections occur at all levels of the CNS, but the most prominent one connects the two halves of the cerebral hemispheres (corpus callosum; see Figs. 6.26 and 6.27). In humans, this pathway contains approximately 200 million axons.

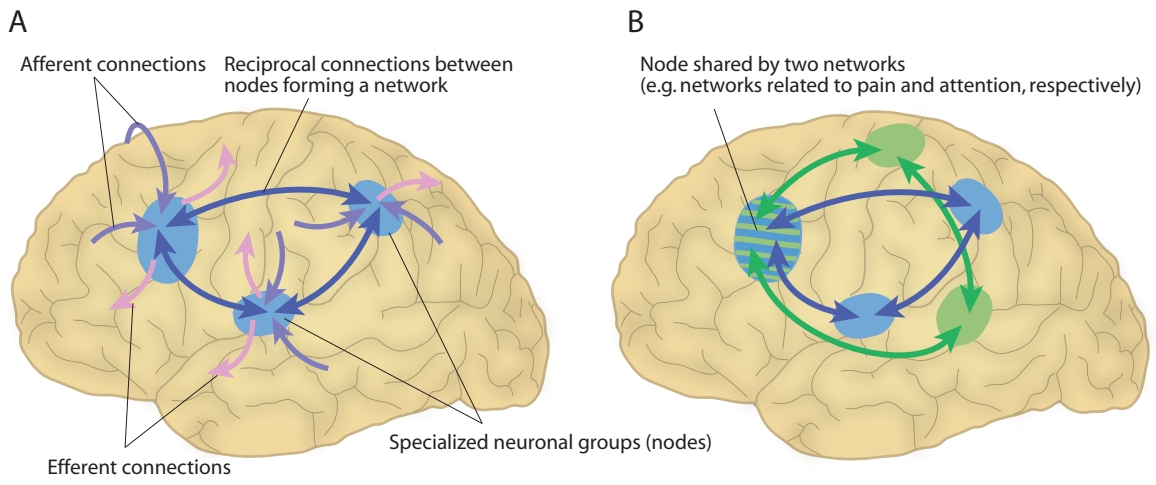
Single Neurons Are Parts of Neural Networks

The tasks of a neuron can be understood only in conjunction with the thousands of neurons with which it is synaptically interconnected. Further, functions of the brain are very seldom the responsibility of one neuronal group or "center" but, rather, the result of cooperation among many neuronal groups. Such cooperating groups or nuclei often lie far apart. For example, proper voluntary movements require cooperation among specific neuronal groups in the cerebral cortex, the cerebellum, and the basal ganglia deep in the cerebral hemispheres. Today we use the term **distributed system** rather than **center** when referring to the parts of the brain that are responsible for a specific function. Such a distributed system is a complicated **neural network** of spatially separate but densely interconnected neuronal groups. Figure 1.23A gives a very simplified example of such a network that could be dedicated to, for example, the sensation of pain. Owing to the abundance of reciprocal connections, the signal traffic can take various routes within the network, and each neuronal group has connections outside the network. This means that a variety of inputs can activate the network—all presumably giving the same functional result (the sensation of pain, a specific memory, an emotion, and so forth). Nevertheless, it should not be surprising that each group, or **node**, might participate in several different, function-specific networks (Fig. 1.23B). Thus, as a rule, one neuronal group participates in several tasks.

The **anatomic connectivity** determines the possible interactions among different nodes, whereas the **functional connectivity** reflects the connections that are actively transmitting signals at any moment. Most likely, **synchronized**, **oscillatory** electrical activity is the "signature" of the operations of a network. Modern imaging techniques make it possible to study the relation between a certain behavior and the functional connectivity of specific networks.

The organization of the brain in distributed systems is particularly clear with regard to higher **mental functions**. Language is a good example: there is not one center for language but specific neuronal groups in many parts of the cerebral cortex that cooperate. Other networks are responsible for attention, spatial

Figure 1.23



Distributed neural networks. Highly simplified. **A:** Three nodes (groups of neurons) in the cerebral cortex are shown in light blue. They differ with regard to many of their afferent and efferent connections. Significantly, however, they share reciprocal connections, thus forming a network. The collective activity of the three parts of the network is responsible for its "product"—for example, the sensation of pain. **B:** Exemplifies that one node participates in more than one network.

orientation, object identification, short-term memory, and so forth. Data-based models of neural networks have provided new insight into the workings of the cerebral cortex and how symptoms arise from partial destruction of networks.

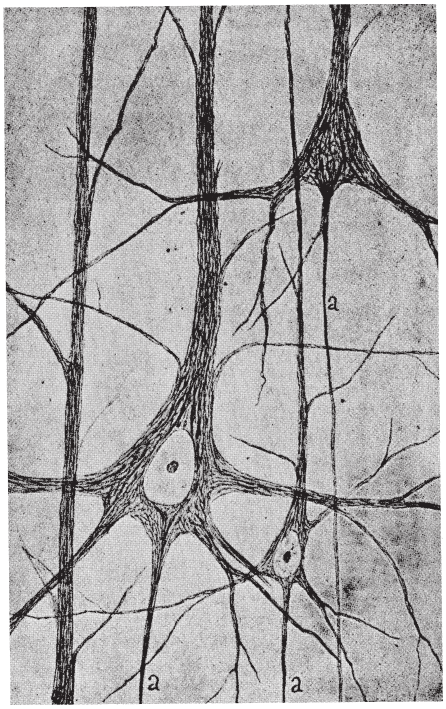
Injuries of Neural Networks

An important feature of distributed systems is that **partial damage** can degrade their performance but seldom eliminate it. Sometimes partial damage may become evident only in situations with very high demands, for example, with regard to the speed and accuracy of movements, the capacity of short-term memory, and so forth. If the number of neurons participating in the network undergoes further reduction, however, performance may deteriorate severely. In such cases, symptoms may occur rather abruptly, even though the disease process responsible for the cell loss may have been progressing slowly for years. This is typical of degenerative brain diseases such as Parkinson's disease and Alzheimer's disease.

THE CYTOSKELETON AND AXONAL TRANSPORT

The cell bodies and processes of neurons contain thin threads called **neurofibrils**, which can be observed in specially stained microscopic sections (Fig. 1.24). The neurofibrils are of different kinds but together they form the **cytoskeleton**—the name refers to its importance for development and maintenance of **neuronal shape**. The fact that neurons have very different shapes—with regard to dendrites, cell bodies, and axons—is due to cytoskeletal specializations. For example, the neurofibrils have a decisive role when axons grow for long distances (see Fig. 9.16), and the cytoskeleton serves to anchor synaptic elements at the postsynaptic density (see Fig. 4.2).The neurofibrils of the cytoskeleton are also responsible for another important cellular function: the transport of **organelles** and **particles** in the neuronal processes. Although such transport takes place in both dendrites and axons, **axonal transport** (Fig. 1.25) has been most studied (mainly because, for technical reasons, transport in dendrites is much harder to study). It is obvious that neurons need direction-specific transport mechanisms. Thus, the organelles necessary for protein synthesis and degradation of particles are present almost exclusively in the cell body. Nevertheless, dendrites contain small amounts of mRNA located at the base of dendritic spines, which may enable a limited amount of protein synthesis important for synaptic changes related to learning and memory.

Figure 1.24



The cytoskeleton in neurons. Drawing of neurons from the cerebral cortex, as appearing in sections stained with heavy metals to visualize neurofibrils. Both dendrites and axons (a) contain numerous neurofibrils. (From Cajal 1952.)

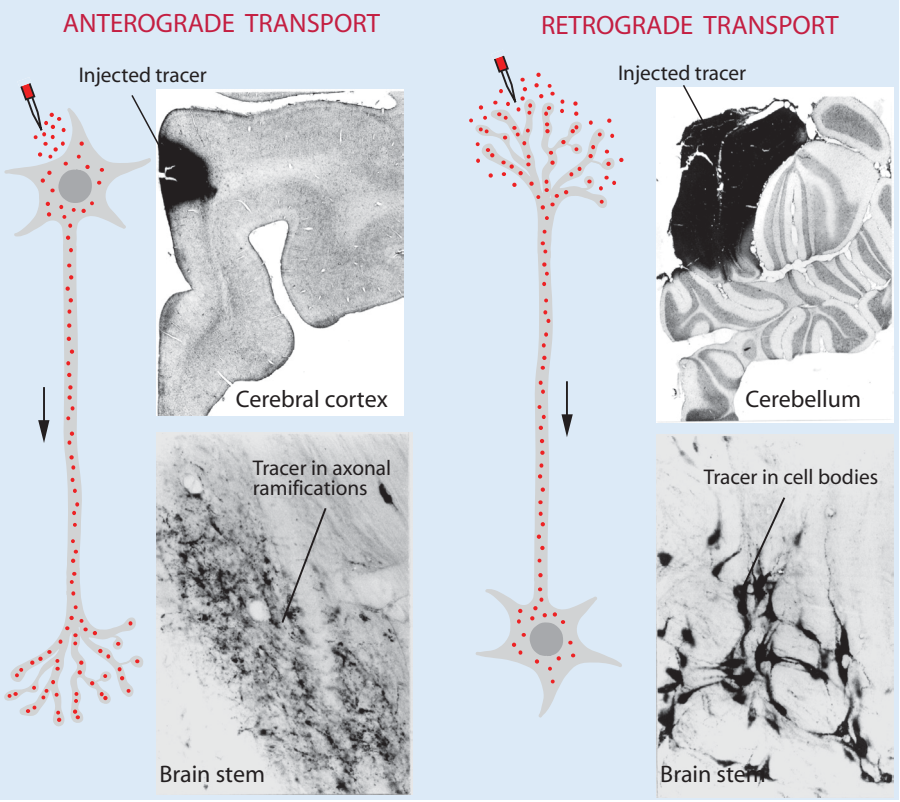
Components of the Cytoskeleton

Electron microscopic and biochemical analyses have shown that the cytoskeleton consists of various kinds of fibrillary proteins, making threads of three main kinds:

1. **Actin filaments** (microfilaments) and associated protein molecules (approximately 5 nm thick)
2. **Microtubules** (narrow tubes) and associated proteins (approximately 20 nm thick)
3. **Intermediate filaments** or neurofilaments (approximately 10 nm thick)

Actin (microfilaments) is present in the axon, among other places. In the axon actin has an important role during development. When the axon elongates, actin together with microtubules serves to produce movements of the **growth cone** (see Fig. 9.16) at the tip of the axon (in general, actin is present in cells capable of movement, such as muscle cells). The growth cone continuously sends out thin fingerlike extensions (filopodia) in various directions. These

Figure 1.25



Axonal transport. The photomicrographs illustrate the use of axonal transport for tract tracing, that is, to map the connections in the CNS. A cat received injections of an enzyme (horseradish peroxidase) in the cerebellum and in the cerebral cortex (0.2 μL in each). The enzyme was taken up by endocytosis of neuronal cell bodies and terminals. Vesicles with enzyme were then transported anterogradely from the cerebral cortex to the brain stem (left) and retrogradely from the cerebellum to the brain stem (right). A black reaction product in the upper photomicrographs shows the extension of the tracer at the injection site. The anterogradely labeled terminal ramifications of the axons appear as black dust in the left lower photomicrograph, while retrogradely labeled cell bodies are seen in the right lower photomicrograph. Magnifications, ×8 (**upper**) and ×150 (**lower**).

probably explore the environment for specific molecules that mark the correct direction of growth. In addition, actin is probably important in maintaining the shape of the fully grown axon. Furthermore, actin is important for the functions of dendritic **spines**. Figure 4.13 gives an example of actin transporting transmitter receptor proteins from the base of the spine to the synaptic site at the top. Also, other pre- and postsynaptic proteins depend on actin for their correct functioning. Thus, synaptic changes associated with **learning** appear to depend critically upon the contribution of actin.

Microtubules and **microtubule-associated proteins** (**MAPs**) are present in all kinds of neuronal processes and are most likely important for their shape (Fig. 1.7; see also Fig. 2.7). Of special interest is the relation of microtubules to the transport of substances in the neuronal processes. As mentioned, there is a continuous movement of organelles, proteins, and other particles in the axons and dendrites. Destruction of microtubules by drugs (such as **colchicine**) stops axonal transport.

The functional role of the **intermediate filaments** (**neurofilaments**) is not fully known, although they make up about 10% of axonal proteins and are abundant in astroglial cells (see Fig. 2.2). One function is to support axonal radial growth and maintain axonal diameter, as internal scaffolding. Furthermore, networks of intermediate filaments may—due to their viscoelastic properties—prevent injury when nervous tissue is subjected to mechanical stress. It is noteworthy that neurofilaments are altered in several degenerative neurological diseases. In Alzheimer's disease, for example, a characteristic feature is disorganized tangles of intermediate filaments in the cerebral cortex (neurofibrillary tangles).

Anterograde and Retrograde Axonal Transport

Transport from the cell body toward the nerve terminals is called **anterograde** axonal transport (Fig. 1.25). Examples of particles transported anterogradely are mitochondria, synaptic vesicles, proteins to be inserted in the axonal membrane, and enzymes for transmitter synthesis and degradation in the nerve terminals. Growth factors, synthesized in the cell body but liberated far away at the synapses, also require efficient anterograde axonal transport. Transport toward the cell body from the nerve terminals is called **retrograde** axonal transport. Retrograde transport brings signal molecules of various kinds that are taken up by the nerve terminals to the cell body (Fig. 1.25). Often such molecules are produced by postsynaptic cells and released to the extracellular space. In the cell body (nucleus) of the neuron, the signal molecules can influence genetic expressions—that is, they can change protein synthesis. In this way, the properties of the neuron can be changed transiently or in some instances permanently. For example, growth and maintenance of many neurons in the spinal cord depend on retrograde transport of **neurotrophins** (growth factors) from the organs they innervate. This is a form of **feedback**: ensuring that the neuron is informed of its effects on other cells and of the state of its target cells. In some instances, neurons even require this kind of feedback to survive. Thus, growth factors switch off cell-death programs, which otherwise would lead to destruction of the neuron (a vast number of neurons are eliminated during early development of the nervous system). Retrograde transport also moves "worn-out" organelles to the cell body for degradation in lysosomes. Injections into nervous tissue of substances that are transported axonally and later can be detected in tissue sections are widely used for **tract tracing**, that is, to reveal the "wiring pattern" of the brain (Fig. 1.25).

More about Axonal Transport and Its Machinery

The injection of radioactively labeled substances taken up by neurons has shown that axonally transported material moves in at least **two phases**. One phase is **rapid**, with particles moving up to half a meter per day; the other is **slow**, with movement of between 1 and 3 mm per day. The rapid phase carries mainly organelles and vesicles, that is, membrane-bound structures. The slow phase carries primarily enzymes and components of the cytoskeleton. As mentioned, microtubules are of particular importance for axonal transport. Each microtubule is composed of smaller building blocks of the protein **tubulin**. **MAPs** help the formation of tubes from many tubulin molecules. MAPs also anchor the microtubules to the cell membrane and to other parts of the cytoskeleton, such as neurofilaments. Two kinds of MAPs found only in neurons—**MAP2** and **tau**—stiffen the microtubules. Specific kinds of MAPs perform anterograde and retrograde transport, respectively, serving as the "motors" of axonal transport. These MAPs are ATPases (enzymes that split ATP), and the released energy alters their form, thus producing movement. The transported particles, such as vesicles and mitochondria, move by temporarily binding to MAPs protruding from the microtubule, so that they appear to "walk" along the microtubule. One microtubule can transport in both directions, depending on the kind of motor to which a particle binds. Proteins belonging to the **kinesin** superfamily are responsible for anterograde movement. Different varieties of kinesin appear to transport different "cargo"; for example, one variety transports mitochondria and another transports precursors of synaptic vesicles. **Dynein**, which is a more complex protein than kinesin, is responsible for the bulk of retrograde transport, although certain kinesins probably also contribute.

2 Glia

OVERVIEW

Glial cells are the most numerous cells in the brain and are indispensable for neuronal functioning. Glial cells are of three kinds that differ structurally and functionally. **Astrocytes** have numerous processes that contact capillaries and the lining of the cerebral ventricles. They serve important **homeostatic functions** by controlling the concentrations of ions and the osmotic pressure of the extracellular fluid (ECF), thereby helping to keep the neuronal environment optimal. Astrocytes are also involved in transmitter uptake and synapse formation and elimination. They respond to all kinds of injury and participate in **repair processes**. **Oligodendrocytes** insulate axons by producing **myelin sheaths** in the central nervous system (CNS), thus increasing the conduction velocity of the axons. **Microglial** cells seem to constantly survey the local environment of the neurons. Upon activation, they are transformed to **macrophages** that remove unwanted material. **Schwann cells** are a specialized form of glial cells that form myelin sheaths in the peripheral nervous system (PNS). Apart from these specific functions, glial cells are involved in the prenatal **development** of the nervous system, for example, by providing surfaces and scaffoldings for migrating neurons and outgrowing axons.

Although the glial cells are essential for proper neuronal functioning, **neuroinflammation** caused by activated glial cells are thought to contribute to the pathology in a number of diseases (depression, Alzheimer's disease, persistent pain, and several others).

GLIAL CELLS IN GENERAL

Types of Glial Cells

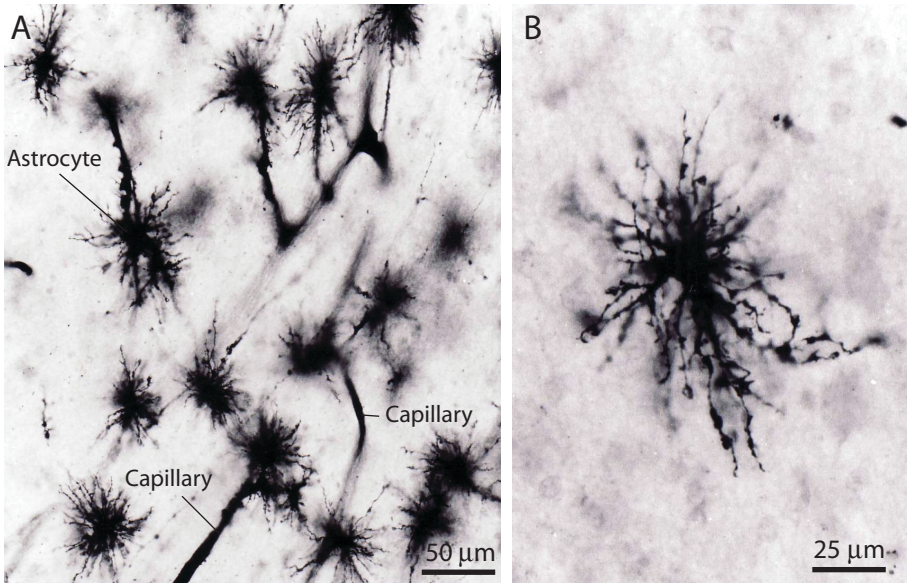
It is customary to group glial cells into three categories that differ structurally and functionally: **astrocytes**, or astroglia; **oligodendrocytes**, or oligodendroglia; and **microglial cells**, or microglia. All three types have small cell bodies (compared with neurons) and send out several processes (Fig. 2.1.; see also Fig. 2.5 showing the difference in size between glial and neuronal nuclei in routinely stained sections). Astrocytes have numerous processes of various shapes (Fig. 2.1), whereas oligodendrocytes have relatively few and short processes (*oligo* means few, little). Microglial cells are—as the name implies—smaller than the other kinds. Reliable identification of the various types, however, requires immunocytochemical methods that identify specific cytoskeletal proteins. Fig. 2.2 exemplifies the identification of astrocytes by detection of **glial fibrillary acidic protein** (**GFAP**). Furthermore, differences in gene expression of receptors and signal substances help to characterize subgroups of the three main kinds of glial cell. For example, astroglia differs with regard to molecular biology in different parts of the CNS.[1]

Glial Cells Perform Many Tasks

Although they do not take part in the fast and precise information processing in the brain, glial cells are nevertheless of crucial importance to proper functioning of neurons. The name *glia* derives from the older notion that glial cells served as a kind of glue, keeping the neurons together. We now know, however, that glial cells (and astrocytes in particular) fulfill many important tasks apart from serving as a sort of scaffolding for the neurons: They serve homeostasis, regulate synaptic function, are crucial for axonal conductance, supply neurons with energy, and participate in the prenatal development of the nervous system. During infections and after trauma, glial cells are activated and carry out reparatory processes but may also contribute to tissue damage.

1. Such differences may help explain why **astrocytomas** (which are among the most common tumors in the CNS) arise preferentially in certain parts. Thus, astrocytes in different parts of the brain differ with regard to the expression of a tumor-suppression gene.

Figure 2.1

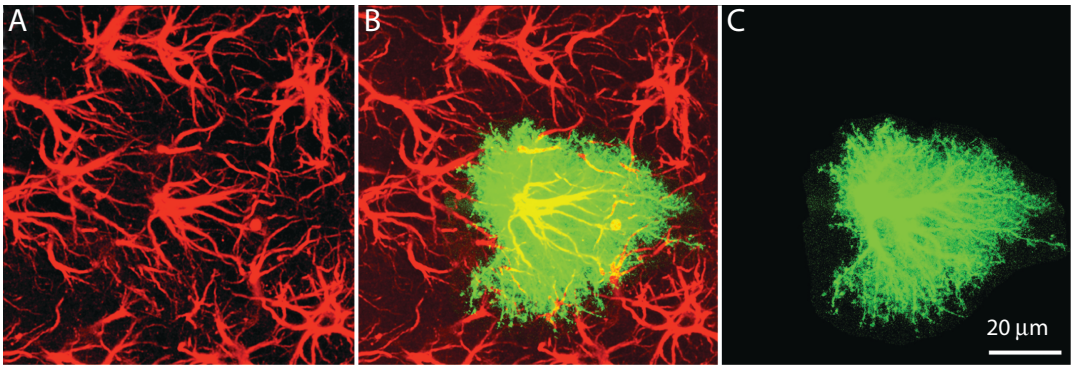


Astrocytes. Photomicrographs of Golgi-stained sections from the cerebral cortex. No neurons are visible. Note the close relationship between astrocytic processes and capillaries.

Number of Glial Cells

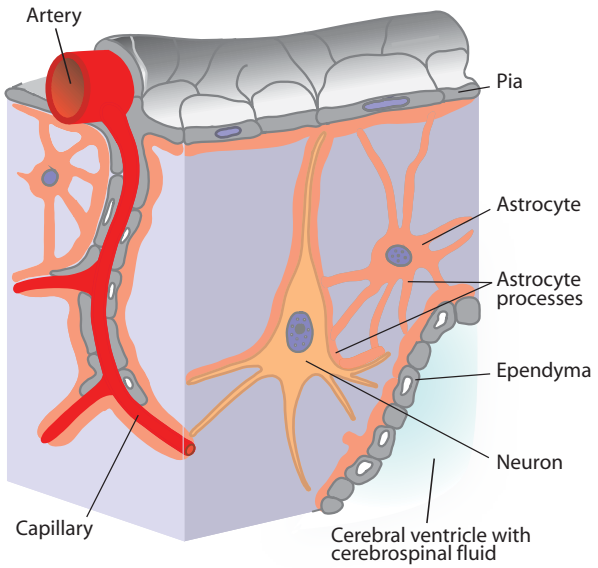
The number of glial cells increases during evolution and is higher than the number of neurons in humans. Thus, the ratio of glial cells to neurons in nematodes is only 0.2:1, while it is 0.4:1 in rodents and 1.4:1 in the human cerebral cortex (in other parts of the human brain the dominance of glial cells may be even greater). The absolute and relative increase in glial cells emphasize their importance for brain functioning and, more specifically, that the most complex brains are most dependent upon glial control of the neuronal local environment.

Figure 2.2



Astrocytes. **A:** Astrocytic processes visualized using an antibody against GFAP present in intermediary filaments. The antibody was labeled with a substance with red fluorescence. **B:** One of the astrocytes in A has been filled completely with intracellular injection of a substance with green fluorescence (Lucifer yellow) and reconstructed three-dimensionally. It is obvious that the astrocytic processes are much more abundant and of finer caliber than in **A. C:** View of the injected astrocyte in **B** in isolation, showing to advantage its dense and bushy halo of processes. (Reproduced with permission from Wilhelmsson et al. [2004] and *The Journal of Neuroscience*.)

Figure 2.3



The relationship between astroglia and neurons, blood vessels and the CSF. The astrocytes cover the surface of the neurons and are also closely related to vessels, ependymal cells, and the innermost part of the cerebral meninges (pia).

Specialized Forms of Glial Cells

In addition to the three main kinds, there are other, specialized forms of glial cells. The surface of the cavities inside the CNS is lined with a layer of cylindrical cells called **ependyma** (Fig. 2.3; see also Fig. 9.6). There are also special types of astroglial cells in the retina (**Müller cells**), the cerebellum (**Bergman cells**), and the posterior pituitary gland (**pituicytes**). **Olfactory ensheathing cells** are a special kind of Schwann cells, present in the olfactory nerve. They have attracted special interest because they—after implantation in the CNS—can stimulate **regeneration** of axons.

ASTROGLIA AND HOMEOSTASIS

Astrocytes Contact Capillaries, Cerebrospinal Fluid, and Neurons

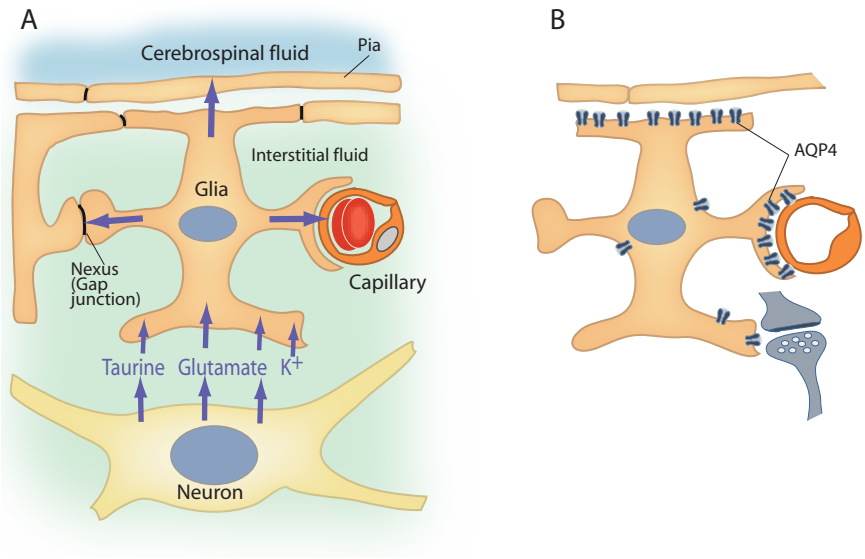
Astrocytes have structural features that make them well suited to control the extracellular environment of the neurons:

1. They have numerous short or long processes that extend in all directions (Figs. 2.1 and 2.2). Thus, the astrocytes have a very large **surface area** that enables efficient exchange of ions and molecules with the ECF.
2. Some processes contact the surface of **capillaries** with expanded **end "feet"** and cover most of the capillary surface (Figs. 2.3 and 2.4).
3. Some processes form a continuous, thin sheet (membrana **limitans**, also called glia limitans) where nervous tissue borders the **cerebrospinal fluid (CSF)**, that is, in the cavities inside the CNS and against the connective tissue membranes on its exterior (Fig. 2.3).
4. Other processes contact **neuronal surfaces**; in this manner, parts not contacted by boutons are covered by glia (Figs. 2.3 and 2.5). Glial processes usually enclose the nerve terminal (see Figs. 1.6 and 1.7).
5. Numerous **gap junctions** (nexus) couple astrocytes, allowing free passage of ions and other small particles among them (Fig. 2.4). Thus, apart from allowing electric currents to spread, astrocytes form continuous, large fluid volumes for distribution of substances removed from the ECF.

Glial Cells Communicate with Electric Signals and Influence Cerebral Blood Flow

Although glial cells do not send precise signals over long distances, they can produce brief electric impulses (currents) by opening of membrane **channels for Ca^{2+}**. Such an opening can be evoked by binding of neurotransmitters (e.g., glutamate) to G-protein–coupled receptors in the glial cell membrane. Thus, neuronal activity can directly influence the astrocytes, whereas the latter affects neuronal activity. Due to the electric coupling (nexus) of the astrocytes, a **calcium signal** can presumably spread rapidly in **networks** of astroglial cells and thus influence many neurons almost simultaneously, which, among other roles, can help **synchronize** the activity of the neurons. In light of the electric coupling among astrocytes, one might expect the population of neurons influenced by an astrocytic network to be quite large. Recent data, however, indicate that the population can be surprisingly small, enabling spatially precise interactions among neurons and astrocytes. Thus, while it is well known that a specific sensory input (e.g., from a small spot in the visual field) activates neurons in a precisely defined, small part of the cortex, recent experiments (Schummers et al. 2008) suggest that astroglial cells are activated in a similarly precise manner (although a few seconds later than the neurons). Presumably, inputs from the periphery activate

Figure 2.4



Astroglia and the homeostasis of nervous tissue. **A:** Schematic shows the close contacts between astroglial cells on the one hand and neurons, capillaries, and the CSF on the other. The astroglial cells are coupled by nexus (gap junctions) and thus form a large fluid volume for distribution of substances. Some important substances handled by astroglia are indicated (the transport is not always in the direction of the arrows). Surplus of water, K^+ ions, and the amino acid taurine can be transported to the blood and the CSF, thereby preventing their accumulation in the ECF. Next to glutamate, taurine is the amino acid with the highest concentration in the CNS and therefore significantly contributes to the osmolarity of the ECF. Taurine does not appear to function as a neurotransmitter, but its transport in and out of astroglia may be a mechanism for controlling the volume of the neurons. The neurotransmitter glutamate is treated differently, however. Glutamate is transformed to glutamine after uptake in glia and thus loses its transmitter actions and becomes neutral to the neurons. Glutamine can therefore be returned to the ECF for subsequent uptake into neurons where it is used for resynthesis of glutamate. Because the neurons need large amounts of glutamate, this is an economic means to ensure a sufficient supply. **B:** The AQP4 channels are highly concentrated at the astrocytic end feet facing capillaries and the pia. (Based on Nagelhus 1998; Nagelhus and Ottersen 2013.)

neurons that in turn activate astrocytes in their immediate vicinity. Furthermore, animal experiments show that **arousal** (via norepinephrine release) can activate cortical astrocytes. When activated, the astrocytes increase local **blood flow** (see Chapter 8, under "Regional Cerebral Blood Flow and Neuronal Activity").

Astroglia and Control of the Neuronal Environment

Their intimate contact with neurons, capillaries, and the CSF places astroglial cells in a unique position to control the environment of the neurons, that is, the **interstitial** (extracellular) **fluid** of the brain (Fig. 2.4). Such control is vitally important for four main reasons. First, neurons are exquisitely sensitive to changes in extracellular concentrations of ions and neurotransmitters. Second, the osmotic pressure (the water concentration) must be tightly controlled because the brain cannot expand in the skull. Third, adding even minute amounts of a substance may produce a substantial increase in its extracellular concentration, owing to the very limited **interstitial space** in the brain (less than 20% of total volume), as illustrated in electron micrographs showing only narrow slits between the cellular elements (see Figs. 1.3 and 1.7). Further, the tortuous shape of the interstitial space hampers free diffusion of particles. Finally, the layer of astrocytic processes surrounding brain capillaries helps to prevent many potentially harmful substances from entering the brain, thus contributing to the **blood–brain barrier** (see Chapter 8).

Astrocytes as Providers of Energy

Although the astrocytes contain most of the **glycogen** present in the brain, the amount is very small compared with muscle and liver. It was therefore assumed that glycogen is not a significant source of energy for neurons. However, recent evidence shows that glycogen in astrocytes is degraded to **lactate** and transferred

to neurons, where it is metabolized aerobically. Therefore, it seems that astrocytes can deliver substrates for energy metabolism to the neurons. It is thought that this process may be important in situations with **hypoglycemia** and during periods with especially high neuronal activity.

Control of Ions

With regard to extracellular **ions**, the control of $\mathbf{K^+}$ (potassium ions) is particularly important. Thus, neuronal excitability is strongly influenced even by small changes in the amount of K^+ ions extracellularly, and as neurons fire impulses, K^+ ions pass out of the cell (Fig. 2.4A). Prolonged or intense neuronal activity would therefore easily produce dangerously high extracellular levels of K^+ ions were it not for their efficient removal by glia. Further, astrocytes contribute to **extracellular pH** control by removing $\mathbf{CO_2}$.

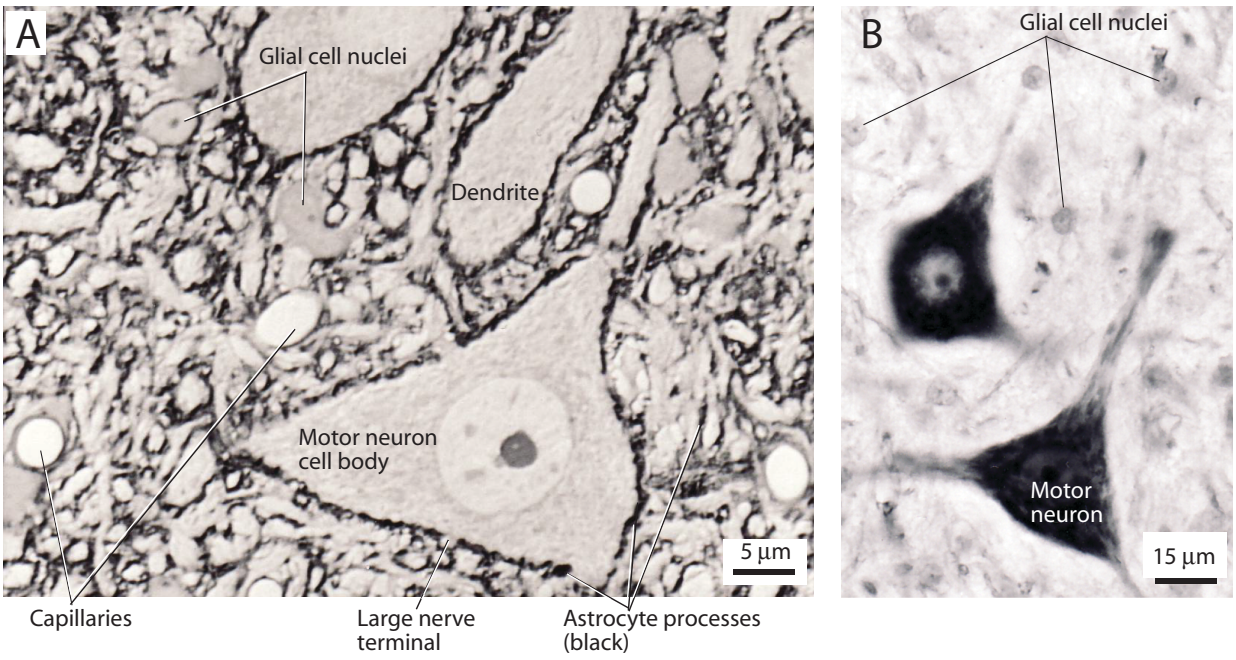
Control of Neurotransmitters

Extracellular **neurotransmitter concentration** must be tightly controlled, because proper synaptic functioning requires that their extracellular concentrations be very low, except during the brief moments of synaptic release. Most neurotransmitters are indeed removed from the ECF near the synapses by **transporter proteins** in the membranes of neurons and astrocytes. Specific transporters have been identified for several neurotransmitters (discussed further in Chapter 5). Figure 2.5 gives an impression of the abundance of a specific kind of transporter proteins (for the ubiquitous neurotransmitter glutamate, which is neurotoxic in abnormally high concentrations).

Aquaporins and Control of Water

As mentioned, astrocytes are also involved in the control of the extracellular osmotic pressure, that is, in controlling

Figure 2.5



Astroglial processes in nervous tissue. **A:** Photomicrograph showing the distribution of a glutamate-transporter protein, as visualized via an immunocytochemical technique. In this 1-µm-thick section from the spinal cord, the dark spots and bands are astrocytic processes expressing glutamate transporters. They outline the somata, dendrites, and capillaries. The picture illustrates both the capacity of astroglia to take up glutamate from the ECF and the enormous astroglial surface facing neurons and capillaries. The contours of dendrites and neuronal somata are uneven because of synaptic contacts (thin arrow) breaking the otherwise continuous layer of astroglia. Capillaries are marked with asterisks. The cell body of an astroglial cell is marked with a thick arrow. (Courtesy of Drs. J. Storm-Mathisen and N.C. Danbolt, Department of Anatomy, University of Oslo.) **B:** For comparison, a photomicrograph of a thionine-stained section from the same part of the spinal cord as in **A**.

the **water balance** of the brain (Fig. 2.4A). Of particular interest in this respect are channels for transport of water—**aquaporins**—that are present in the membranes of astrocytes. Aquaporins were first described in kidney tubular systems, where they were shown to increase significantly the capacity for water passage. Interestingly, in the brain they are most abundant on the glial processes that are in close contact with capillaries and the CSF, that is, where one would expect them to be if they were involved in brain water balance (Fig. 2.4B). For example, **synaptic activity** causes rapid changes in the extracellular volume, and most likely aquaporins are instrumental in controlling such dynamic changes. Exchange by astroglial cells of small neutral molecules, such as the amino acid **taurine**, may be another mechanism to control extracellular osmolarity.

Recent research suggests that the functional role of aquaporins is not limited to regulation of the extracellular volume, although the latter has received the most attention. Thus, brain aquaporins have been implicated in tasks such as clearance of extracellular waste products, control of extracellular potassium, CSF circulation, neuroinflammation, and cell migration.

Aquaporins in Health and Disease

Two varieties of aquaporin predominate in the brain. **AQP4** is located in the astrocyte membrane and is particularly concentrated in the end-feet region close to capillaries and in glial processes bordering the CSF (Fig. 2.4B). **AQP1** is present in epithelial cells of the choroid plexus (which produces the CSF; see Chapter 7). In general, aquaporins increase water permeability of the cell membrane, thus allowing water to follow osmotic gradients and active ion transport. A function of AQP4 in the normal brain is probably to facilitate export of water. Thus, AQP4-deficient mice have increased interstitial (extracellular) fluid volume compared to normal mice. Further, in so-called **vasogenic brain edema**, wherein water accumulates extracellularly, AQP4 contributes to removal of excess water. This kind of edema arises when the brain capillaries become leaky due to, for example, traumatic brain injury. On the other hand, when water accumulates intracellularly, as typically occurs in cerebral ischemia or hypoxia (e.g., in stroke), the presence of AQP4 seems to *increase* the edema by allowing more water to enter the astrocytes. Such **cytotoxic brain edema** is caused by failure of energy-dependent ion pumping, which reduces the ability of the cells to maintain osmotic stability. Brain edema is a serious and often life-threatening complication in many brain disorders, such as stroke and traumatic brain injuries. Therefore, the discovery of a relationship between aquaporins and brain edema led to an intensive search for drugs that can modulate the activity of aquaporins. In animal experiments, inhibitors of AQP4 can reduce cytotoxic edema whereas they seem to worsen vasogenic edema. This complicates the search for the ideal drug because in human brain disorders the two kinds of brain edema usually coexist (although one may dominate depending on the specific disorder).

INSULATION AND PROTECTION OF AXONS

Oligodendrocytes and Schwann Cells

The myelin sheaths, which insulate axons, are formed by oligodendrocytes[2] in the CNS and by Schwann cells in the PNS. Although the structure and function of the myelin sheaths they produce are the same, oligodendrocytes and Schwann cells are not identical. One difference is that a single oligodendrocyte usually sends out processes to produce myelin segments for several axons (up to 40), whereas each Schwann cell forms a myelin segment for only one axon (Fig. 2.6). A particularly interesting difference concerns their differential influence on **regeneration** of damaged axons. In the PNS, a cut axon can regenerate under favorable conditions, provided that viable Schwann cells are present. In the CNS, however, such regeneration of axons does not normally occur, mainly because of inhibiting factors produced by oligodendrocytes.

In addition to forming myelin sheaths, oligodendrocytes and Schwann cells are important for **survival of the axons**. Thus, diseases affecting oligodendrocytes or Schwann cells produce axonal loss in addition to loss of myelin. In addition, oligodendrocytes and Schwann cells influence axonal thickness and **axonal transport**.

Differences between Oligodendrocytes and Schwann Cells

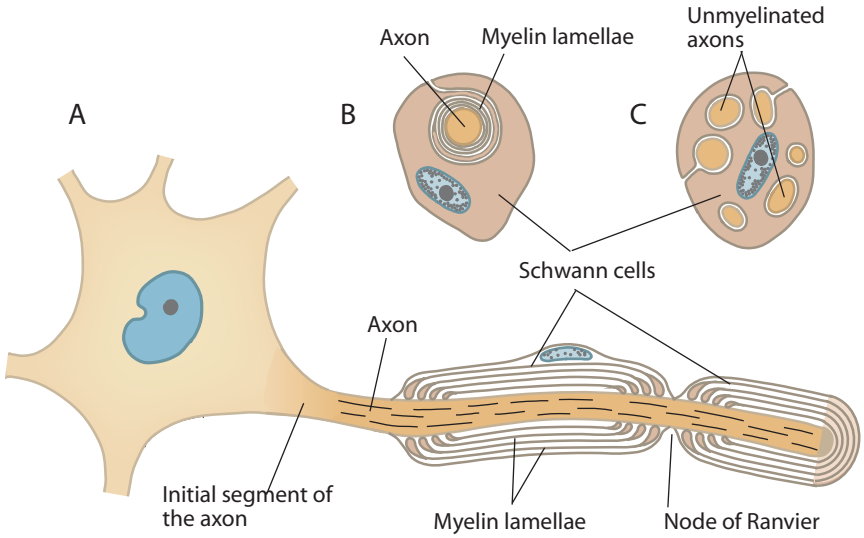
Even though the myelin sheaths produced by oligodendroglial cells and by Schwann cells look the same, they differ significantly in their lipid and protein composition. For example, myelin basic protein (MBP) makes up a much larger fraction of the total myelin protein in the CNS than in the PNS, whereas **peripheral myelin protein-22** (PMP-22) is absent in the CNS. Another example is **myelin-oligodendrocyte glycoprotein** (MOG), which is expressed in the CNS only. Such differences may help explain why some diseases affect only myelinated axons in the CNS (e.g., multiple sclerosis), whereas others are restricted to peripheral axons.

The Myelin Sheath

The **myelin sheath** forms an insulating cylinder around the axons (Fig. 2.6), reducing the loss of current from the axon to the surrounding tissue fluid during impulse conduction.

2. We do not know whether *all* oligodendrocytes form myelin. Thus, their cell bodies are often closely apposed to neuronal cell bodies, suggesting that they may have other tasks in addition to myelination.

Figure 2.6



Myelin sheath, myelination, and unmyelinated axons. Schematics based on electron microscopic observations. **A:** Cell body with proximal parts of the dendrites and myelinated axon. The myelin sheath consists of lamellae formed by the membrane of glial cells (oligodendroglia, or Schwann cells). Each cell produces one segment of myelin. The node of Ranvier is the site of contact between two segments of myelin. The nerve impulse usually starts in the initial segment of the axon and then "jumps" from one node of Ranvier to the next. **B:** Cross section of an axon in the process of becoming myelinated. The myelin sheath is formed when a glial cell wraps itself around the axon. **C:** Unmyelinated axons in the peripheral nervous system are surrounded by Schwann cell cytoplasm.

This contributes to the much higher conduction velocity in myelinated axons than in unmyelinated axons (discussed further in Chapter 3 under "Impulse Conduction in Unmyelinated Axons" and "Impulse Conduction in Myelinated Axons"). The thickest myelinated axons conduct at approximately 120 m/sec (versus less than 1 m/sec in unmyelinated axons).

The myelin sheath consists almost exclusively of numerous layers of cell membrane, as evident from electron micrographs (Figs. 2.6 and 2.7). The layers, or **lamellae**, are formed when a glial cell wraps itself around the axon (Fig. 2.6B). During this process, the cytoplasm of the glial cell is squeezed away so that the layers of cell membrane lie closely apposed. The composite of material ensheathing the axons is called **myelin**. Myelin is whitish in color because of its high lipid content.

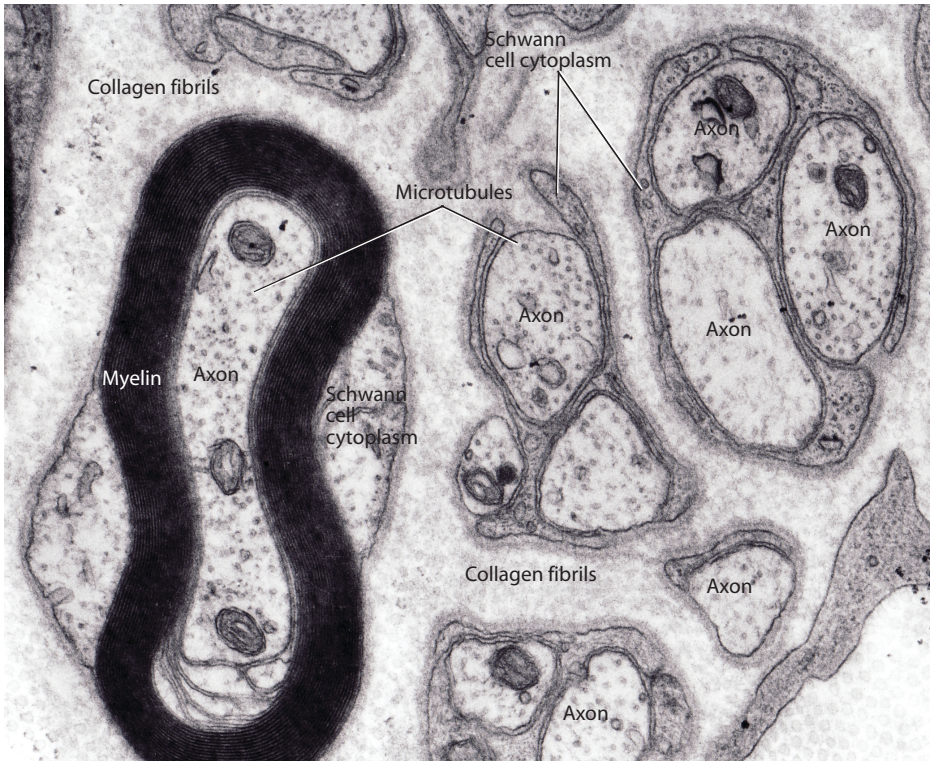
The cell membrane forming the myelin has a unique lipid and protein composition. Among other components, myelin has a high content of cholesterol and various **glycolipids**. The glycolipids appear to be crucial for the insulating properties of myelin. Certain **membrane proteins** related to the immunoglobulins bind the external (apposing) sides of the membranes tightly together. Another membrane protein, **myelin basic protein** (MBP), seals the cytoplasmic sides of the membranes in the myelin lamellae so that very little cytoplasm (with poor insulating properties) takes up space in the myelin sheath. Mice with a mutation of the *MBP* gene make abnormal myelin and develop serious movement disorders.

Myelination of the axons starts prenatally, but many neural pathways in the human are not fully myelinated until 2 years after birth (see Chapter 9, under "Myelination Is Required for Neuronal Connections to Function Optimally"). The process of myelination is closely related to functional maturation of the brain. Furthermore, myelination seems to be **use-dependent**. For example, stimulation of the premotor cortex in mice increased production of oligodendrocytes and myelination and improved motor function of the corresponding limb. Thus, the improved performance associated with meaningful use of neuronal networks may depend not only on synaptic changes but also on faster and more reliable signal conduction.

Nodes of Ranvier

Longitudinal views of axons show that the myelin sheath is interrupted at intervals, forming the **nodes of Ranvier**

Figure 2.7



Myelinated and unmyelinated axons. (Detail from Fig. 2.8.) An axon is surrounded by myelin. The myelin lamellae are seen as dark stripes, arranged concentrically. The cytoplasm of the Schwann cell that is responsible for producing the myelin is seen externally. The unmyelinated axons are completely surrounded by Schwann cells. Between the axons are numerous collagen fibrils. Magnification, ×30,000.

(Fig. 2.6A). The nodes of Ranvier exist because the glial cells forming myelin lie in a row along the axon, each cell making myelin only for a restricted length, or segment, of the axon. When viewed with an electron microscope, the axolemma (the axonal membrane) is "naked" at the node; that is, it is exposed to the ECF. Thus, only at the node of Ranvier can current in the form of ions pass from the axon to the ECF (and in the opposite direction). This arrangement makes it possible for the nerve impulse to "jump" from node to node, thus increasing the speed of impulse propagation (discussed further in Chapter 3). The distance between two nodes of Ranvier in the PNS may be 0.5 mm or greater.

Multiple Sclerosis

In **demyelinating diseases** of the nervous system, the myelin sheaths degenerate. The most common of these diseases is **multiple sclerosis** (MS), which typically manifests in young adults and usually has a long course of increasing disability. Its cause is still unknown, but most likely environmental factors precipitate an inflammatory process in individuals with a certain inherited susceptibility. Histopathologically, isolated and apparently randomly distributed regions of inflammation and demyelination are characteristic. In these regions, called **plaques**, impulse conduction in the axons is severely slowed or halted, and usually the symptoms are ascribed to the loss of myelin. For some reason, the optic nerve is often the first to be affected, resulting in disturbed vision. Later symptoms that usually occur in varying proportions are muscle weakness, lack of coordination, and sensory disturbances. In most patients, exacerbations of the symptoms occur episodically in the beginning, associated with fluctuation in the inflammatory process. Thus, periods of marked symptoms (such as paresis of extremities) are followed by periods of partial recovery. The improvement of symptoms is ascribed to partial remyelination of the affected regions. After a variable time (often many years), the disease becomes progressive, with a steady deterioration of the patient's condition.

There is not always a clear relationship between degree of demyelination and symptoms, suggesting that the disease process also directly harms axonal conductance and axonal viability. Indeed, it is now well established that in MS not only myelin sheets but also axons degenerate from the beginning of the disease. Presumably, the number of axons lost at early stages is modest and brain plasticity may compensate for their loss. As the disease progresses, however, the axon loss becomes so large that permanent and steadily progressing disability ensues.

Intense research activity is devoted to clarifying the etiology and pathogenesis of MS. Although clearly the disease process includes both inflammation and degeneration, it was long held that inflammation was the primary phenomenon (perhaps evoked by

autoimmunity) and that loss of nervous tissue was secondary. This is now being questioned, however. Thus, it seems possible that "people who develop multiple sclerosis will be shown to have a (genetically determined) diathesis [disease disposition] that does indeed predispose to neurodegeneration . . . but the exposure of that vulnerability requires an inflammatory insult without which the degenerative component does not manifest" (Compston, 2006, p. 563).

With regard to the inflammatory process, **T lymphocytes**, **microglial cells**, **brain endothelial cells**, and numerous **immune mediators** are involved, but their relative contributions are not fully understood. The role of microglia in the disease process illustrates the complexity: they may contribute both to destruction of myelin and axons and to regenerative processes (such as remyelination), presumably depending on the local situation.

Most current **therapies** aim at systemic **immune modulation** and appear to reduce significantly the frequency of disease episodes (relapses). Autologous stem cell transplantation—aiming to replace pathogenic T-cell populations—is now a promising option for patients with aggressive, relapsing MS.

Unmyelinated Axons

As mentioned, unmyelinated axons conduct much more slowly (at less than 1 m/sec) than myelinated ones, because they are thinner and lack the extra insulation provided by the myelin sheath. In the CNS, unmyelinated axons often lie in closely packed bundles without any glial cells separating them (see Fig. 1.7B). In the PNS, however, unmyelinated axons are always ensheathed in Schwann cells that do not make layers of myelin (Figs. 2.6, 2.7, and 2.8). During early development, several axons become embedded in the cytoplasm of the Schwann cells by invagination of the Schwann cell membrane. This arrangement probably serves to protect the axon from harmful substances in the interstitial fluid. Such protection may not be necessary in the CNS, as the composition of the interstitial fluid is governed by astroglia cells and by the blood–brain barrier.

Peripheral Nerves Are Built for Protection of the Axons

Fresh nervous tissue is soft, almost jellylike, with virtually no mechanical strength in itself. Protection of the CNS against external mechanical forces is afforded by its location within the skull and the vertebral canal and by its "wrapping" in membranes of connective tissue. For peripheral parts of the nervous system, the situation is different. Often located superficially, the peripheral bundles of axons and groups of nerve cells are exposed to various mechanical stresses. They are also subject to considerable stretching forces by movements of the body. Axons can be stretched only slightly before their impulse conduction suffers, and they may even break. To prevent this, peripheral nerves contain large amounts of dense connective tissue with numerous collagen fibers arranged largely longitudinally (Fig. 2.7). The collagen fibers, specialized to resist stretching, protect the axons effectively. The presence of connective tissue in peripheral nerves is the reason that the nerves become much thicker where they leave the skull or the vertebral canal.

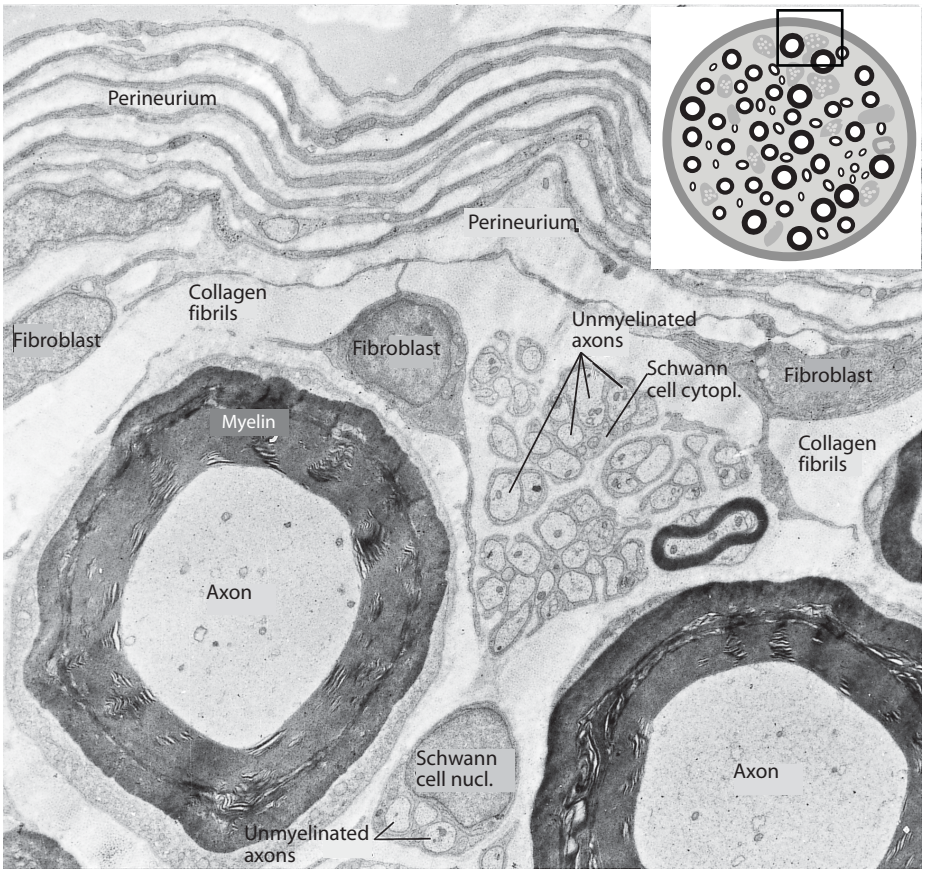
The connective tissue components of peripheral nerves form distinctive layers. The **epineurium** is an external thick layer of mostly longitudinally running collagen fibers. Internal to this layer, the axons are arranged into smaller bundles, or **fascicles**, which are wrapped in the perineural sheath or **perineurium** (Fig. 2.8). The collagen fibers and fibroblasts within the fascicles constitute the **endoneurium**. The perineurium is special in that it contains several layers of flattened cells. The cells, which in some respects resemble epithelial cells, interconnect through various kinds of junctions. In addition, the capillaries within the endoneurium are unusually tight and prevent passage of many substances from reaching the axons, consistent with experimental data showing that the perineurium constitutes a **blood–nerve barrier** preventing certain substances from reaching the interior of the fascicles with the axons. It is not surprising that PNS tissue also needs extra protective mechanisms to ensure that its environment is kept optimal for conducting impulses. The protection is not as efficient as in the CNS, however, and may perhaps explain why peripheral nerves are often subject to diseases that affect their conductive properties.

Diseases of Peripheral Nerves

Diseases involving peripheral nerves are called **neuropathies** and can have various causes. Whatever the cause, the symptoms are due to transitory or permanent disturbances of impulse conduction. Often there is a mixture of loss of axons and remaining axons that become hyperexcitable and spontaneously active. The latter evokes **paresthesias** (abnormal, nonpainful sensations such as tingling, pricking, vibration, coldness, and so forth) and (sometimes) persistent pain. Loss of axons produces muscle weakness and sensory loss (but can paradoxically also give persistent pain).

Axons and their myelin sheaths express membrane proteins that are specific to whether the axons are motor or sensory, thick or thin, and so forth. Thus, it may be understandable why neuropathies often affect certain nerves only or certain kinds of axons only. When motor axons are affected, the patient presents with pareses in certain muscles, while affection of sensory axons might produce loss of cutaneous sensation and joint sense. Neuropathies may also affect subgroups of sensory axons, for example, affecting only the very thin axons mediating sensations of pain and temperature but sparing axons related to touch. In other cases, only axons mediating joint sense are affected, whereas cutaneous sensation is spared (examples are

Figure 2.8



Peripheral nerve. Electron micrograph of cross section of the sciatic nerve. The picture shows a small, peripheral part of a nerve fascicle. The perineurium surrounding the fascicle is formed by several lamellae of flattened cells. Note the large difference in diameter among various myelinated axons. The thickness of the myelin sheath increases apace with the increase in axonal diameter. Between the myelinated axons are numerous unmyelinated ones. Collagen fibrils, produced by fibroblasts, fill most of the space between the axons. Magnification, ×4,000.

described in Chapter 13, under "Clinical Examples of Loss of Somatosensory Information").

Neuropathy is a well-known complication of metabolic diseases such as **diabetes** but can also be caused by toxic substances (e.g., lead). **Alcohol** abuse is a common cause of neuropathy. It is also a common side effect of **cytotoxic drugs** used for cancer treatment. Some neuropathies are due to attacks of the **immune system** on axons or myelin. This sometimes occurs after an infectious disease or in the course of cancer, probably because the immune system produces antibodies that cross-react with normal antigens expressed by axonal or Schwann cell membranes. An example is the **Guillan-Barré Syndrome** (acute inflammatory demyelinating polyradiculitis) that affects primarily the nerve roots (see Figs. 6.5 and 6.6). The disease usually starts with pareses and paresthesias in distal parts of the legs but ascends gradually to affect both extremities and sometimes the whole body.

A large group of neuropathies is **inherited**, among them, **Charcot–Marie–Tooth disease** (peroneal muscle atrophy). In most cases, the disease is inherited dominantly. The disease usually starts before the age of 20 years and leads to gradually increasing pareses and sensory loss, starting distally in the legs. Loss of myelin and degeneration of axons cause the symptoms. Most patients with Charcot–Marie–Tooth disease have a doubling of the gene coding for the peripheral myelin protein **(PMP-22)**. Animal models with overexpression of PMP-22 suggest that this defect alone can cause deficient myelination and symptoms corresponding to Charcot–Marie–Tooth disease in humans.

MICROGLIA AND REACTIONS OF THE CNS TO INJURY

Microglial Cells Monitor the Nervous Tissue

The third kind of glial cell, **microglia**, is so named because of its small size. Studies with immunocytochemical identification of specific membrane proteins show unequivocally

that microglial cells constitute a distinct kind. Estimates indicate that microglia may constitute 5% to 20% of all glial cells and are fairly evenly distributed through all parts of the CNS. As with astrocytes, recent research has increased the list of possible tasks of microglial cells. They now are implicated in, among others, maintenance and regulation of synapses, persistent pain, and neurodegenerative diseases.

Microglial cells are of **mesodermal** origin. Thus, animal experiments indicate that **monocytes** invade the nervous system from the bone marrow during embryonic development and perhaps shortly after birth. This may correspond with periods of high rate of cell death (a surplus of neurons is formed in early embryonic life, with subsequent elimination of a large number). After invading nervous tissue, the monocytes undergo changes—such as development of processes—that transform them to microglial cells, as identified in the adult. Nevertheless, microglial cells retain the typical **phagocytic** capacity of monocytes. Further, several surface markers (antigens) are common to blood monocytes and microglia, and cells that express such antigens first occur in the CNS (of rodents) in late embryonic development.

The number of microglial cells is relatively stable after the prenatal invasion. Under normal conditions, the stock of microglial cells does not appear to be supplemented from the bloodstream. After **injury**, however, the number of cells with phagocytic activity (macrophages) increases in the CNS. The increase appears to be due both to invasion of monocytes from the bloodstream and to activation of local microglial cells. The invasion of monocytes after injury probably depends on damage to the **blood–brain barrier** (i.e., brain capillaries allow passage of elements of the blood they normally restrict).

In the **normal brain**, microglial cells are probably not solely in a "resting" state in anticipation of challenges (e.g., intruding microorganisms, trauma, ischemia, and so forth). Thus, their processes are steadily moving and renewed and are therefore believed to constantly **"scan"** their immediate environment for foreign material and sick or dead cellular elements. In addition, microglial cells are equipped with receptors for several neurotransmitters, suggesting that they also may sense the state of neuronal activity in their vicinity. For example, microglia helps remove unwanted synapses, thus contributing to use-dependent plasticity. If they detect something unusual, more microglial cells move quickly to the site. They release inflammatory mediators and phagocytose foreign or dead material. These responses of microglial cells generally serve to minimize damage and protect neurons; that is, microglial cells serve to conserve **homeostasis.** For example, animal experiments show that the presence of microglial cells reduces ischemic brain damage (after loss of blood supply). Removal of dead material by microglia seems to be necessary for regeneration of neuronal processes to occur.

Nevertheless, in certain diseases with strong activation of microglial cells (and astrocytes), the glial cells promote tissue injury rather than repair. This concerns **Alzheimer's** disease and **Parkinson's** disease. Furthermore, it seems that microglial activity may enhance neuronal excitability in **epilepsy**. Activation of microglial cells in the spinal cord also seems to contribute to persistence of **pain** after nerve damage (neuropathic pain).

Reaction of Nervous Tissue to Injury and Inflammation

Tissue damage leads to an inflammatory reaction in which the invasion and activation of immunocompetent cells have a central role. The purpose of the invasion is to kill microorganisms, remove debris, and aid reparative processes. However, the inflammatory reaction is different in the CNS than in other tissues. Thus, there is often no invasion of neutrophil granulocytes, and the activation of microglia and invading monocytes to macrophages may take several days. Overall, immune reactions are weaker and slower in the CNS than elsewhere. This may be explained—at least in part—by the lack of lymphatic drainage from the CNS. The immune system, therefore, does not possess much information about nervous tissue conditions, in contrast to tissues of most other organs. Normally, only a small number of T lymphocytes and monocytes, entering from the bloodstream, patrol the CNS. Perhaps these special conditions are necessary to prevent neuronal damage from the potent substances that are liberated from granulocytes and activated macrophages. For example, edema—a central component of inflammation—may become harmful and even life-threatening when it occurs in the brain (because of the limited possibilities of expansion within the skull). Nevertheless, immune reactions *do* occur in the brain, sometimes with serious consequences, as in MS. In such cases, opening of the blood–brain barrier, which normally prevents granulocytes from entering, worsens the situation.

The main task of **astrocytes** after injury is probably to strengthen their normal function of keeping the ECF composition constant. Tissue damage—regardless of whether

it is caused by bleeding, contusion, or circulatory arrest—increases the flow of ions and transmitters from the neurons to the ECF. Astrocytes increase their uptake to counteract such disturbances of the neuronal environment. Because the substances taken up are osmotically active, the astrocytes may swell quickly—seconds or minutes after the damage (if the normal uptake capacity is surpassed). This may contribute to brain edema, a dangerous complication of head injuries. In the long term, astrocytes produce a kind of **scar tissue** at sites where neurons are lost.

In Chapters 9 and 11 we discuss the plastic processes of the nervous system that permit functional recovery after injuries (such as stroke).

AIDS and the CNS

AIDS (Acquired Immune Deficiency Syndrome), caused by **HIV** (Human Immune Deficiency Virus) also affects the nervous system. Even though HIV does not infect neurons, the disease causes considerable neuronal death (even in the absence of other CNS infections). Patients may suffer from impairments of movement, sensation, and cognition. The virus probably enters the CNS via infected T lymphocytes (as mentioned, a small number of T lymphocytes and monocytes patrol the brain). Microglial cells then become infected because they express on their surface the CD4 antigen that binds HIV. After being infected, microglial cells secrete toxic substances that kill neurons, perhaps by binding to NMDA receptors (see Chapter 5, under "NMDA Receptors: Mediators of Both Learning and Neuronal Damage").

3 Neuronal Excitability

OVERVIEW

In Chapter 1 we considered some of the characteristic properties of neurons, such as their excitability and their ability to conduct impulses. The term **excitability** means that when a cell is sufficiently stimulated, it can react with a brief electrical discharge, called an action potential. The **action potential** (the nerve impulse) travels along the axon and is a major component in the communication among nerve cells and between nerve cells and other cells of the body. The action potential results from movement of charged particles—ions—through the cell membrane. A prerequisite for such a current across the membrane is an electric potential—the **membrane potential**—between the interior and the exterior of the cell and the presence of **ion channels** that are more or less selective for the passage of particular ions. The opening of ion channels is controlled by neurotransmitters binding to the channel (**transmitter** or **ligand-gated channels**) or by the magnitude of the membrane potential (**voltage-gated channels**). The membrane potential results from an unequal distribution of positively and negatively charged particles on either side of the membrane.[1] Energy-requiring **ion pumps** are responsible for maintaining the membrane potential. The **resting potential**, that is, the membrane potential when the neuron is not receiving any stimulation, is due mainly to unequal distribution of K^+ ions and the fact that the membrane is virtually impermeable to all ions other than K^+ in the resting state. The resting potential, with the interior of the cell negative compared with the exterior, is typically approximately −60 mV (millivolts). The **action potential** is a brief change of the membrane potential, caused by opening of channels that allow cations (especially Na^+) to enter the neuron, followed by an outward flow of K^+ ions. A net influx of cations reduces the membrane potential by making the interior less negative. This is called **depolarization**, and if it is sufficiently strong, an action potential is elicited due to opening of voltage-gated Na^+ channels. After the brief depolarization caused by influx of Na^+ ions, the membrane potential is restored by the outward flow of K^+ ions. Restoration of the membrane potential is called **repolarization**. An increase of the membrane potential—**hyperpolarization**—makes the neuron less excitable (more depolarization is necessary to elicit an action potential). During a short period of time after an action potential, the membrane is in a **refractory state**, which means that another action potential cannot be elicited. This ensures that neurons can maintain the correct ion concentration balance.

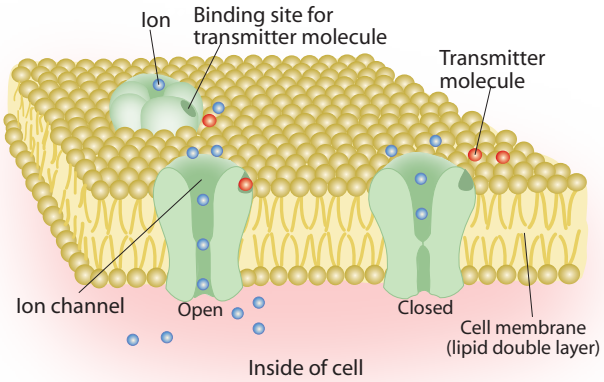
Once an action potential is elicited, it is conducted along the axon. This is not merely a passive movement of charged particles in the fluid inside the axon. Because axons are poor conductors (compared with a metal thread), the action potential has to be renewed along the axonal membrane by cycles of depolarization and repolarization. In **unmyelinated** axons, these cycles move along the axon as a continuous wave, while in **myelinated** axons renewal of the action potential occurs only at the **nodes of Ranvier**. Because the process of depolarization–repolarization takes some time, the speed of conduction is much slower in unmyelinated axons than in myelinated ones. The action potential, when first elicited, is of the same magnitude. Neurons are nevertheless able to vary their messages because of the varying frequency and pattern of action potentials. Generally, the more synaptic inputs depolarize a neuron, the higher the frequency of axonal action potentials.

BASIS OF EXCITABILITY

The most basic property of neurons is their **excitability**—that is, their ability to respond to stimuli with an electric discharge. The discharges of billion of neurons can be recorded by placing electrodes on the head (electroencephalography [EEG]). Indeed, a "flat" EEG is used as a criterion of **brain death**, because it tells us that there are no functioning neurons left. The neuronal excitability is determined by properties of the cell membrane and active mechanisms creating and maintaining different concentrations of electrically charged particles (ions) inside and outside the cell.

1. Neither membrane potentials nor action potentials are properties unique to nerve cells. All cells have a membrane potential, although usually of less magnitude than that of neurons. Muscle cells and endocrine gland cells also produce action potentials in relation to contraction and secretion, respectively.

Figure 3.1



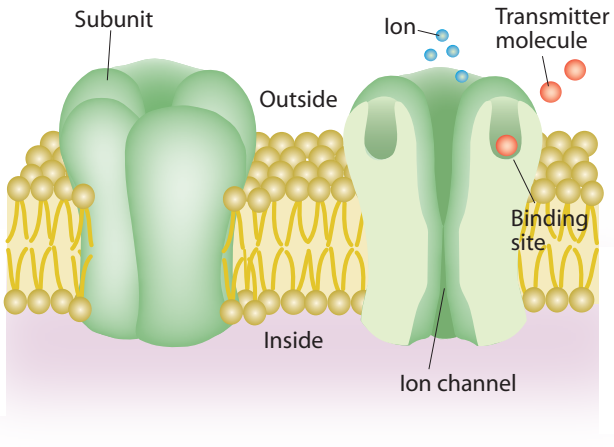
Ion channels. Schematic of a small part of the lipid bilayer of the cell membrane with interspersed ion channels. Binding of a transmitter molecule alters the opening state of the ion channel.

Cell Membrane Permeability Is Determined by Ion Channels

Ions cross the cell membrane almost exclusively through specific, water-filled channels because their electrical charges prevent them from passing through the lipid bilayer (Figs. 3.1 and 3.2). The channels are more or less **selective** for particular ions; that is, some ions pass more easily through a channel than others. Some channels are very selective, allowing passage of only one kind of ion (e.g., Na^+ ions), whereas other channels are less selective (e.g., letting through several cations such as Na^+, K^+, and Ca^{2+}). It follows that the ease with which an ion can pass through the membrane—that is, the **membrane permeability**[2] to that particular kind of ion—depends on (a) the presence of channels that let the ion through, (b) how densely these channels are distributed in the membrane, and (c) their opening state.

The current of ions through the membrane, however, does not depend solely on the density and opening of channels; an additional important factor is the **concentration gradient** across the membrane for the ion. That is, the steeper the gradient, the greater the flow of ions from high to low concentration (provided that the membrane is not totally impermeable to the ion). Further, because ions are electrically charged particles, the **voltage gradient** across the membrane (i.e., the membrane potential) will also be important (Fig. 3.3). This means that if the interior of the cell is negative in relation to the exterior, the **cations**

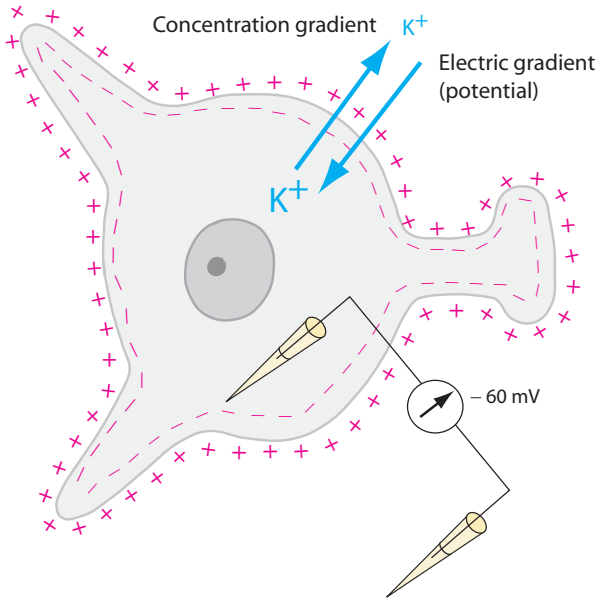
Figure 3.2



Ion channels. Five protein subunits are arranged around a central opening that can admit ions. At the outer side, the channel proteins are equipped with receptor sites for neurotransmitter molecules that regulate the opening of the channel. The figure shows the probable appearance of an acetylcholine receptor. (Based on Changeux 1993.)

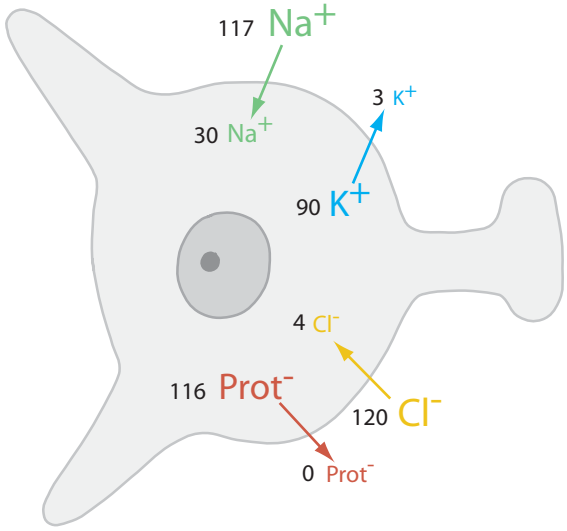
2. The term **conductance** expresses the membrane permeability of a particular kind of ion more precisely. The conductance is the inverse of the membrane resistance. In an electrical circuit the current is $I = V/R$, where V is the voltage and R is the resistance (Ohm's law). This may be rewritten by using conductance (g) instead of R, as $I = g \bullet V$. In this way, one may obtain quantitative measures of membrane permeability under various conditions. For our purpose, however, it is sufficient to use the less precise term "permeability."

Figure 3.3



Forces acting on the K⁺ ions. At the resting potential there is equilibrium between the inward and outward forces (large arrows) acting on the K⁺ ions. One intracellular and one extracellular electrode (cones) measure the membrane potential.

Figure 3.4



Distribution of ions of particular importance for the membrane potential. The exact concentrations depend on the resting potential (in this case –85 mV). Concentrations in mM.

(positively charged ions) on the exterior will be exposed to a force that attracts them into the cell, while the interior cations will be subjected to forces that tend to drive them out. The strength of these attractive and expulsive forces depends on the magnitude of the membrane potential. Therefore, the concentration gradient and the membrane potential together determine the flow of a particular ion through the membrane (Fig. 3.3).

The Membrane Potential and the Equilibrium Potential of Ions

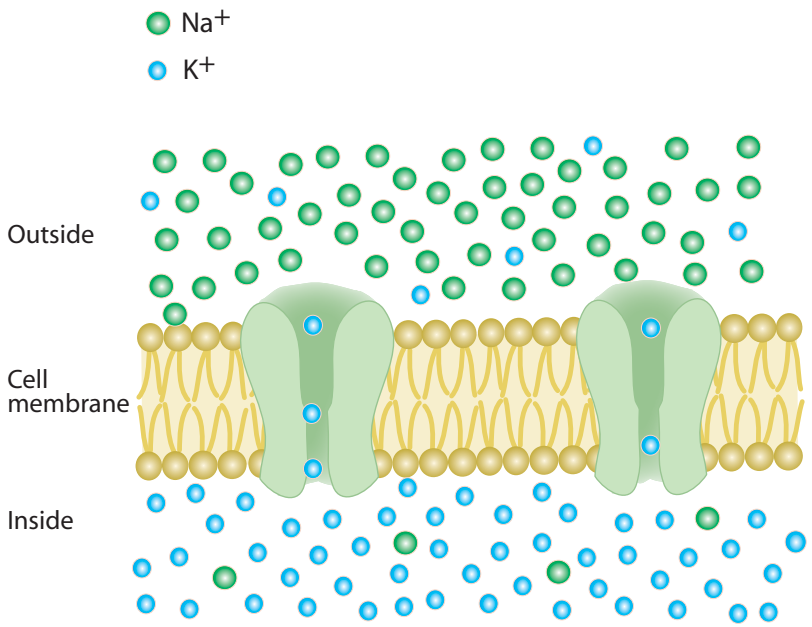
In a typical nerve cell, the potential across the cell membrane is stable at approximately 60 mV in the resting state, that is, as long as the cell is not exposed to any stimuli. We therefore use the term **resting potential** in this situation (in different kinds of nerve cells, the resting potential may vary from about 45 mV to approximately 75 mV). The resting potential is due to a small surplus of negatively charged ions, **anions**, inside the cell versus the outside, and it has arbitrarily been decided to define the resting potential as negative, for example, –60 mV (Fig. 3.3).

The resting potential is caused primarily by two factors:

1. The **concentration of K⁺ ions** is about 30 times higher inside than outside the cell (Figs. 3.4 and 3.5).
2. The cell membrane is **selectively permeable** to K⁺ ions in the resting state (Fig. 3.5); that is, no other ions pass the membrane with comparable ease (the membrane is about 50 times more permeable to K⁺ than to Na⁺).

Although the concentration differs greatly inside and outside the cell for ions other than K⁺ (Fig. 3.4), the membrane is, as mentioned, almost impermeable to them (there are, e.g., very few open Na⁺ channels in the resting state). Other ions therefore influence the resting membrane potential only slightly. Therefore, to explain the membrane potential we can, for the time being, ignore ions other than K⁺. The concentration gradient will tend to drive K⁺ out of the cell, and, further, K⁺ ions can pass the membrane with relative ease through a particular kind of potassium channel that is open in the resting state. This means that positive charges are lost from the interior of the cell, making the interior negative compared to the exterior, thereby creating a membrane potential. The membrane potential reaches only a certain value, however, because it will oppose the movement of K⁺ ions out of the cell. Two opposite forces are at work: the concentration gradient tending to drive K⁺ out of the cell and the electrical gradient (the membrane

Figure 3.5



The unequal distribution of K^+ and Na^+ ions, together with open K^+ channels, largely explain the resting membrane potential.

potential) tending to drive K^+ into the cell (Fig. 3.3). When the membrane potential is about −75 mV, these two forces are equally strong: that is, the flow of K^+ into the cell equals the flow out. This is therefore called the **equilibrium potential for K^+**, and its magnitude is determined by the concentration gradient for K^+ ions (the concentration gradient varies somewhat among neurons).

The resting potential in most neurons, however, is lower than the equilibrium potential for K^+ because the cell membrane is slightly permeable to Na^+ (about 1/50th of the permeability to K^+). Therefore, some positive charges (Na^+) pass into the cell, driven by both the concentration gradient and the membrane potential, making the interior of the cell less negative than the equilibrium potential for K^+. The membrane potential is consequently changed somewhat in the direction of the **equilibrium potential for Na^+**: that is, +55 mV. In the resting state, the inflow of positive charges is equal to their outflow, and the membrane potential is therefore stable. Even though the two opposite currents of K^+ and Na^+ are small, over time they would eliminate the concentration gradients across the membrane. This is prevented, however, by energy-requiring "pumps" in the cell membrane that actively transport ions through the membrane against a concentration gradient. This **sodium–potassium pump** expels Na^+ ions from the interior, in exchange for K^+, at the same rate that the ions leak through the membrane. In this way, the concentration gradients across the cell membrane are maintained.

Recording of Single-Cell Activity

Microelectrodes, with tips less than 1 µm thick, can be used to record the activity of single neurons and their processes (single units) intracellularly. Among other benefits, this has made it possible to study in detail the electrical events at the synapses and how they are influenced by various experimental manipulations. The effects of different concentrations of intra- and extracellular ions have been studied, as have the synaptic effects of various transmitter candidates and drugs. The **voltage clamp** technique, which permits manipulation of the membrane potential, has been instrumental to our understanding of the properties of synapses and the basic mechanisms underlying their operations. Likewise, great progress has been made with the **patch clamp technique**, making possible measurements of ion currents limited to even a single ion channel. The study of the properties of ion channels and membrane receptors is today highly interdisciplinary. **Implanted extracellular electrodes** can be used to record the activity of single neurons in relation to specific stimuli or behavioral tasks. This method has, for example, provided new insight into functional specializations within various areas of the cerebral cortex. By combining anatomic and physiologic techniques, it has been possible to determine the functional properties of structurally defined cell types. After an intracellular recording has been made from a neuronal cell body or its axon, it can be filled with a tracer substance through the same pipette. Afterward, the neuron with all its processes can be visualized in sections.

Anions Are Also Unevenly Distributed

For simplicity, we have so far dealt with only two cations, K^+ and Na^+, because they are the most important ones for the membrane potential and also for the action potential (discussed later in this chapter). Nevertheless, there are as many anions as cations. Chloride ions (Cl^-) and negatively charged protein molecules ($Prot^-$) are the major anions (Fig. 3.4). These ions are also unevenly distributed across the cell membrane: the concentration of Cl^- is 20 to 30 times higher outside than inside the cell, whereas the opposite situation exists for $Prot^-$. Therefore, **chloride** is the major extracellular anion, whereas **proteins** are the major intracellular ones. The proteins are so large that they cannot pass through the membrane; the membrane is impermeable to protein molecules. The membrane is somewhat permeable to Cl^-, however. The concentration gradient tends to drive chloride into the cell, whereas the membrane potential tends to drive it out, making the net flow of Cl^- small. In fact, the **equilibrium potential for Cl^-**, −65 mV, is close to the resting potential of most nerve cells. Therefore, no active mechanism for pumping of chloride is needed.

The Sodium–Potassium Pump and Osmotic Equilibrium

All cells depend on the sodium–potassium pump to maintain the membrane potential and osmotic equilibrium between the intracellular and extracellular fluid compartments. Particular to neurons is their need for increased pumping in association with the firing of action potentials, which arise because of a current of Na^+ into the cell and of K^+ out of it. The speed of pumping increases with increasing intracellular Na^+ concentration. A significant part of our energy in the form of ATP is spent on driving the sodium–potassium pump. In the resting state of nerve cells, this may constitute approximately one-third of the total energy requirement, whereas after high-frequency trains of action potentials it may increase to two-thirds.

The unequal distribution of ions is of fundamental importance also for the ability of neurons to maintain **osmotic equilibrium**. The distribution of ions must be such that the total concentrations of water-dissolved particles are equal inside and outside the cell. In other words, osmotic equilibrium means that the **water concentration** is equal inside and outside the cell (osmosis is the movement of water molecules from sites of high water concentration to sites of low water concentration). In case of osmotic imbalance, the cell will either swell or shrink (depending on whether the water concentration is lower inside or outside, respectively). An essential condition for osmotic balance is the low resting membrane permeability to Na^+, as both the concentration gradient and the membrane potential tend to drive Na^+ into the cell. This situation changes dramatically when the cells fire action potentials, because the membrane then becomes highly permeable to Na^+. Long trains of high-frequency action potentials may threaten the osmotic balance because more Na^+ ions enter the cell than can be pumped out. Fortunately, neurons have properties that limit their maximal firing rate and the duration of active periods. Under pathological conditions, however, these safeguards may fail. In severe **epileptic seizures**, for example, neurons fire with abnormal frequency for long periods, and this probably contributes to cell damage by causing osmotic imbalance. Further, in situations with insufficient blood supply (ischemia), for example, after a **stroke**, ATP production suffers, resulting in slowing of the sodium–potassium pump. This, in turn, leads to osmotic imbalance and swelling of neurons. Such swelling is dangerous because neurons may be injured directly but also because swelling of the brain inside the skull (**brain edema**) reduces the blood supply.

Transmitter-Gated Ion Channels

Neurotransmitters control neuronal excitability by changing the opening state of ion channels (Figs. 3.1 and 3.2). A channel that is controlled by neurotransmitters (or other chemical substances) is called **transmitter-gated** or **ligand-gated** (the term "transmitter-activated" is also used). A large number of ion channels are now characterized that differ with regard to ion selectivity and transmitter specificity, that is, the ions that can pass a channel and the transmitter that controls it. The transmitter can either bind **directly** to the channel proteins or act **indirectly** via chemical intermediates (this is treated further in Chapter 4, under "Transmitters Act on Ionotropic and Metabotropic Receptors"). In most known cases, the transmitter opens the channel to increase the permeability of the relevant ions. We consider here only the effects of directly acting neurotransmitters (indirect effects are discussed later in this chapter). Binding of a transmitter molecule to a specific **receptor site** at the external face of a channel polypeptide may change the form of the polypeptides, thereby changing the diameter of the channel (Figs. 3.1 and 3.2). Usually, the channel is open only briefly after the binding of a transmitter molecule, allowing a brief current of ions to pass through the membrane. In this way, a chemical signal from a presynaptic neuron—the neurotransmitter—elicits an electric current through the postsynaptic membrane.

As mentioned, ion channels are more or less **selectively permeable**; that is, they let certain kinds of ions pass through more easily than others. Some channels are highly selective, allowing the passage of one kind only (such as Ca^{2+} ions), whereas others are less selective and will allow passage of, for example, most cations. Channels that are permeable for anions in general are usually termed chloride (Cl^-) channels because Cl^- is the only abundant anion that can pass through the membrane. Size and charge of the ion

influence its permeability. For example, the Na^+ ions are more hydrated (bind more water molecules) than the K^+ ion and therefore are larger (Fig. 3.5). This may explain some of their differences in permeability. By regulating the channel opening, the transmitter controls the flow of ions through the postsynaptic membrane. However, the transmitter alters only the **probability** of the channel being in an open state; it does not induce a permanent open or closed state.

Voltage-Gated Ion Channels

Many channels are not controlled primarily by chemical substances but by the magnitude of the membrane potential and are therefore called **voltage-gated**. Voltage-gated Na^+ and K^+ channels, for example, are responsible for the action potential and therefore also for the propagation of impulses in the axons. There are also several kinds of voltage-gated Ca^{2+} channels, which control many important neuronal processes, for example, the release of neurotransmitters (see Fig. 4.1).

Voltage-gated channels are responsible for the activation of nerves and muscles by external **electrical stimulation**. Electrical stimulation of a peripheral nerve may produce muscle twitches by activating motor nerve fibers, as well as sensations due to activation of sensory nerve fibers. For some channels, their opening state is controlled by neurotransmitters and the magnitude of the membrane potential—that is, they are both ligand and voltage gated. An example is the so-called **NMDA receptor** (N-methyl-D-aspartate), which is part of a Ca^{2+} channel. Binding of glutamate opens the channel but only when the membrane potential is reduced (depolarized) compared with the resting potential (the NMDA receptor is discussed in Chapter 5).

The Structure of Ion Channels

The **ligand-gated** ion channels consist of five polypeptide subunits arranged around a central pore. The subunits span the membrane and extend to the external and internal faces of the membrane (Fig. 3.2). Therefore, signal molecules inside the cell may also influence the opening of ion channels. Three families of ligand-gated channels have been identified: the **nicotinic receptor superfamily** ($GABA_A$, glycine, serotonin, and nicotinic acetylcholine receptors), the **glutamate receptor family**, and the **ionotropic ATP receptors**. As an example, members of the nicotinic receptor family consist of five equal subunits (Fig. 3.2), all contributing to the wall of the channel. The subunits are large polypeptides with molecular masses of approximately 300,000. The transmitter binds extracellularly at the transition between two subunits, but it is still unknown how the rapid binding (in less than 1 msec) produces conformational change in parts of the channel located, relatively speaking, far away. Most likely, the binding of the transmitter elicits a wave of conformational change in specific parts of the channel polypeptides. The actual opening of the channel may be caused by conformational change of just one specific amino acid.

Voltage-gated channels resemble ligand-gated ones: they consist of four subunits arranged around a central pore. The amino-acid sequence has been determined for several of the subunits, although lack of three-dimensional data has prevented clarification of the mechanisms that control their opening and ion selectivity. Presumably, subtle differences between the subunits forming the channel explain their high selectivity to particular ions.

Inherited Channelopathies

Many different genes code for channel proteins. Because ion channels determine the excitability of neurons, it is not surprising that **mutations** of such genes are associated with dysfunctions of neurons and muscle cells. Common to many such **channelopathies** is that the symptoms occur in bouts. Of particular clinical interest is that many of the channelopathies affecting neurons are associated with **epilepsy** and **migraine**. For example, mutations associated with epilepsy affect ligand-gated channels that are receptors for the neurotransmitters γ-aminobutyric acid (GABA) and acetylcholine and voltage-gated Na^+ and Ca^{2+} channels. Although channelopathies may not be the primary cause in the majority of patients with epilepsy, they may increase the susceptibility to other factors.

Mutations affecting channels gated by **glycine** (an inhibitory transmitter) are associated with abnormal **startle reactions**. This may be related to the fact that glycine is preferentially involved in inhibition of motor neurons.

Mutations of genes coding for a particular **voltage gated Ca^{2+}** channel ($Ca_v2.1$) are associated with several rare neurological diseases with disturbed synaptic transmission (the channel is necessary for synaptic transmitter release). $Ca_v2.1$ channel diseases include a certain kind of headache—**familial hemiplegic migraine**. Other mutations of the same gene are associated with **cerebellar ataxia** (jerky, uncoordinated movements) and a kind of epilepsy with **absences** (short episodes of disturbed consciousness).

Mutations of a kind of **voltage-gated potassium channel** ($K_V\alpha1.1$)—expressed in highest density around the initial segment of axons—produce abnormal repolarization of motor axons and lead to repetitive discharges. This may explain the **muscle cramps** of such patients. Mutations of **voltage-gated sodium channels** cause bursts of intense **pain** (see also Chapter 13, under

"Nociceptors, Voltage-Gated Sodium and Potassium Channels, and Inherited Channelopathies"). A number of mutations affect channels in **striated muscle** membranes, many of them associated with **myotonia** (inability to relax after a voluntary muscle contraction).

Different mutations of one gene can give different **phenotypes**, such as reduced density of channels or reduced opening probability. It is noteworthy, however, that the same mutation can produce different symptoms in different individuals, even within the same family. This strongly suggests that the genes coding for the proteins of a channel do not alone determine its final properties. Additional factors, such as the products of other genes and environmental factors, must also contribute.

Many features of channelopathies are still unexplained—that they tend to occur episodically, that the symptoms often start at a certain age (in spite of the defect being present from birth), and that some forms remit spontaneously.

Alteration of the Membrane Potential: Depolarization and Hyperpolarization

As previously mentioned, in the resting state the membrane permeability for Na^+ is low. If for some reason Na^+ channels are opened so that the permeability is increased, Na^+ ions will flow into the cell and thereby reduce the magnitude of the membrane potential. Such a reduction of the membrane potential is called **depolarization**. The membrane potential is made less negative by depolarization. Correspondingly, one may predict that when the membrane permeability for K^+ is increased, more positive charges will leave the cell and the membrane potential will become more negative than the resting potential. This is called **hyperpolarization**. The same would be achieved by opening channels for chloride ions, enabling negative charges (Cl^-) to flow into the cell, provided that the membrane potential is more negative than the resting potential of Cl^-.

In conclusion, the membrane potential is determined by the **relative permeability** of the various ions that can pass through the membrane. At rest, the membrane is permeable primarily to K^+, and the resting potential is therefore close to the equilibrium potential of K^+. Synaptic influences can change this situation by opening Na^+ channels, thereby making the permeability to Na^+ dominant. This changes the membrane potential toward the equilibrium potential of Na^+ (at 55 mV). As shown in the following discussion, the action potential is caused by a further, sudden increase in the Na^+ permeability.

Markers of Neuronal Activity

Several methods can be used to visualize the activity of neurons. One method involves intracellular injection of a **voltage-sensitive fluorescent dye**. The intensity of fluorescence (as recorded with fluorescence microscopy and advanced computer technology) gives an impression of neuronal activity at a given time. Thus, this (indirect) measure of activity can be correlated with experimental manipulation of a specific transmitter, the execution of specific tasks, and so forth.

Another method takes advantage of the fact that **optic properties** of nervous tissue change with the degree of neuronal activity. This enables the recording of slow as well as rapid changes in neuronal activity in relation to experimental influences (it has been applied, e.g., in conscious persons during neurosurgery that necessitates exposure of the cerebral cortex). Other methods enable mapping of variations in neuronal activity at the time of death in experimental animals. Cells take up intravenously injected radiolabeled **deoxyglucose** in the same way as glucose. It is not broken down, however, and therefore accumulates in the cells. Because glucose is the substrate for oxidative metabolism in the neurons, its uptake correlates with degree of neuronal activity. After exposing an animal to certain kinds of stimulation or eliciting certain behaviors, one can afterward determine with autoradiography which neuronal groups were particularly active during stimulation or at the time of certain actions.

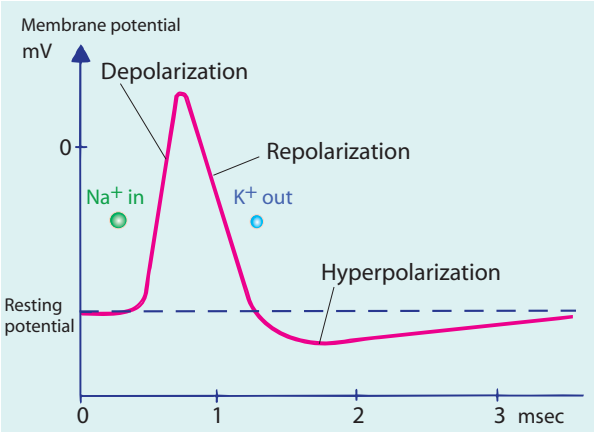
Another method utilizes the fact that a few minutes with excitatory synaptic input induces expression of so-called **immediate early-genes** in many neurons. Most studied among such genes is **c-*fos***. Without extra stimulation, C-*fos* mRNA and its protein product are present in only minute amounts in most neurons. Detection of increased levels of c-*fos* mRNA in tissue sections is therefore used as a marker of neurons that were particularly active in a certain experimental situation. This method is also used to determine where in the brain a drug exerts its effect. The method has its limitations, however. Thus, c-*fos* expression may be caused by nonspecific influences, and not all neurons express c-*fos* even when properly activated.

THE ACTION POTENTIAL

Voltage-Gated Sodium Channels Are Instrumental in Evoking an Action Potential

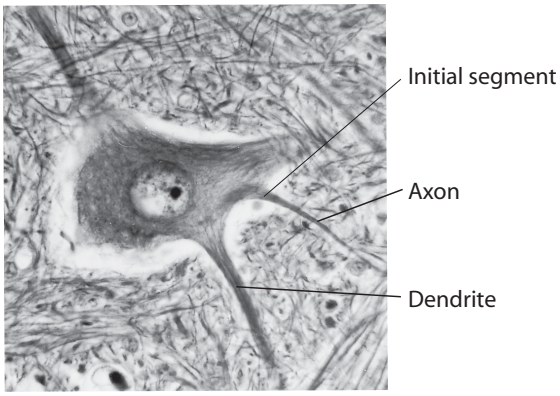
The basis of the action potential is found in the presence of **voltage-gated Na^+ channels**, which are opened by depolarization of the membrane (Fig. 3.6). Depolarization may be induced in several ways; for example, under artificial conditions by direct electrical stimulation. Normally, however, it is caused by neurotransmitters acting on transmitter-gated channels. The opening of transmitter-gated Na^+ channels often starts depolarization. Opening of the voltage-gated channels requires that the membrane be depolarized to a certain **threshold** value, that is, the threshold for producing an action potential (Fig. 3.6). When voltage-gated channels are opened, the permeability to Na^+ is increased beyond what was achieved by the opening of transmitter-gated channels, and Na^+ flows into the cell driven by both the concentration

Figure 3.6



The action potential.

Figure 3.7



The initial segment of the axon is where the action potential usually arises. Photomicrograph of a motoneuron from the spinal cord stained with a silver-impregnation method.

gradient and the membrane potential. The membrane becomes more depolarized; in turn, this opens more voltage-gated channels and so on. In this way, as soon as the membrane is depolarized to the threshold value, the permeability to Na^+ increases in an explosive manner. Even with all sodium channels fully open, however, the inward current of Na^+ ions stops when the membrane is depolarized to +55 mV; at that value the inward concentration force is equal to the outward electrical force (the membrane potential). As mentioned, +55 mV is the equilibrium potential of Na^+. Figure 3.6 shows how, during an action potential, the membrane potential quickly changes to positive values and then returns almost as rapidly to approximately the resting value. This occurs because the membrane again becomes impermeable to Na^+; the Na^+ channels are closed or **inactivated**.[3] Therefore, at the peak of the action potential and for a short time afterward, no Na^+ can pass through the membrane. In this situation with a positive membrane potential, K^+ is driven out by both the concentration gradient and the membrane potential (electrical force). Because no Na^+ can enter the cell, there is a net outward flow of positive charges, again making the interior of the cell negative. We say that the membrane is **repolarized**. The speed of repolarization is increased by the presence of **voltage-gated K^+ channels**, which open when the membrane is sufficiently depolarized. The opening of the voltage-gated K^+ channels is somewhat delayed compared with the Na^+ channels, but whereas the Na^+ channels inactivate after about 1 msec, the K^+ channels stay open for several milliseconds.

3. **Inactivation** and **closure** involve different parts of the voltage-gated Na^+ channel. This is indicated by, among other findings, that whereas closure of the channel lasts as long as the membrane potential remains below threshold, inactivation is transitory and lasts only some milliseconds.

In sum, the action potential is caused by a brief inward current of Na^+ ions, followed by an outward current of K^+ ions. The whole sequence of depolarization–repolarization is generally completed in 1 to 2 msec. If the threshold is reached, an action potential of a certain magnitude arises, regardless of the strength of the stimulus that produced the depolarization.

Where Does the Action Potential Arise?

The action potential usually arises in the first part of the axon, the **initial segment** (Fig. 3.7; see also Fig. 2.6), where the density of voltage-gated Na^+ channels is higher than in the membrane of the dendrites and the cell soma. The current spreads electrotonically (passively) from dendritic and somatic synapses toward the initial segment. If the depolarization is sufficiently strong (reaches threshold), voltage-gated Na^+ and K^+ channels open and produce an action potential that is propagated along the axon. Although action potentials can be elicited in dendrites, their threshold is usually much higher than in the initial segment owing to lower density of voltage-gated channels.

The Action Potential and Changes of Ion Concentrations

One might think that an action potential would cause significant changes in the concentrations of Na^+ and K^+ on the two sides of the membrane, but this is not the case. The number of ions actually passing through the membrane during an action potential is extremely small compared with the total number inside the cell and in its immediate surroundings. Even in an axon with a diameter of about 1 μm, with a very small intracellular volume compared to the membrane surface area, only 1 of 3,000 K^+ ions moves out during the action potential. In addition,

active pumping (the sodium–potassium pump) ensures that Na^+ is moved out and K^+ is moved in between each action potential and during periods of rest. Even when the sodium–potassium pump is blocked experimentally, a nerve cell can produce several thousand action potentials before concentration gradients are reduced so much that the cell loses its excitability.

The Refractory Period

After an action potential, some time must elapse before the neuron can again produce an action potential in response to a stimulus. The cell is said to be in a **refractory state**. This ensures at least a minimal rest for the cell between each action potential and thereby puts an upper limit on the frequency with which the cell can fire. The length of the refractory period, and therefore also the maximal frequency of firing, varies considerably among different kinds of nerve cells.

Two conditions are responsible for the refractory period. One is the aforementioned inactivation of the voltage-gated Na^+ channels, and the other is the fact that the membrane is hyperpolarized immediately after the action potential (Fig. 3.6). The inactivation of Na^+ channels means that they cannot be opened, regardless of the strength of the stimulus and the ensuing depolarization. Hyperpolarization occurs because the K^+ channels remain open longer than required just to bring the membrane potential back to resting value. These two different mechanisms can account for why the refractory period consists of two phases. During the first phase, the **absolute refractory period**, the cell cannot be made to discharge, however strong the stimulus may be; during the **relative refractory period**, stronger depolarization than normal is needed to produce an action potential.

Calcium and Neuronal Excitability

A cation other than Na^+—namely, Ca^{2+}—may also contribute to the rising phase of the action potential. For Ca^{2+}, as for Na^+, the extracellular concentration is much higher than the intracellular one, and there are voltage-gated calcium channels in the membrane. Cellular influx of calcium can be visualized after intracellular injection of a substance that fluoresces when Ca^{2+} binds to it. During the action potential, calcium enters the cell—partly through Na^+ channels and partly through voltage-gated calcium channels, which have a more prolonged opening–closing phase than the sodium channels. There are also transmitter-gated calcium channels. In most neurons, the contribution of Ca^{2+} to the action potential is nevertheless small compared with that of Na^+. In certain other cells such as heart muscle, however, calcium is the ion largely responsible for the action potential. Because the calcium channels open and close more slowly than the Na^+ channels, an action potential produced by calcium currents lasts longer than one produced by flow of Na^+.

Another aspect of the functional role of calcium is that the extracellular calcium concentration influences the membrane excitability, which is most likely mediated through effects on the Na^+ and K^+ channels. Reducing the calcium concentration in the blood and interstitial fluid—**hypocalcemia**—lowers the threshold for evoking action potentials in neurons and muscle cells, whereas increasing the concentration—**hypercalcemia**—has the opposite effect. A typical symptom of hypocalcemia is muscle spasms—**tetany**—due to hyperexcitability of nerves and muscles. Severe hypercalcemia can cause drowsiness, nausea, and anorexia.

Neuronal Homeostasis and Control of Extracellular Potassium

Normally, the extracellular K^+ concentration is under tight control, as discussed in Chapter 2 ("Astroglia and the Control of Neuronal Environment"). Such control is necessary because even small alterations influence the excitability of neurons significantly. When the neurons produce action potentials, K^+ ions move out, increasing the extracellular concentration. This increases the excitability of the neurons in the immediate vicinity, and for each new action potential the extracellular K^+ concentration rises a little more. If not counteracted, this positive feedback situation would cause uncontrolled firing of neurons. Even if it initially would affect only a few neurons, the activity would spread in networks connected with the hyperexcitable neurons. This is the situation with **epileptic seizures** (see Chapter 22, under "Epileptic Seizures Starting in MI").

Under normal conditions, however, **negative feedback** mechanisms prevent the loss of homeostatic control. First the permeability (conductance) of a special kind of K^+ channel increases in situations with high-frequency firing. This brings the resting potential closer to the equilibrium potential of K^+—that is, the membrane becomes less depolarized.[4] Furthermore, **astroglia** contributes by removing excess K^+ from the extracellular fluid. The **refractory period** represents another homeostatic mechanism by limiting the maximal firing frequency. Although these mechanisms are effective in the short run, in the long run the

4. Presumably, the large repertoire of selective K^+ channels reflects the importance of stabilization of membrane polarization. Some channels are ligand gated; others are voltage gated (K_v channels). A particular kind is **inwardly rectifying** K^+ **channels** (Kir), which means that the channel preferentially let K^+ ions *into* the cell (unlike the K^+ channel responsible for the repolarization phase of the action potential, Fig. 3.6). $Ca2^+$ plays an important role in regulation of several K^+ channels.

sodium-potassium pump is all-important for control of K^+ concentrations. Finally, **inhibitory synapses** are instrumental in controlling neuronal excitability.

IMPULSE PROPAGATION

Electrical Properties of Axons

We now consider how the action potential moves along the axon. The ability of the axon to conduct electrical current depends on several conditions, some of which are given by the physical properties of axons, which are very different from, for example, those of copper wire. In addition, some conditions vary among axons of different kinds. An axon is a poor conductor compared with electrical conductors made of metal because the axoplasm through which the current has to pass consists of a weak solution of electrolytes (i.e., low concentrations of charged particles in water). In addition, the diameter of an axon is small (from <1 to 20 μm) with a correspondingly enormous **internal resistance** to the current in the axoplasm. Further, the axonal membrane is not a perfect insulator, so charged particles are lost from the interior of the axon as the current passes along its length. The amount of current lost is determined by the degree of **membrane resistance** (i.e., the resistance of the membrane to charged particles trying to pass). Finally, the axonal membrane (like all cell membranes) has an **electrical capacity**; that is, it can store a certain number of charged particles in the same way a battery does. This further contributes to the rapid attenuation of a current that is conducted along an axon: the membrane has to be charged before the current can move on.

The Action Potential Is Regenerated as It Moves Along the Axon

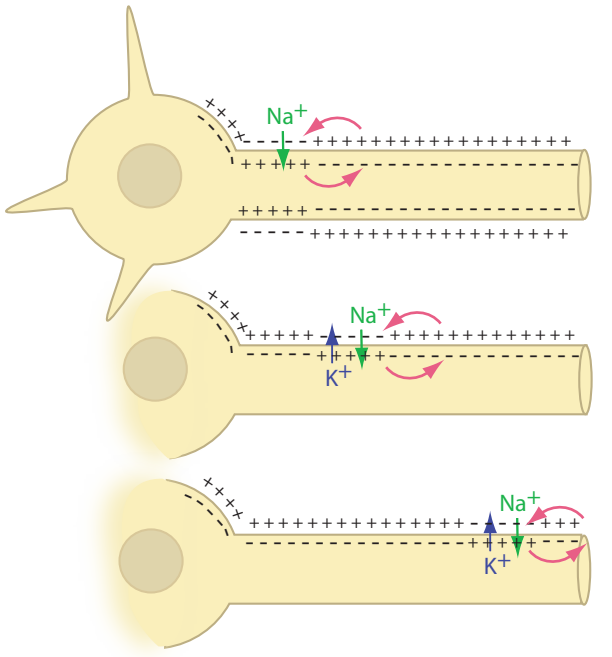
From the foregoing it can be concluded that how well the current is conducted in an axon depends on its internal resistance (its diameter), the membrane resistance (how well insulated it is), and the capacity of the axonal membrane. If the propagation of the action potential along the axon occurred only by passive, electrotonic movement of charged particles, the internal resistance and loss of charges to the exterior would cause the action potential to move only a short distance before it "died out." The solution to this problem is that the action potential is **regenerated** as it moves along the axon. Therefore, it is propagated with undiminished strength all the way from the cell body to the nerve terminals. As discussed, the strength of the action potential—that is, the magnitude of the changes of the membrane potential taking place—is the same regardless of the strength of the stimulus that produced it (as long as the stimulus depolarizes the membrane to threshold). Thus, increasing the strength of the stimulus increases the frequency of action potentials, whereas the magnitude of each action potential remains constant.

When the cell membrane at the initial segment (Fig. 3.7) is depolarized to threshold, an action potential is produced and is conducted passively a short distance along the axon. From then on, what occurs differs somewhat in myelinated and unmyelinated axons (Figs. 3.8 and 3.9).

Impulse Conduction in Unmyelinated Axons

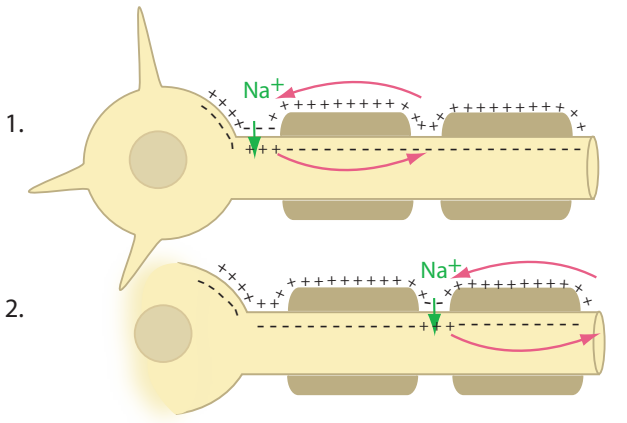
The action potential is produced by positive charges penetrating to the interior of the axon, which at that point becomes positive relative to more distal parts along its

Figure 3.8



Impulse conduction in unmyelinated axons. Arrows show direction of movement of charged particles. The action potential is renewed continuously along the axonal membrane by a wave of depolarization–repolarization.

Figure 3.9



Impulse conduction in myelinated axons. Arrows show direction of movement of charged particles. The current moves electrotonically in the myelinated part of the axons, and the action potential is renewed only at the node of Ranvier, causing a small delay in impulse propagation.

length (Fig. 3.8). Positive charges then start moving in the distal direction (along the electrical gradient that has been set up). Outside the axon, a corresponding current of positive charges moves in the opposite direction, so that an **electrical circuit** is established. Movement of positive charges in the distal direction inside the axon means that the membrane is depolarized as the charges move along. This depolarization leads to the opening of enough voltage-gated Na^+ and K^+ channels to produce a "new" action potential. In this manner, the action potential moves along the axon at a speed that depends on the speed with which the charged particles (i.e., ions) move inside the axon and on the time needed for full opening of the ion channels. The membrane capacity represents a further factor slowing the propagation because the membrane has to be charged before there can be a net flow of charges through it.

In essence, the action potential is propagated as a wave of depolarization, followed closely by a corresponding wave of repolarization. When the membrane has just completed this cycle, it is in the refractory state for some milliseconds. This delay prevents the action potential from spreading "backward" toward the cell body (**antidromic** impulse conduction) and ensures that under normal conditions the impulse conduction is unidirectional. If, however, the axon is artificially stimulated (e.g., electrically) at some distance from the cell body, the action potential spreads toward both the cell body and the end ramifications (**orthodromic** impulse conduction). Antidromic impulse conduction may occur in branches of peripheral sensory axons on natural stimulation and may play a part in certain disease symptoms (see Chapter 29, "Antidromic Impulses and the Axonal Reflex").

Impulse Conduction in Myelinated Axons

In myelinated axons, the action potential is also regenerated along the axon (Fig. 3.9). However, in contrast to that in unmyelinated axons, the action potential is regenerated only at each **node of Ranvier**—that is, where the axon membrane lacks a myelin covering and is in direct contact with the extracellular fluid (see Fig. 2.6). As in unmyelinated axons, the action potential arises in the initial segment of the axon. The current then spreads passively (electrotonically) to the first node of Ranvier. Here, the depolarization of the membrane leads to opening of voltage-gated channels and a "new" action potential. The density of voltage-gated sodium channels is particularly high in the axonal membrane at the node of Ranvier. The current can flow electrotonically as far as the first node of Ranvier (and probably sometimes farther) because the axon is so well insulated by myelin, preventing loss of charges from the interior of the axon. (Myelin dramatically increases the resistance across the membrane and also reduces the membrane capacity.) In addition, the axonal diameter is larger in myelinated than in unmyelinated axons, thus reducing the internal resistance.

In conclusion, in myelinated axons the action potential does not move smoothly and slowly along, as in unmyelinated axons, but instead "jumps" from one node of Ranvier to the next. This is also called **saltatory conduction**. Although the impulse propagation is very rapid between nodes, at each node there is a delay due to the time required for opening of channels and establishment of sufficient flow of current.

Conduction Velocities in Myelinated and Unmyelinated Axons

The main reason myelinated axons conduct so much more rapidly than unmyelinated ones is that the action potential must be regenerated only at certain sites. A figure for conduction velocity (expressed in meters per second) in myelinated axons is obtained by multiplying the axonal diameter (in micrometers) by 6. An axon of 20 µm (the maximal diameter) therefore conducts at approximately

120 m/sec, whereas the thinnest myelinated axons of about 3 μm conduct at 18 m/sec. In comparison, a typical unmyelinated axon of about 1 μm conducts at less than 1 m/sec.

Orthodromic, Antidromic, and Ephaptic Impulse Conduction

The normal situation in most neurons is that the action potential travels from the soma toward the nerve terminals. This is called **orthodromic** impulse conduction. Propagation of the action potential in the opposite direction is called **antidromic** impulse conduction. This is prevented, however, by the refractory state that arises just after membrane depolarization. (In peripheral sensory neurons, orthodromic conduction is from the terminals toward the cell body [see Fig. 1.5], whereas antidromic conduction is from the cell body toward the nerve terminals.) When an axon is stimulated artificially (e.g., electrically) somewhere along its course, action potentials travel both orthodromically and antidromically.

Antidromic impulse conduction can occur in peripheral branches of **sensory neurons** when action potentials arise in only some of the branches. The action potentials then travel orthodromically toward the CNS but also antidromically (outward) in nonstimulated nerve fiber branches. This phenomenon is important in certain disease states because the antidromically activated terminals release substances that induce tissue **inflammation** (see Chapter 13, under "Inflammatory Diseases and Release of Neuropeptides from Peripheral Branches of Sensory Neurons," and Chapter 29, under "Antidromic Impulses and the Axonal Reflex").

Under **pathologic conditions**, especially with partial damage of nerves, action potentials can spread from one axon to a neighboring one by **ephaptic** transmission. In such cases the action potential spreads most likely in both directions—that is, centrally to the CNS and peripherally to terminal axonal branches. Ephaptic transmission occurs in certain painful **neuropathies** (see Chapter 2, under "Diseases of Peripheral Nerves"). One example is **trigeminal neuralgia**, which is a condition with bouts of intense facial pain, in most cases due to compression of the trigeminal nerve by a blood vessel. The compression causes loss of myelin and abnormal axonal excitability with ephaptic transmission that most likely explains the pain.

HOW NERVE CELLS VARY THEIR MESSAGES

So far we have treated the action potential as a unitary phenomenon. As mentioned, the strength of each action potential of a neuron does not vary: whenever depolarized to the threshold, the cell fires action potentials of constant magnitude. Therefore, the action potential is an **all-or-none** phenomenon, and one might think that each neuron would be able to tell only whether or not a stimulus occurs. We know, however, that the individual nerve cell can communicate to others about the strength of the stimulation it receives—such as the intensity of light or a sound, of something touching the skin, and so forth. It does so by varying the **frequency** and **pattern** of action potentials.

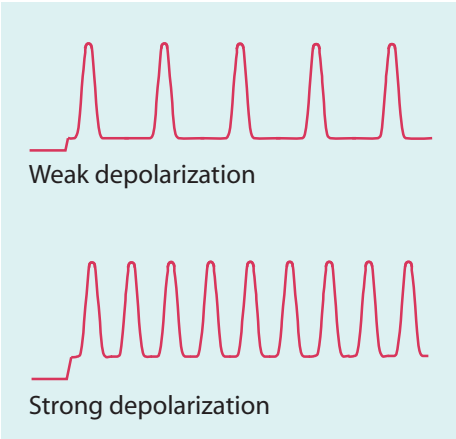
Frequency Coding

To understand how the neuron can vary its firing frequency, we need to know that a neuron is more or less continuously influenced by impulses from many other neurons. A sustained synaptic input that is strong enough to depolarize the cell to threshold does not merely produce one action potential but rather several in succession. The stronger the depolarization, the shorter the time required for reaching the threshold after each action potential. Consequently, the firing frequency depends on the strength of depolarization (Fig. 3.10). We say that the neuron uses a **frequency code** to tell how strongly it has been stimulated. The **maximal frequency** of action potentials in some neurons is more than 100 per second (100 Hz), whereas in others it is much lower.

Pattern of Action Potentials

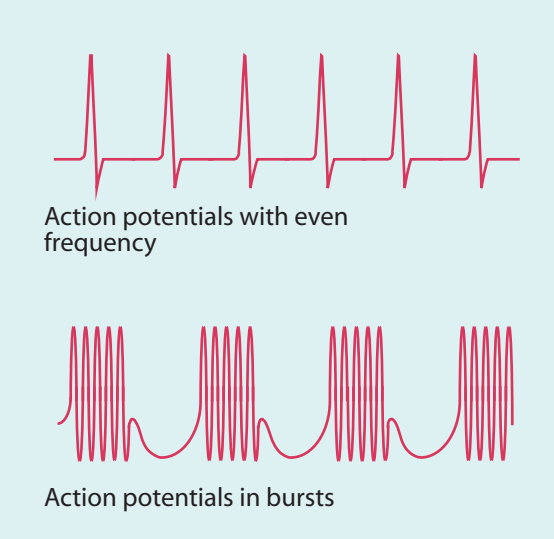
The average firing frequency is not the only way by which the neuron can alter its message. The **firing pattern** also carries information, and each neuronal type has its characteristic firing pattern that is caused by differences in membrane properties and synaptic inputs (see "The Refractory Period," earlier in this chapter). Two neurons may both fire

Figure 3.10



The frequency of action potentials depends on the magnitude of depolarization. Therefore, the frequency of action potentials reflects the total synaptic input to a neuron.

Figure 3.11



Different patterns of nerve impulses provide neurons with an additional means to vary the information they send to other neurons and muscle cells.

with an average frequency of, for example, 10 per second but nevertheless influence a postsynaptic cell differently. So-called **burst neurons** produce trains of action potentials with a high frequency and then pause for a while before a new train (burst) of impulses arises. Other neurons—so-called **single-spike neurons**—produce action potentials with regular intervals (Fig. 3.11).

Switching Between Regular Spikes and Bursts

Some neurons can switch between these two modes of firing. In such cases, the relationship is not linear between the strength of synaptic input and the firing frequency. The transition between the different firing patterns is evoked by a specific **neurotransmitter** (e.g., serotonin), which does not in itself produce action potentials in the postsynaptic cell but changes its reactions to other inputs. For example, the neuron may change from burst to single-spike patterns or from a high firing frequency to no firing at all.

Plateau Potentials

In some neurons, the occurrence of so-called plateau potentials causes the switch from low-frequency firing to high-frequency or bursting firing pattern. This has been shown for many neurons that control **rhythmic muscle contractions**. Plateau potentials are produced by a slow, depolarizing current, for example, by certain voltage-gated Ca^{2+} channels that are open in a limited range of membrane potentials. Such a neuron can therefore change abruptly between two entirely different behaviors. The neurotransmitter **serotonin** can evoke plateau potentials in groups of spinal motor neurons (see Chapter 21, under "Muscle Cramps and Plateau Potentials," and Chapter 22, under "Monoaminergic Pathways from the Brain Stem to the Spinal Cord"). Release of this transmitter relates to motivation and attention rather than to specific information.

Synaptic Function 4

OVERVIEW

In Chapter 3 we discussed the basis of nerve impulses and their conduction in axons. This chapter deals with the properties of synapses. We discuss mainly **chemical synapses**: synapses in which the signal is mediated by a neurotransmitter. Synapses with direct **electric coupling** (gap junctions) are common among glial cells but occur infrequently among neurons. The key events underlying signal transfer at chemical synapses are as follows: First, an action potential reaches the nerve terminal (bouton) and **depolarizes** it. This depolarization opens **Ca^{2+} channels**, enabling Ca^{2+} to enter the nerve terminal. Increase in intracellular Ca^{2+} concentration is a signal for release of **neurotransmitter** from vesicles by exocytosis. This produces a high concentration of neurotransmitter in the synaptic cleft. The released transmitter binds briefly to **receptors** in the **postsynaptic membrane**. After activation of the receptor, the transmitter must be **inactivated** quickly to reestablish a low background activity of the receptors, that is, to ensure a high **signal-to-noise ratio** at the synapse. Inactivation occurs partly by diffusion of the transmitter, partly by **enzymatic degradation** and partly by specific uptake mechanisms (**transporter proteins**).

There are two main kinds of transmitter receptors. **Ionotropic receptors** are parts of ion channels and therefore influence the functional state of the channel directly. Therefore, transmitter actions elicited by ionotropic receptors are fast and precise. **Metabotropic receptors** are coupled indirectly (via intracellular second messengers) to ion channels. Their effects are therefore slower to start and longer lasting than effects mediated by ionotropic receptors. We also use the term **modulatory** of the synaptic effects of metabotropic receptors, because they adjust the excitability of the postsynaptic neuron so that it responds more or less vigorously to the precise effects of ionotropic receptors (in addition, metabotropic receptors may have effects on the growth and survival of the postsynaptic neuron).

The change of the membrane potential arising as a result of synaptic influence is called a **synaptic potential**. If the synaptic influence depolarizes the postsynaptic cell, the probability that the cell will fire action potentials is increased. This synaptic effect is called an **excitatory postsynaptic potential (EPSP)**. If the synaptic potential hyperpolarizes the cell, it is called an inhibitory postsynaptic potential (IPSP) because the probability of the cell's firing is diminished. If the transmitter produces an EPSP, we use the terms **excitatory synapse** and **excitatory transmitter**. Likewise, an **inhibitory transmitter** produces an IPSP at an **inhibitory synapse**.

Because the depolarization caused by one EPSP is small, **summation** of many EPSPs is usually needed to reach a threshold for eliciting an action potential. This enables the neuron to integrate information from often many thousand synapses.

Synapses are **plastic**; that is, they can change their properties by use. This implies that certain kinds of activity can enhance or reduce the subsequent effect of a synapse on the postsynaptic neuron for a variable period (from milliseconds to years). Most likely, such **use-dependent** synaptic plasticity is the neuronal basis for **learning** and **memory**.

NEUROTRANSMITTER HANDLING AT THE SYNAPSE

The vast majority of the synapses between neurons and between neurons and muscles are chemical, and this chapter deals with this kind. Their main structural features were described in Chapter 1.

Unusual Synapses: Electrotonic and Dendrodendritic Transmission

Although it is rare, the pre- and postsynaptic elements are electrically rather than chemically coupled at some synapses. Electron microscopically, such **electrotonic (electric) synapses** differ from chemical synapses in that the synaptic cleft is only 2 nm

compared to about 20 nm. This kind of cell contact is called a **nexus** or **gap junction**; it consists of channels that span the synaptic cleft. (Electrical coupling by gap junctions is much more common among **glial cells** than among neurons, and it occurs regularly among cardiac, smooth-muscle, and epithelial cells.) Through these channels ion currents can pass directly and quickly from one cell to another with no synaptic delay. In invertebrates and lower vertebrates, electrotonic synapses are formed between neurons mediating short-latency responses to stimuli (e.g., escape reactions). Electrotonic synapses may also provide electrical coupling between many neurons in a group, so that their activity may be **synchronized**. Chemical synapses may occur close to electrical ones and serve to uncouple the electrical synapse so that these apparently can be switched on and off. Even a small number of gap junctions between nerve cells—too small to produce efficient electric coupling—may be important by enabling transfer of small signal molecules, such as Ca^{2+}, cyclic AMP, and inositol triphosphate (IP_3). In this way, one neuron may alter the properties of another without ordinary synaptic contact.

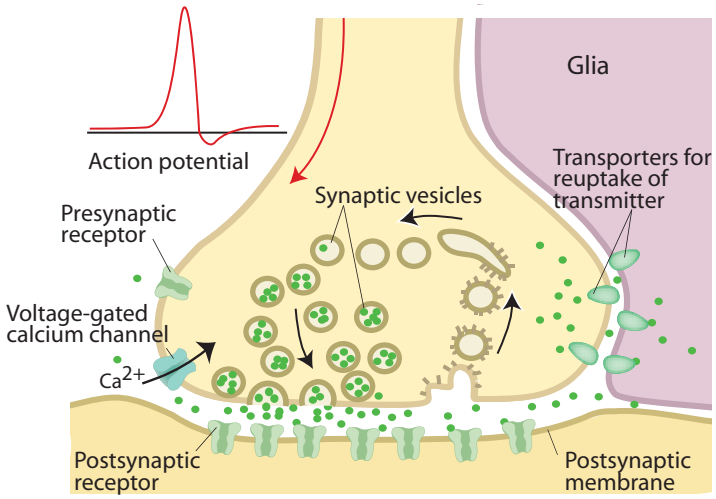
There are also other unusual types of synapses. Contacts between dendrites with all the morphological characteristics of synapses have been observed in several places in the central nervous system (CNS). Such **dendrodendritic synapses** are often part of more complex synaptic arrangements. Through dendrodendritic synapses, adjacent neurons can influence each other without being connected with axons. The function of such synapses, however, is not fully understood.

Release of Neurotransmitters

We have previously described transmitter-containing synaptic vesicles, aggregated near the presynaptic membrane of boutons (Fig. 4.1; see also Figs. 1.7 and 5.9). Depolarization of the presynaptic membrane by an action potential is the normal event preceding transmitter release. The depolarization opens **voltage-gated calcium channels** and allows a flow of Ca^{2+} ions into the bouton. The rise in Ca^{2+} concentration triggers the release of transmitter by exocytosis of vesicles (Fig. 4.1). The more calcium that enters, the more transmitter is released. By exocytosis, the membrane of synaptic vesicles fuses with the presynaptic membrane. The **fusion** opens the vesicle so that its content flows quickly into the cleft (Figs. 4.1 and 4.2). It takes only 0.1 to 0.2 msec from calcium inflow to the occurrence of release, which means that only vesicles already attached to the presynaptic membrane empty their contents. Further, although voltage-gated Ca^{2+} channels are present in all parts of the nerve terminal membrane, only those situated in the presynaptic membrane can influence the fusion of the vesicle with the presynaptic membrane. This is because the fusion requires a very high concentration of Ca^{2+}, which occurs only close to the intracellular opening of the channel. In fact, there is evidence that the calcium channel constitutes a part of the protein complex that binds the vesicle to the presynaptic membrane. This ensures maximal Ca^{2+} concentration around the vesicle.

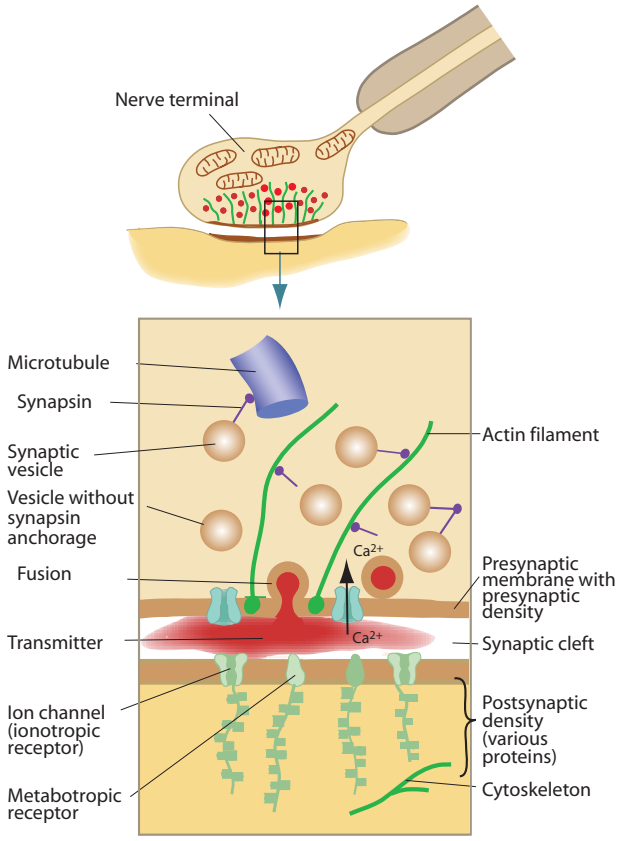
The part of the synapse where the vesicles attach to the presynaptic membrane is called the **active zone**, and it is characterized by cytoskeletal components that probably bind the vesicles to the calcium channels. The active zone is seen in electron micrographs as a **presynaptic density** (Fig. 4.2; see also Figs. 1.6B and 1.7). That fusion really occurs during release is supported by, among other data,

Figure 4.1



Signal transmission at the synapse. Schematic of some important features: calcium-dependent transmitter release, reuptake of transmitter by glia and neurons, and recycling of synaptic vesicles.

Figure 4.2



Transmitter release and some of its machinery. Calcium channels are located close to where the vesicles fuse with the presynaptic membrane. (Based on Walmsey et al. 1998.)

electron microscopic observations showing that the number of vesicles drops with long-term stimulation (trains of action potentials), while the number increases after a period of rest.

Exocytosis of vesicles is controlled by a large number of regulatory proteins that appear to be the same in all kinds of cells. Two features are nevertheless specific to exocytosis in neurons as compared with that in other cells: one is the speed of the process (<1 msec from arrival of the action potential to release); the other is that the release is restricted to a specific site (the synapse). This indicates that some proteins are specific to the control of exocytosis in neurons. The fusion requires specific binding of vesicle-surface receptors to receptors in the presynaptic membrane. In addition, during fusion, various proteins dissolved in the cytoplasm participate by binding to the membrane-bound receptors, thus forming large complexes.

New, empty vesicles are formed by the opposite process of exocytosis, **endocytosis**. The endocytotic vesicles are **coated** with proteins (among them **clathrin** and **dynamin**) that are thought to help in budding of the vesicles from the membrane and in selecting their content. The recycled vesicles undergo a series of regulated steps until they are again filled with neurotransmitter (Fig. 4.1).

Several of the proteins involved in vesicle transport and fusion alter their activity in a use-dependent manner; that is, they may be involved in **synaptic plasticity** during development, recovery after brain damage, and learning in general. Some are also targets of drugs and toxins.

Mechanisms for Vesicle Transport and Fusion

Specific **transporter proteins** in the vesicle membrane fill the vesicles with neurotransmitter. After filling, the vesicles are moved toward the presynaptic membrane by a regulated process (Fig. 4.2). While some vesicles empty their contents, others move toward the presynaptic membrane and prepare for fusion. The synaptic vesicles can therefore be divided into two main groups: those situated close to the membrane that are ready for release when the Ca^{2+} concentration rises around them and those that must move to the membrane before they can release their contents. The movement of vesicles requires the presence of **actin** filaments, and **microtubules** may also play a role. A group of proteins, **synapsins**, bind the vesicles to the actin filaments (Fig. 4.2), which probably serves to assemble the vesicles in positions for further movement and is triggered by the rise in the calcium concentration. Certain **protein kinases** (phosphorylating proteins) regulate the activity of the synapsins. Phosphorylation of synapsins increases mobility of the vesicles and is most likely another way of controlling the amount of transmitter released by an action potential, for example, in response to altered use of the synapse. Several proteins take part in the **docking** of the vesicle at the presynaptic membrane, and they probably also prepare the vesicles for fusion. Vesicle-bound receptors, such as **synaptobrevin/VAMP** (vesicle-associated membrane protein), mediate attachment to receptors in the presynaptic membrane (**syntaxin** is one such receptor). These receptors interact with several others—among them, **SNAP-25** that is free in the cytoplasm—thus forming large protein complexes that anchor the vesicles to the presynaptic membrane. The fusion appears to require that the complex include **synaptotagmin**, which binds Ca^{2+} with low affinity (i.e., the concentration of Ca^{2+} must be high for bonding to occur). According to one hypothesis, synaptotagmin acts as a brake on fusion, and the binding of Ca^{2+} releases the brake. Mice lacking the gene for synaptotagmin have only reduced transmitter release, however, suggesting that other factors also play a role.

Neurotransmitters Are Released in Quanta

There is convincing evidence that transmitters are released in packets, or **quanta,** corresponding to the transmitter content of one vesicle. For synapses between motor nerve terminals and striated **muscle cells** (see Fig. 21.5), one vesicle contains on average 10,000 transmitter molecules. Only a few thousand molecules of each quantum are likely to bind

to a receptor before they diffuse away or are removed by other means. Release of one quantum elicits a tiny excitatory postsynaptic potential (EPSP)—a **miniature EPSP**. If stimulation is increased, so that more transmitter is released, the depolarization of the muscle cell membrane increases in steps corresponding to one miniature EPSP.

In the **CNS**, each bouton probably releases from none to a few quanta for each presynaptic action potential. This means that an action potential does not necessarily elicit transmitter release; it merely increases the **probability of release**. As discussed later, many presynaptic action potentials must coincide to fire a postsynaptic neuron. The probability of release seems to be related to the **size of the active zone**, that is, to the number of vesicles that are ready for fusion. Interestingly, the size of the active zone can increase within minutes after proper use of the synapse, presumably as an expression of **use-dependent plasticity**.

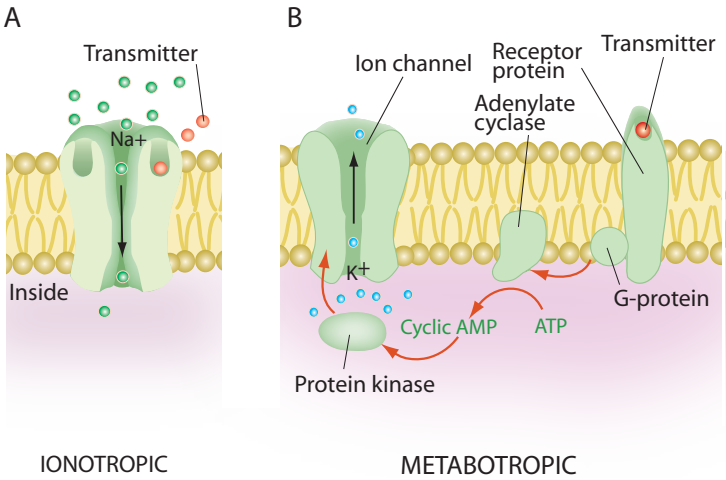
Transmitters Act on Ionotropic and Metabotropic Receptors

The effects of a neurotransmitter depend primarily on the properties and localization of the receptors it can activate. There are two main kinds of transmitter receptors: ionotropic and metabotropic. **Ionotropic receptors** are parts of ion channels (Fig. 4.3A). Ionotropic receptors that are parts of Na^+ or Ca^{2+} channels evoke fast and brief **depolarizations** of the postsynaptic membrane, thus exerting **excitatory** actions. Ionotropic receptors coupled to Cl^- channels as a rule **hyperpolarize** the postsynaptic membrane and **inhibit** the postsynaptic neuron. Synapses equipped with ionotropic receptors mediate **fast** and **precise information**—for example, about "when," "what," and "where" concerning a sensory stimulus.

The other main kind—the **metabotropic receptor**—is not coupled directly to ion channels but acts indirectly by way of **G proteins** and intracellular second messengers (Fig. 4.3B). G proteins may be regarded as universal translators, translating various kinds of extracellular signals to a cellular response (e.g., the "translation" of light and of gaseous and watery chemical substances to nerve impulses).

Most neurotransmitters act on both ionotropic and metabotropic receptors. That is, a neurotransmitter can exert both fast, direct synaptic effects and slow, indirect ones (at the same or different synapses). **Glutamate** and **GABA** (γ-aminobutyric acid) are by far the most abundant and ubiquitous transmitters acting on ionotropic receptors, although they also act on several kinds of metabotropic receptors. Several important neurotransmitters, such as **norepinephrine**, **dopamine**, and **serotonin**, exert their main actions on metabotropic receptors. We can conclude that to predict the actions of a neurotransmitter on a neuronal group, we must know the repertoire of receptors expressed by those neurons. Further, because the distribution of receptors differs,

Figure 4.3



Two kinds of transmitter receptor. **A:** Ionotropic receptor with direct action on the ion channel. Note that the receptor is part of the channel proteins. **B:** Metabotropic receptor with indirect action on ion channels. Schematic. All indirectly coupled receptors act via G proteins, whereas other elements of the intracellular signal pathway may vary among different receptors. In this example cyclic AMP serves as the second messenger.

one transmitter may exert different actions in different parts of the brain.

Toxins Can Prevent Transmitter Release

Some of the proteins necessary for fusion are degraded by **tetanus toxin** and **botulinum toxin** (produced in certain foods if not treated properly). Both toxins are produced by anaerobic bacteria (i.e., they only grow in the absence of oxygen) and produce violent muscle spasms and paralysis, respectively. The toxins are proteases acting on the proteins that are involved in docking and fusion of synaptic vesicles. While tetanus toxin and some botulinum toxins degrade synaptobrevin, other botulinum toxins destroy SNAP-25, or syntaxin. Even extremely small amounts of the toxins produce muscle spasms (tetanus toxin) or paralysis (botulinum toxins) by preventing transmitter release. They evoke opposite effects because they act on different kinds of synapses: the botulinum toxin acts at the neuromuscular junction (see Fig. 21.5), preventing release of the excitatory transmitter acetylcholine, whereas the tetanus toxin is taken up by nerve terminals in the periphery and moved by axonal transport to the cord. There the toxin affects primarily a type of inhibitory synapse on motor neurons, making them fire action potentials with a high, uncontrolled frequency (see Chapter 5, under "Inhibitory Amino Acid Transmitters: GABA and Glycine").

Inactivation of Neurotransmitters

Synaptic signal transfer is characterized by a precisely timed start and stop. We have looked into the mechanisms responsible for precise timing of transmitter release. It is also necessary, however, that the transmitter, once released, be quickly removed from the synaptic cleft after receptor activation. Simple **diffusion** of the transmitter seems to play an important part, especially during the first few milliseconds after release. Some transmitters (acetylcholine and neuropeptides) are degraded extracellularly by specific **enzymes**. The majority of transmitters, however, are removed from the extracellular fluid by **uptake** into glial cells or neurons (see also Chapter 2, under "Astroglia and Control of the Neuronal Environment"). Specific **transporter proteins** in the cell membrane (Fig. 4.1) carry out the transmitter uptake. The transmitter transporters are driven by ion-concentration gradients across the cell membrane. There are two **families** of such transporter proteins. One is driven by the concentration gradients of Na^+ and Cl^- and transports the transmitters **GABA, glycine, dopamine, norepinephrine**, and **serotonin**. The other comprises five different transporters for **glutamate** and is driven by the concentration gradients of Na^+ and K^+ (see Chapter 5, under "Glutamate Transporters").

The task of the transporters is not to remove all traces of neurotransmitters from the extracellular fluid. Because both number and activity of the transporters are regulated, they rather serve to modulate up or down a certain baseline extracellular transmitter concentration. Even a small alteration of transporter activity can cause changes of transmitter–receptor activation. In areas with a high density of transporters (see Fig. 2.5), they also influence the ease by which neurotransmitters may activate receptors outside the synaptic cleft (on nerve terminals, dendrites, and cell bodies). In this way, the transmitter transporters participate in the control of synaptic transmission and neuronal excitability.

Because the transporter proteins have important physiologic roles, they are also interesting pharmacologically. Drugs that alter their function can be used therapeutically (such as **antidepressants** that are selective serotonin reuptake inhibitors), but some also have potential for abuse (such as **cocaine**, which inhibits the dopamine-reuptake transporter).

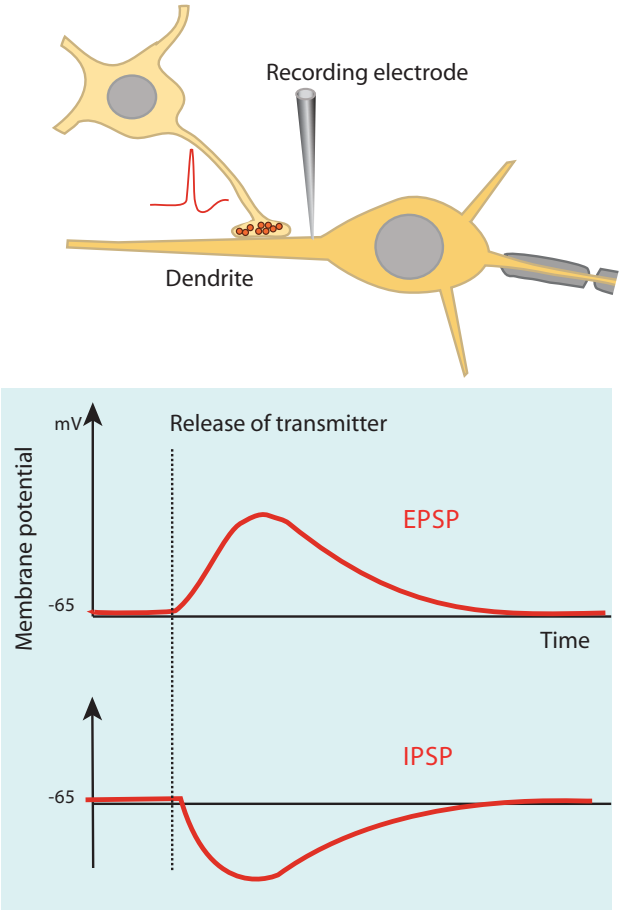
SYNAPTIC POTENTIALS AND TYPES OF SYNAPSES

Mechanisms of Postsynaptic Potentials (EPSPs and IPSPs)

Synaptic potentials arise when neurotransmitters activate ion channels. An **excitatory postsynaptic potential** (**EPSP**) arises at synapses where the transmitter **depolarizes** the postsynaptic membrane. An **inhibitory post-synaptic potential** (**IPSP**) arises at synapses where the transmitter **hyperpolarizes** the membrane (Fig. 4.4).

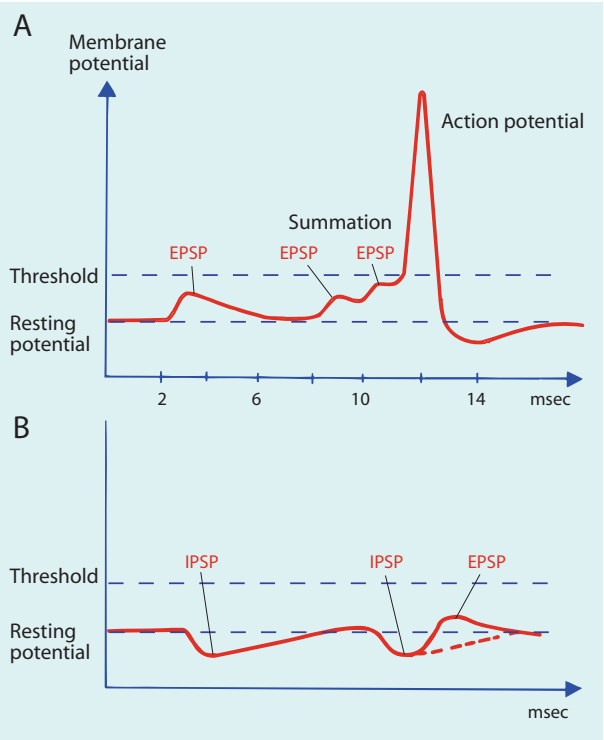
Opening of cation channels allowing Na^+ to enter and K^+ to leave the cell produces an EPSP. Because the cations outside the cell are driven inward, by both the concentration gradient and the membrane potential, whereas K^+ inside the cell is driven out only by its concentration gradient, at first the inward current is largest (see Figs. 3.3, 3.4, and 3.5). As the membrane becomes more and more depolarized, however, the outward flow of K^+ increases and counteracts further depolarization (Fig. 4.4). Transmitter-gated channel opening is not subject to self-reinforcement, unlike the voltage-gated channels that produce the action potential. This means that the synaptic potentials rise and fall gradually (Fig. 4.4 and 4.5) and last longer than the action potential. We use the term **graded potential**, as opposed to the all-or-none behavior of the action potential. The current spreads passively (electrotonically) from the synapse outward in all directions along the cell membrane. In this way,

Figure 4.4



Synaptic potentials. Alterations of the membrane potential evoked by a single presynaptic action potential that releases a transmitter into the synaptic cleft. An EPSP is evoked by an excitatory transmitter (typically glutamate), while an inhibitory transmitter (typically GABA) produces an IPSP (inhibitory postsynaptic synaptic potential).

Figure 4.5



Synaptic potentials. **A:** The time course and polarity of an EPSP. In this example, one EPSP alone does not depolarize the membrane to threshold for eliciting an action potential, but if one EPSP (or more) follows shortly after the first one, the threshold is reached (summation). **B:** The time course and polarity of an IPSP and how the hyperpolarization is reduced when an EPSP is added to an IPSP.

the potential becomes gradually weaker, unlike the action potential, which is constantly regenerated. Because typical EPSPs in neurons are small (<1 mV), and the membrane has to be depolarized at about 10 mV near the initial segment to reach **threshold** for an action potential, it follows that many EPSPs must be summated to fire the neuron. We return to summation of EPSPs later.

The mechanism behind an **IPSP** is usually the opening of transmitter-gated K^+ or Cl^- channels. This results in an outward flow of K^+ or an inward flow of Cl^-. In both cases, the inside of the cell becomes more negative; that is, the membrane is hyperpolarized. This is true only if the membrane potential is less negative than the equilibrium potentials of the ions in question, however. Although this is the normal situation for K^+ (equilibrium potential –90 mV), the equilibrium potential of Cl^- is close to the resting potential in many neurons. If the resting potential is equal to the equilibrium potential of Cl^-, there is no net flow of Cl^- ions, and, consequently, no IPSP is evoked.[1] Even in this case, however, opening of chloride channels can counteract the effects of excitatory transmitters. Thus, as long as the chloride channels remain open, even the slightest depolarization will cause Cl^- ions to flow into the cell and thereby minimize the change of the membrane potential. In this case, opening of chloride channels by an inhibitory transmitter **short-circuits** the depolarizing currents at nearby excitatory synapses.

1. If the resting potential is more negative than the equilibrium potential of Cl^-, the opening of chloride channels causes a net outward flow of chloride ions and the cell is depolarized. This is the case in early **embryologic development**: the transmitter GABA, which is inhibitory in the adult nervous systems, has excitatory actions in the immature brain.

Summation of Stimuli Is Necessary to Evoke an Action Potential

One or a few presynaptic action potentials leading to transmitter release do not evoke an action potential in the postsynaptic cell. As previously mentioned, the membrane has to be depolarized to a **threshold** value (Fig. 4.5A) for an action potential to be evoked. Usually, the threshold is approximately 10 mV more positive than the resting potential, and the size of an EPSP is probably in most cases less than 1 mV. As previously mentioned, to produce an action potential the current produced at synaptic sites must be strong enough to reach the initial segment and depolarize the membrane to threshold (by opening voltage-gated Na^+ channels).

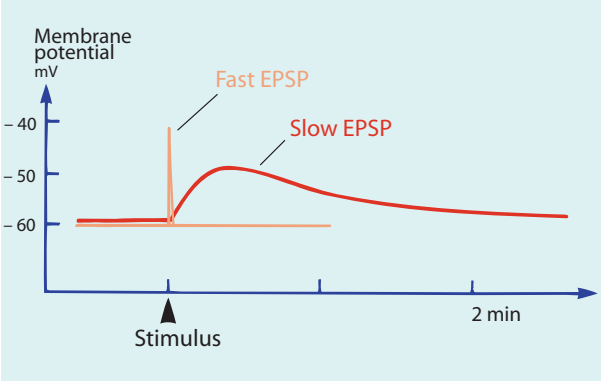
A subthreshold depolarization may nevertheless be of functional significance if the synaptic potential is followed by another depolarization before the membrane potential has returned to resting value. Then the second depolarization is added to the first one so that threshold is reached. This phenomenon is called **summation** (Fig. 4.5A). The summation may be in time, as in the previous example, and is then called **temporal summation**, or it may be in space and is then called **spatial summation**. In temporal summation, impulses may follow one another in rapid succession in one terminal, whereas in spatial summation, nerve terminals at different places on the cell surface release transmitter and depolarize the cell almost simultaneously. Also, IPSPs are subject to spatial and temporal summation.

An EPSP increases the **probability** that the postsynaptic neuron will produce an action potential: for a moment, the neuron is more responsive to other inputs. Likewise, an IPSP decreases this probability.

Slow Synaptic Effects Modulate the Effect of Fast Ones

Because neurons are equipped with both ionotropic and metabotropic transmitter receptors, we may safely assume that every neuron receives both fast (direct) and slow (indirect) synaptic inputs. The slow effects modulate the effects of the fast ones, and we therefore use the term **modulatory transmitter actions**. A modulatory transmitter (when binding to an indirectly acting receptor) does not by itself evoke action potentials but alters the response of a neuron to fast, ionotropic transmitter actions. Usually, modulatory synaptic effects are mediated by altering opening states of K^+ or Ca^{2+} channels, thereby modulating both the membrane potential and the refractory period. The effects are nevertheless much more varied because there are several kinds of potassium and calcium channels, and several transmitters may influence each channel.

Figure 4.6



Fast and slow synaptic actions. Schematic. A fast EPSP lasts milliseconds and is caused by binding of transmitter molecules directly to channel proteins. A slow EPSP may last seconds or minutes and is due to activation of receptors indirectly coupled to ion channels.

A brief train of impulses in axons releasing a transmitter that binds to indirectly acting receptors may keep the membrane depolarized or hyperpolarized for seconds after the train of impulses ends (slow EPSP or IPSP; Fig. 4.6). More intense stimulation may produce depolarization that lasts minutes in some neurons.

An example may make this clearer: motor neurons in the cord receive fast, excitatory synaptic input from the cerebral cortex. These signals mediate the precise, voluntary control of muscle contraction. In addition, the motor neurons receive slow, modulatory synaptic inputs from cell groups in the brain stem whose activity is related to the degree of motivation for a particular movement. The modulatory input influences the strength of the response (frequency of action potentials) to signals from the cerebral cortex, that is, how fast the movement will be. However, the modulatory input does not initiate movements on its own.

Mechanisms of Modulatory Synaptic Effects

Slow EPSPs may be mediated by transmitters closing a kind of **voltage-gated K^+ channel** that is open at the resting membrane potential. This leads to lowered K^+ permeability and reduced flow of K^+ out of the cell, which results in depolarization. Because the membrane potential is shifted toward the threshold, fast depolarization is more likely to elicit an action potential. In addition, the effect on this kind of channel makes a fast EPSP larger and longer-lasting because

the fast transmitter opens the K^+ channel during the repolarization phase of the EPSP. When the modulatory transmitter counteracts the opening of the channel in this phase, the depolarization becomes stronger and the repolarization phase is prolonged. In this way the fast transmitter may produce a train of action potentials rather than just one.

Modulatory synaptic effects may not change the resting membrane potential if they are confined to channels that are not open at the resting potential. Thus, a kind of K^+ channel—closed at the resting potential—is opened by Ca^{2+} (together with Na^+) entering the cell during the action potential. This produces a relatively long-lasting hyperpolarization (the refractory period). A modulatory transmitter that reduces the opening of this K^+ channel would shorten the refractory period. As in the preceding example, a fast excitatory input might produce a train of impulses rather than only one, or the frequency of impulses during a train might be higher than without the modulatory influence.

Slow **IPSPs** are usually mediated by the indirect opening of K^+ channels. As we discuss later, the ubiquitous inhibitory transmitter GABA can act on receptors with such effect.

A Neuron Integrates Information from Many Others

We have seen that as a rule many impulses must reach a neuron almost simultaneously to make it fire, that is, to send an action potential through its axon. In other words, summation of excitatory synaptic effects is necessary. The stronger the sum of excitatory effects, the shorter the time necessary to depolarize the cell to the threshold for eliciting another action potential. This means that the frequency of action potentials, or **firing frequency**, is an expression of the **total synaptic input** to a neuron. Total synaptic input here means the sum of both excitatory and inhibitory synaptic influences. Most neurons receive thousands of synapses; for example, large neurons in the motor cortex of the monkey may receive as many as 60,000 synapses. Often a neuron is strongly influenced (many synaptic contacts) by one neuronal group and weakly influenced by many others. This means that while such a neuron primarily transmits signals from one nucleus to another, many other cell groups facilitate or inhibit the efficiency of signal transmission.

Examples of Synaptic Integration

Here we provide two examples of the integration of different synaptic inputs. The first concerns **motor neurons** of the spinal cord. Such a neuron—sending its axon to innervate hundreds of striated muscle cells in a particular muscle—is synaptically contacted by neurons in many parts of the nervous system. It may receive around 20,000 synapses, distributed over its dendrites and cell body. Some synapses inform the cell about sensory stimuli that are important for the movement produced by the muscle, others about the posture of the body, others about how fast an intended movement should be, and so forth. The sum of all these synaptic inputs—some of them excitatory, others inhibitory—determines the frequency of action potentials sent to the muscle and by that means the force of muscle contraction (each muscle, however, is governed by many such neurons, so that their collective activity determines the behavior of the whole muscle).

The other example concerns neurons in the spinal cord that mediate information about **painful stimuli**. Although such a neuron receives its strongest synaptic input (most synapses) from sensory organs reacting to painful stimuli, it is also contacted by thousands of synapses from other sources, such as cell groups that are active when the person is anxious. This means that the final firing frequency of this sensory neuron depends not only on the actual stimuli reaching the receptors but also on the activity within the CNS itself. This correlates well with the everyday experience that the pain we feel depends not only on the strength of the peripheral painful stimulus (such as dental drilling) but also on our state of mind. Although the main task of the neuron is to convey sensory information to the brain, this information is integrated in the spinal cord with signals from other sources conveying information about the salience of the sensory information.

The Placement of Synapses Has Functional Significance

Where a synapse is located on the neuronal surface is obviously not a matter of chance (see Fig. 1.8). There are several examples of axons arising from different cell groups that end on different parts: for example, some end only on proximal dendrites, others on distal dendrites or a particular segment of the dendrite. Further, **inhibitory** synapses are often located on or near the soma of the nerve cell, whereas **excitatory** ones are most abundant on dendrites. The placement can be of functional importance, because synapses close to the **initial segment** of the axon would be expected to have a greater chance of eliciting (or preventing) an action potential than synapses far out on the dendrites. (This is due to the loss of current during electrotonic spread of the synaptic potential over long distances.) In some neurons, powerful inhibitory synapses are even located on the initial segment itself, thereby forming a very efficient "brake" on neuronal firing.

In general, a synapse far out on a dendrite would be expected to exert a weaker effect on the excitability of the neuron than one placed close to the soma, and, consequently, more summation would be needed for distal synapses than for proximal ones to fire the neuron. New findings suggest that this may not always hold true, however. Studies of pyramidal neurons (in the hippocampus) indicate that an EPSP recorded in the soma is of about equal magnitude regardless of whether it is evoked by a synapse that is proximal or distal on a dendrite. This means that a stronger depolarizing

action at **distal synapses** compensates for their greater loss of current by electrotonic spread.[2]

Another important point regarding the placement of synapses is that most excitatory synapses are located on dendritic **spines** (see Fig. 1.8). A spine typically consists of a narrow neck and an expanded part called the **spine head** (see Fig. 1.9). Most of the neurons in the cerebral cortex are of the axospinous kind. Because cortical neurons constitute a large proportion of all neurons in the human brain, it is believed that about 90% of all excitatory synapses are located on spines.

Temporal Sequence of Synaptic Activation Provides Information

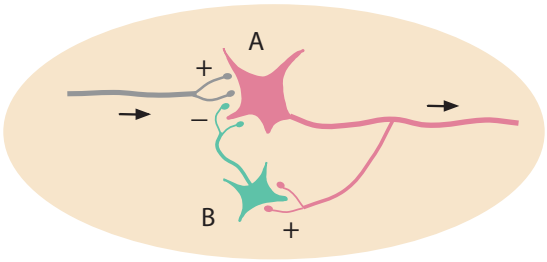
The temporal sequence of synaptic actions along the dendrite also seems to influence the effect of a synapse. Thus, if a sequence of synaptic activation starts distally and moves proximally, the effect at the soma is stronger than if the activation starts proximally. Whether distal or proximal synapses are activated first may depend on the direction a moving stimulus (e.g., on the skin or in the visual field). This kind of discriminative capacity was demonstrated with **two-photon microscopy** of in vitro slices of cerebral cortex, where single synapses were stimulated in a temporal and spatial sequence (Branco et al. 2010). The neuron may therefore discriminate between directions of movement and forward this information to other neurons.

Why Do We Need Inhibitory Synapses?

Inhibitory synapses are present everywhere in the CNS and are of vital importance in interrupting or **dampen excitation**, which might otherwise lead to neuronal damage. Thus, inhibition serves to maintain **homeostasis**. Figure 4.7 shows how an excitatory neuron can limit its firing by way of an **inhibitory interneuron**. Although not shown in the figure, the interneuron is influenced by many other neurons that serve to "adjust the brake," as it were. Such arrangements are common, for example, among the motor neurons that control muscle contractions (see Fig. 21.14). In general, inhibitory interneurons increase the **flexibility** of the nervous system.

2. Although this is shown so far only for cortical pyramidal neurons, there is reason to assume that it applies to dendrites in general. The different properties of distal and proximal dendrites relate to a higher density of NMDA receptors on distal dendrites and the fact that voltage-gated cation channels open more easily on distal than on proximal dendrites (Branco and Häusser 2011).

Figure 4.7



*Inhibitory interneuron (**B**) mediating negative feedback to the projection neuron (**A**).* Arrows show the direction of impulse conduction.

A salient example of the importance of inhibition is the effect of **strychnine**, which blocks inhibitory glycinergic synapses and elicits life-threatening muscle spasms. As mentioned, **epileptic seizures** are due to uncontrolled firing of groups of neurons, and drugs reducing the tendency for seizures generally increase the effect of inhibitory transmitters. Furthermore, inhibition is necessary to suppress irrelevant **sensory information**, thereby enabling us to concentrate on certain events and leave others out. Inhibitory synapses also serve to increase the precision of sensory information by, for example, enhancing contrast between regions with different light intensity in visual images.

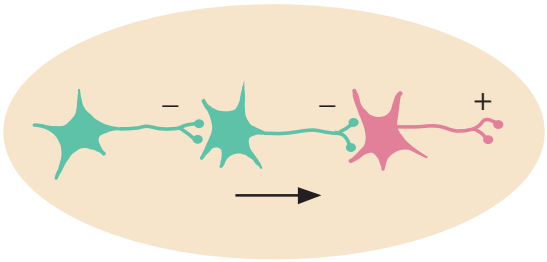
Inhibition is also crucial for movements by patterning and coordinating the activity of motor neurons. For example, the rhythmic pattern of muscle activation in **locomotion** depends on properly functioning inhibitory interneurons in the spinal cord.

Finally, inhibitory interneurons are instrumental in shaping the dynamic patterns of activity in distributed **cortical networks,** characterized by rhythmic **oscillations**.

Signaling by Disinhibition

In some instances, inhibitory synaptic couplings may lead to increased rather than decreased excitation. This occurs when inhibitory neurons inhibit other inhibitory neurons that in their turn act on excitatory ones (Fig. 4.8). With such an arrangement, firing of the first inhibitory interneuron (green) inhibits the next inhibitory interneuron, which thereby reduces its activity. Thus, the excitatory neuron (red) receives less inhibition and increases its firing. This is called **disinhibition**, and it plays an important role in diverse structures such as the retina and the basal ganglia (see Fig. 23.14). If an inhibitory interneuron contacts both excitatory and inhibitory neurons, it might produce both inhibition and

Figure 4.8



Disinhibition. Two inhibitory neurons (green) coupled in series increases the activity of an excitatory neuron (red).

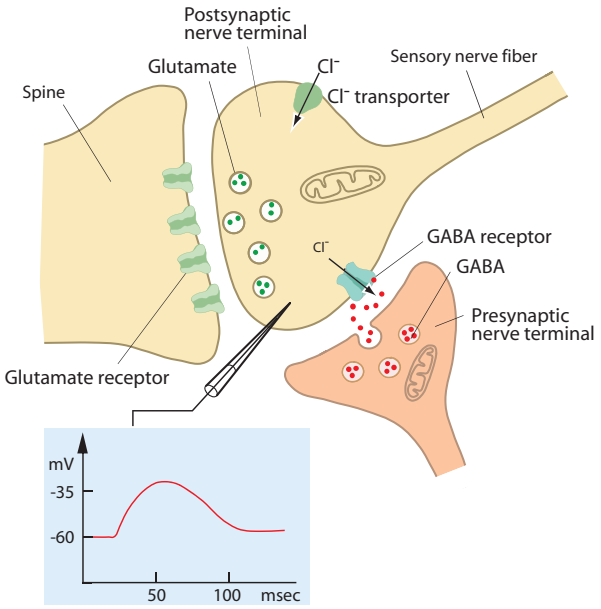
disinhibition at the same time in different neurons. By controlling the firing of such interneurons, central command centers—such as the motor cortex—can direct the signals in the desired direction. This occurs, for example, in the spinal cord where inhibitory interneurons serve to select the muscles that are best suited for a particular task.

Axoaxonic Synapses Enable Presynaptic Control of Transmitter Release

In axoaxonic synapses, the presynaptic bouton makes synaptic contact with a postsynaptic bouton, which, in turn, contacts a cell body or a dendrite (Fig. 4.9). Release of transmitter from the presynaptic bouton serves to regulate the amount of transmitter released by the postsynaptic bouton. This enables inhibition or facilitation of a subset of synaptic inputs to a neuron. The excitability of the postsynaptic neuron is unaltered, in contrast to the situation described previously with postsynaptic inhibition by IPSPs.

In the best-studied kind of axoaxonic contacts, action potentials in the presynaptic bouton lead to reduced transmitter release from the postsynaptic bouton; that is, the effect is inhibitory with regard to the neuron contacted by the postsynaptic bouton (the postsynaptic bouton usually has an excitatory action). A prerequisite for this inhibitory effect to occur, however, is that the presynaptic bouton must be depolarized (by an action potential) at the same time as or immediately before an action potential reaches the postsynaptic bouton. This phenomenon is termed **presynaptic inhibition** to distinguish it from postsynaptic inhibition. Presynaptic inhibition has been found most frequently among fiber systems that transmit sensory information; for example, sensory fibers entering the spinal cord are subject to powerful presynaptic inhibition. In this way, signals to a sensory neuron from pain receptors can be selectively inhibited, while signals from other receptors are passed on unaltered.

Figure 4.9



Presynaptic inhibition is mediated by axoaxonic synapses. The example is from the spinal cord where an inhibitory interneuron contacts the terminal of a sensory nerve fiber (from a spinal ganglion cell). The interneuron releases GABA that opens Cl^- channels and thereby depolarizes the postsynaptic nerve terminal (frame). This leads to release of less transmitter. See text for further explanations. (Based on Alvarez 1998.)

Mechanisms of Presynaptic Inhibition and Facilitation

Several mechanisms may be involved in **presynaptic inhibition**. The phenomenon has been most studied in the spinal cord dorsal horn, where axoaxonic synapses are formed by inhibitory interneurons as they contact terminals of primary sensory afferents (Fig. 4.9). The transmitter released from the interneuron (usually GABA) opens chloride channels in the postsynaptic terminal (bouton). In most neurons, opening of chloride channels either hyperpolarizes or short-circuits the membrane, as described. In the sensory terminals in the cord, however, opening of chloride channels **depolarizes** the membrane, due to an unusually high intracellular chloride concentration. (To uphold this concentration gradient, these sensory neurons are equipped with a special transport mechanism for chloride coupled to the sodium–potassium pump). In this way, the equilibrium potential of Cl^- is more positive (–30 mV) than the resting potential (–65 mV), and, consequently, chloride ions move *out* of the nerve terminal when chloride channels open. But how can depolarization of the presynaptic terminal reduce transmitter release? The answer seems to be that depolarization reduces the amplitude of action potentials as they invade the postsynaptic terminal; in turn, this leads to opening of fewer voltage-gated calcium channels. Because the amount of transmitter released is proportional to the influx of Ca^{2+}, less transmitter will