An Integrated Approach to Neuroscience

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By

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This book is dedicated in loving memory to my grandfather,
Julian A. Pittman.

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FOREWORD

Welcome to Neuroscience: An Integrated Approach. This text provides detailed information about the salient topics typically covered in a traditional introductory neuroscience course, providing a basic overview of brain anatomy and physiology from molecules to the mind in a concise, readable format with the author's hands on experience with brain research, without a substantial amount of peripheral information. This allows the student to focus on the primary concepts without getting lost in ancillary information that may not be relevant to their future careers. This text should also serve as a good review for anyone wanting to refresh their memory on the subject.

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I would like to thank the following individuals for the help and support that they have provided in the preparation of this text. It is not possible to adequately acknowledge the support and encouragement provided by loved ones, especially my wife, my mother, and my grandmother. They have had the patience and understanding to tolerate my absences and my frustrations. They have provided unwavering support. Finally, my thanks go to the skilled project team at Cambridge Scholars Publishing Ltd.

CHAPTER ONE

THE CELLS OF THE NERVOUS SYSTEM

The nervous system, and particularly the brain, is an astonishing piece of biological machinery. Given its accomplishments from animal to man, there is good reason for wanting to understand better how the brain works. The debilitating and costly effects of neurological and psychiatric disease add a further sense of urgency to this mission. The aim of this book is to highlight the intellectual challenges and excitement, as well as uncertainties of what many view as the "last great frontier" of the biological sciences. The information presented should serve as a starting point for undergraduates, medical students, graduate students in the neurosciences, and others who want to better understand how the nervous system operates.

Neuroscience encompasses a broad range of questions about how nervous systems are organized, and how they function to generate behavior. These questions can be explored using the analytical tools of genetics, molecular and cell biology, systems anatomy and physiology, behavioral biology, and psychology. The major challenge presented for a student of neuroscience is to integrate the diverse knowledge derived from these various levels of analysis into a more or less coherent understanding of brain structure and function. Many of the issues that have been explored successfully concern how the principal cells of any nervous system, neurons and glia, perform their basic functions in anatomical, electrophysiological, and molecular terms. The diversities of neurons and supporting glial cells that have been identified are assembled into ensembles called neural circuits, and these circuits are the primary components of neural systems that process specific types of information. Neural systems comprise neurons and circuits in a number of discrete anatomical locations in the brain. These systems serve one of three general functions: (1) sensory systems represent information about the state of the organism and its environment, (2) motor systems organize and generate actions, (3) and associational systems link the sensory and motor sides of the nervous system, providing the basis for "higher-order" functions such

as perception, attention, cognition, emotions, rational thinking, and other complex brain functions.

This chapter will begin with an in-depth discussion of the neuron, the central functional component of the brain, and then move to a discussion of the ways in which individual neurons communicate with each other. What makes the nervous system such a fascinating organ and distinguishes the brain from other organs of the body is not that it has 100 billion cells (neurons), but that nerve cells are capable of communicating with each other in such a highly structured manner as to form what are known as "neuronal networks". To understand neural networks, it is necessary to understand the ways in which one neuron communicates with another through synaptic connections and a process called synaptic transmission. Synaptic transmission comes in two basic forms: (1) excitation and (2) inhibition. As was alluded to above, just a few interconnected neurons can perform sophisticated tasks such as mediate reflexes, process sensory information, generate locomotion and mediate learning and memory.

The approximately 100 billion neurons in the brain share a number of similar features (Figure 1). Neurons are different from most other cells in the body in that they are polarized and have distinct morphological regions, each with specific functions. Dendrites are the region where one neuron receives connections from other neurons. The *cell body* or *soma* contains the nucleus and the other organelles necessary for cellular function, similar to any other "garden variety" cell in the body. The *axon* is a vital component of nerve cells over which information is transmitted from one part of the neuron to the terminal regions of the neuron. Axons can be relatively long extending up to a meter or so in some sensory and motor nerve cells. The *synapse* is the terminal region of the axon and it is here where one neuron forms a connection with another and conveys information through the process known as *synaptic transmission*. One neuron can receive contacts from many different neurons. Therefore, the potential complexity of the networks is immense. Similarly, any one neuron can contact up to 10,000 postsynaptic cells. So most "presynaptic" neurons are "postsynaptic" to some other neuron(s). This is an important point to keep in mind as we continue our discussion.

As was mentioned above, the region of the neuron containing the nucleus is known as the cell body**,** soma, or occasionally some use the terminology perikaryon to refer to this structure as well. The cell body is the principal metabolic center of the neuron. The interior of the soma consists of cytoplasm, a gel-like area within a microtrabecular lattice formed by the microtubules and associated proteins that make up the cytoskeleton. Energy producing metabolism and the synthesis of the

macromolecules used by the cell to maintain its structure and execute its function are the principal activities of the neuronal soma. Embedded within the neuronal cytoplasm are organelles common to other cells in the body such as the nucleus, nucleolus, endoplasmic reticulum, Golgi apparatus, mitochondria, ribosomes, lysosomes, endosomes, and peroxisomes. Many of these cell components are responsible for the expression of genetic information controlling the synthesis of cellular proteins involved in energy production, growth, and replacement of materials lost by attrition.

The membrane of the neuron functions largely as a receptive surface; however, specific inputs (which are termed afferents) from other cells are received primarily on the surface of the cell body and on the surface of the specialized processes of the neuro known as *dendrites*. Dendritic processes may branch extensively and are often covered with projections known as *dendritic spines*. Spines offer a tremendous increase in the surface area available for synaptic contacts. The dendritic processes and spines of neurons are essentially expansions of cytoplasm containing most of the organelles found in the cell body. Dendrites also contain numerous orderly arrays of microtubules. The microtubule associated proteins (MAPs) in the dendrite have a higher molecular weight than those found in the axon. An example is MAP2. In addition, microtubules in dendrites have their positive ends toward the cell soma. Mitochondria are often arranged longitudinally. Rough endoplasmic reticulum and ribosomes are present in large but not small dendrites. The shape and extent of the "dendritic tree" of an individual neuron is indicative of the quantity and variety of information received and processed by that neuron. The dendritic spines often contain microfilaments which are the cytoskeletal element responsible for changes in spine shape observed in some examples of synaptic plasticity. Information is received by the dendrite through an array of receptors on dendrite surface that react to transmitters released from the axon terminals of other neurons. Dendrites may consist of a single twig-like extension from the soma or a multi-branched network capable of receiving inputs from thousands of other cells. For example, an average spinal motor neuron with a moderate-sized dendritic tree, receives over 10,000 contacts, with 2,000 or more of these on the soma and 8,000 or more on the dendrites.

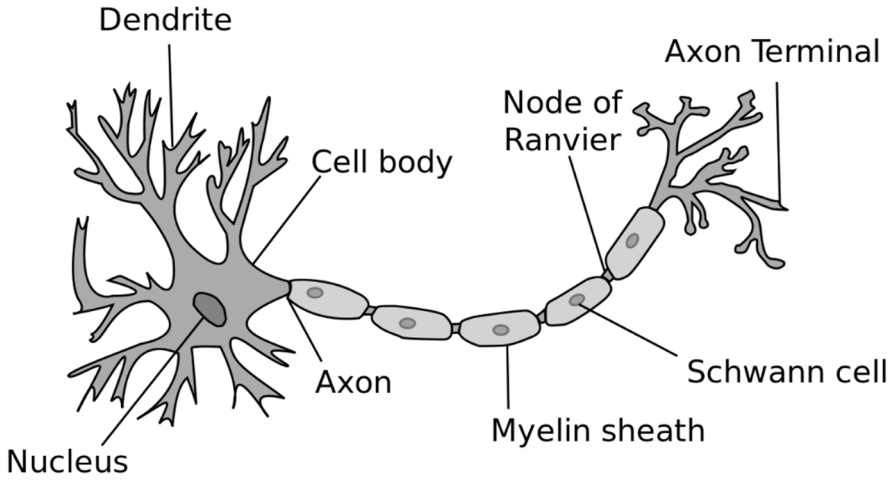

Figure 1.1 The principal components of a “garden variety” neuron. In reality, neurons can exhibit many different shapes and branching patterns than is represented schematically here.

The cone-shaped region of the cell body where the axon originates is termed the *axon hillock*. This area is free of ribosomes and most other cell organelles, with the exception of cytoskeletal elements and organelles that are being transported down the axon. The neurofilaments in the axon hillock become clustered together as fascicles. The region between the axon hillock and the beginning of the myelin sheath is known as the initial segment. In many cases, this region is the anatomical location for the initiation of the action potential. At the distal-most end of the axon and its collaterales are small branches whose tips are button-shaped cytoplasmic enlargements called *terminal boutons* or *nerve endings*.

As is alluded to in the Figure 1.1 legend, numerous variations of the "model" neuron described exist. An important modification, which especially occurs in receptor neurons, involves the designation of a neuronal process as a dendrite or as an axon. Classically, the axon has been identified as the myelinated or unmyelinated process that transmits signals away from the cell body. The classical view of the dendrite is that of an unmyelinated tube of cytoplasm which carries information toward the cell body. However, this distinction does not hold for ALL neurons – a point you will want to file away carefully in your mind. Some cells have a myelinated process that transmits signals toward the cell body. Morphologically the "dendrite" and the "axon" may, therefore, be indistinguishable in some cases. Neither the

position of the cell body nor the presence or absence of myelin is always a useful criterion for understanding the orientation of the neuron. However, with this said, they are histological staining techniques that can aid with the identification process.

The observant reader should note that the presynaptic cell is not directly connected to the postsynaptic cell. The two are separated by a gap known as the *synaptic cleft*. Therefore, to communicate with the postsynaptic cell, the presynaptic neuron needs to release a chemical messenger (Figure 1.2). That messenger is found within the neurotransmitter-containing vesicles. An action potential that invades the presynaptic terminal causes these vesicles to fuse with the inner surface of the presynaptic membrane and release their contents through a process called *exocytosis*. The released transmitter diffuses across the gap between the pre- and the postsynaptic cell and very rapidly reaches the postsynaptic side of the synapse where it binds to specialized receptors that "recognize" the transmitter. The binding to the receptors leads to a change in the permeability of ion channels in the membrane and in turn a change in the membrane potential of the postsynaptic neuron known as a *postsynaptic synaptic potential (PSP)*. Therefore, signaling among neurons is associated with changes in the electrical properties of neurons. To understand neurons and neuronal circuits, it is necessary to understand the electrical properties of nerve cells, which we will explore next.

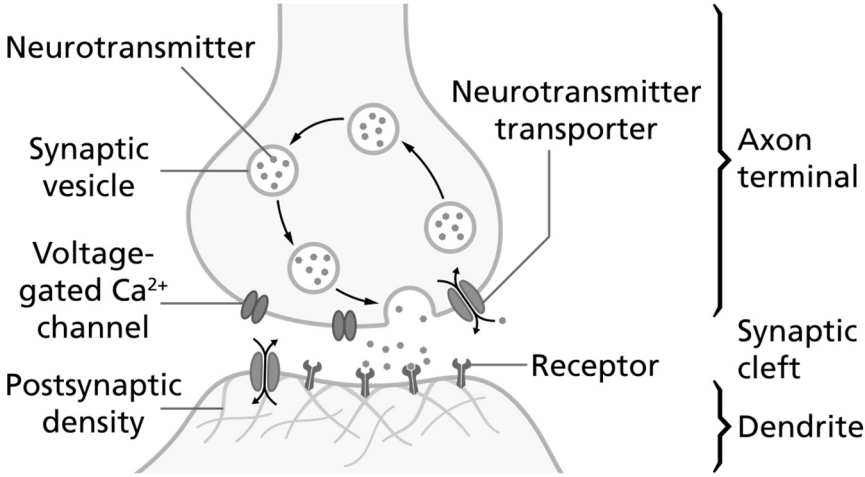

Figure 1.2 Pre- and post-synaptic events between neurons. The translation of an electrical signal into a chemical signal.

Figure 1.3 shows an example of what most neuroscientist would refer to an "idealized nerve cell"; it reflects all the "garden variety" attributes of a neuron we covered above. Placed within the extracellular medium is a microelectrode below. A microelectrode is basically just a small piece of glass capillary tubing that is stretched under heat to produce a very fine tip, about 1 micron in diameter. The microelectrode is filled with a conducting solution and then connected to a recording device such as an oscilloscope or chart recorder of some kind. With the electrode outside the cell in the extracellular medium, a zero potential is recorded because the extracellular medium is "isopotential". If, conversely, the electrode penetrates the cell such that the tip of the electrode is now inside the cell, a sharp deflection is seen on the recording device. A potential of about -60 millivolts inside negative with respect to the outside is recorded. This potential is called the *resting potential* and is constant for indefinite periods of time in the absence of any stimulation. If the electrode is removed, a potential of zero is recorded again. Resting potentials are not just characteristics of nerve cells; all cells in the body have resting potentials. What distinguishes nerve cells and other excitable membranes, for example muscle cells, is that they are capable of changing their resting potential. In the case of nerve cells, for integrating information and transmitting information, whereas, in the case of muscle cells, for producing muscle contractions.

There are two very important features of action potentials. First, they are elicited in an "*all-or-none"* fashion. Either an action potential is elicited with stimuli at or above threshold, or an action potential is not elicited. Secondly, action potentials are very brief events of only several milliseconds in duration. Initiating an action potential is somewhat analogous to applying a match to a fuse. A certain temperature is needed to ignite the fuse, the fuse has a threshold. A match that generates a greater amount of heat than the threshold temperature will not cause the fuse to burn any brighter or faster. Just as action potentials are elicited in an all-or-none fashion, they are also *propagated* in an all-or-none fashion. Once an action potential is initiated in one region of a neuron such as the cell body, that action potential will propagate along the axon (like a burning fuse) and ultimately invade the synapse where it can initiate the process of synaptic transmission.

The action potential consists of several key components. The *threshold* is the value of the membrane potential which, if reached, leads to the all-or-nothing initiation of an action potential. The initial or rising phase of the action potential is called the *depolarizing phase.* The region of the action potential between the 0 mV level and the peak amplitude is the

overshoot. The return of the membrane potential to the resting potential is called the *repolarization phase*. There is also a phase of the action potential during which time the membrane potential can be more negative than the resting potential. This phase of the action potential is called the *undershoot*. The undershoots of the action potentials do not become more negative than the resting potential because they are "riding" on the constant depolarizing stimulus.

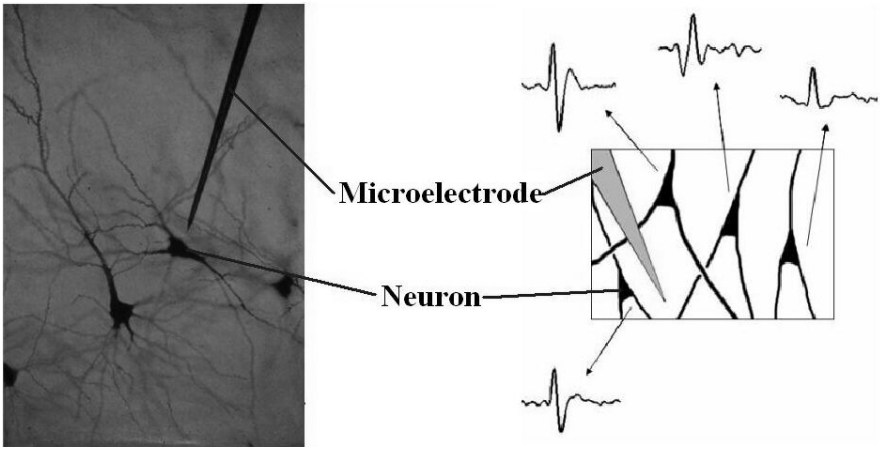

Figure 1.3 Electro-recording of an action potential.

The key to understanding the resting potential is the fact that ions are distributed unequally on the inside and outside of cells, and that cell membranes are selectively permeable to different ions. K^+ is particularly important for the resting potential. The membrane is highly permeable to K^+. In addition, the inside of the cell has a high concentration of K^+ ($[K^+]_i$) and the outside of the cell has a low concentration of K^+ ($[K^+]_o$). Thus, K^+ will naturally move by diffusion from its region of high concentration to its region of low concentration. Consequently, the positive K^+ ions leaving the inner surface of the membrane leave behind some negatively charged ions. That negative charge attracts the positive charge of the K^+ ion that is leaving and tends to "pull it back". Thus, there will be an electrical force directed inward that will tend to counterbalance the diffusional force directed outward. Eventually, equilibrium will be established; the concentration force moving K^+ out will balance the electrical force holding it in. The potential at which that balance is achieved is called the *Nernst Equilibrium Potential*.

Na^+ is critical for the action potential in nerve cells. An action potential is bounded by a region bordered on one extreme by the K^+ equilibrium potential (-75 mV) and on the other extreme by the Na^+ equilibrium potential (+55 mV). The resting potential is -60 mV. Note that the resting potential is not equal to the K^+ equilibrium potential because, as discussed previously, there is a small resting Na^+ permeability that makes the cell slightly more positive. How is it possible for a cell to initially have a resting potential of -60 mV and then, in response to some stimulus (a brief transient depolarization which reaches threshold), change in less than one millisecond to having a potential of approximately +40 mV? In the 1950's, Hodgkin and Huxley, two neurobiologists, provided a hypothesis for this transition. They suggested that the properties of some Na^+ channels in nerve cells (and muscle cells) were unique in that these channels were normally closed but could be opened by a depolarization. This simple hypothesis of voltage-dependent Na^+ channels explains the initiation of the action potential. Suppose a small depolarization causes some of the Na^+ channels to open. The key point is that the increase in Na^+ permeability would produce a greater depolarization, which will lead to an even greater number of Na^+ channels opening and the membrane potential becoming even more depolarized. Once some critical level is reached a positive feedback or regenerative cycle will be initiated, causing the membrane potential to depolarize rapidly from -60 mV to a value approaching the Na^+ equilibrium potential. In order to test the Na^+ hypothesis for the initiation of the action potential, it is necessary to stabilize the membrane potential at a number of different levels and measure the permeability at those potentials. An electronic device known as a voltage-clamp amplifier can "clamp" or stabilize the membrane potential to any desired level and measure the resultant current required for that stabilization. The amount of current necessary to stabilize the potential is proportional to the permeability. Hodgkin and Huxley clamped the membrane potential to various levels and measured the changes in Na^+ conductances (an electrical term for permeability, which for the present discussion can be used interchangeably). The more the cell is depolarized, the greater is the Na^+ conductance. Thus, the experiment provided support for the existence of voltage-dependent Na^+ channels.

In addition to voltage-dependent changes in Na^+ permeability, there are voltage-dependent changes in K^+ permeability. These changes can be measured with the voltage-clamp. There are two important points to consider here. First, just as there are channels in the membrane that are permeable to Na^+ that are normally closed but then open in response to a voltage, there are also channels in the membrane that are selectively

permeable to K^+. These K^+ channels are normally closed, but open in response to depolarization. Secondly, a major difference between the changes in the K^+ channels and the changes in the Na^+ channels is that the K^+ channels are slower to activate or open. Some K^+ channels also do not inactivate. Note that the return of the conductance at the end of the pulse is not the process of inactivation. With the removal of the pulse, the activated channels are deactivated.

Some initial depolarization (a synaptic potential) will begin to open the Na^+ channels. The increase in the Na^+ influx leads to a further depolarization. A positive feedback cycle rapidly moves the membrane potential toward its peak value, which is close but not equal to the Na^+ equilibrium potential. Two processes which contribute to repolarization at the peak of the action potential are then engaged. First, the Na^+ conductance starts to decline due to inactivation. As the Na^+ conductance decreases, another feedback cycle is initiated, but this one is a downward cycle. Sodium conductance declines, the membrane potential begins to repolarize, and the Na^+ channels that are open and not yet inactivated are deactivated and close. Second, the K^+ conductance rises. Initially, there is very little change in the K^+ conductance because these channels are slow to open, but by the peak of the action potential, the K^+ conductance begins to increase significantly and a second force contributes to repolarization. As the result of these two forces, the membrane potential rapidly returns to the resting potential. At the time it reaches -60 mV, the Na^+ conductance has returned to its initial value. Nonetheless, the membrane potential becomes more negative (the undershoot or the hyperpolarizing afterpotential). The key to understanding the hyperpolarizing afterpotential is in the slowness of the K^+ channels. Just as the K^+ channels are slow to open (activate), they are also slow to close (deactivate). Once the membrane potential starts to repolarize, the K^+ channels begin to close because they sense the voltage. However, even though the membrane potential has returned to -60 mV, some of the voltage-dependent K^+ channels remain open. Thus, the membrane potential will be more negative than it was initially. Eventually, these K^+ channels close, and the membrane potential returns to -60 mV. Why does the cell go through these elaborate mechanisms to generate an action potential with a short duration? If the action potential was about one msec in duration, the frequency of action potentials could change from once a second to a thousand a second. Therefore, short action potentials provide the nerve cell with the potential for a large dynamic range of signaling.

Some chemical agents can selectively block voltage-dependent membrane channels. Tetrodotoxin (TTX), which comes from the Japanese

puffer fish, blocks the voltage-dependent changes in Na^+ permeability, but has no effect on the voltage-dependent changes in K^+ permeability. This observation indicates that the Na^+ and K^+ channels are unique; one of these can be selectively blocked and not affect the other. Another agent, tetraethylammonia (TEA), has no effect on the voltage-dependent changes in Na^+ permeability, but it completely abolishes the voltage-dependent changes in K^+ permeability. Use these two agents (TTX and TEA) to test your understanding of the ionic mechanisms of the action potential. What effect would treating an axon with TTX have on an action potential? An action potential would not occur because an action potential in an axon cannot be initiated without voltage-dependent Na^+ channels. How would TEA affect the action potential? It would be longer and would not have an undershoot. In the presence of TEA the initial phase of the action potential is identical, but note that it is much longer and does not have an after-hyperpolarization. There is a repolarization phase, but now the repolarization is due to the process of Na^+ inactivation alone. Note that in the presence of TEA, there is no change in the resting potential. The channels in the membrane that endow the cell with the resting potential are different from the ones that are opened by voltage. They are not blocked by TEA. TEA only affects the voltage-dependent changes in K^+ permeability.

It is easy to get the impression that there is a "gush" of Na^+ that comes into the cell with each action potential. Although, there is some influx of Na^+, it is minute compared to the intracellular concentration of Na^+. The influx is insufficient to make any noticeable change in the intracellular concentration of Na^+. Therefore, the Na^+ equilibrium potential does not change during or after an action potential. For any individual action potential, the amount of Na^+ that comes into the cell and the amount of K^+ that leaves are insignificant and have no effect on the bulk concentrations. However, without some compensatory mechanism, over the long-term (many spikes), Na^+ influx and K^+ efflux would begin to alter the concentrations and the resultant Na^+ and K^+ equilibrium potentials. The Na^+-K^+ pumps in nerve cells provide for the long-term maintenance of these concentration gradients. They keep the intracellular concentrations of K^+ high and the Na^+ low, and thereby maintain the Na^+ equilibrium potential and the K^+ equilibrium potential. The pumps are necessary for the long-term maintenance of the "batteries" so that resting potentials and action potentials can be supported.

The nervous system encodes information not in terms of the changes in the amplitude of action potentials, but rather in their frequency. This is a very universal property. The greater the intensity of a mechanical stimulus to a touch receptor, the greater the number of action potentials; the greater

the amount of stretch to a muscle stretch receptor, the greater the number of action potentials; the greater the intensity of a light, the greater the number of action potentials that is transmitted to the central nervous system. Similarly, in the motor system, the greater the number of action potentials in a motor neuron, the greater will be the contraction of the muscle that receives a synaptic connection from that motor neuron. An action potential in the presynaptic neuron leads to a decrease in the membrane potential of the postsynaptic cell. The membrane potential changes from its resting value of about -60 millivolts to a more depolarized state. This potential is called an *excitatory postsynaptic potential (EPSP)*. It is "excitatory" because it moves the membrane potential toward the threshold and it is "postsynaptic" because it is a potential recorded on the postsynaptic side of the synapse. Generally (and this is an important point), a single action potential in a presynaptic cell does not produce an EPSP large enough to reach threshold and trigger an action potential. But, if multiple action potentials are fired in the presynaptic cell, the corresponding multiple excitatory potentials can summate through a process called *temporal summation* to reach threshold and triggering an action potential. EPSPs can be viewed as a "go signal" to the postsynaptic neuron to transmit information through a network pathway.

Neurons are very much like adding machines if you will. They are constantly adding up the excitatory and the inhibitory synaptic input in time (temporal summation) and over the area of the dendrites receiving synaptic contacts (*spatial summation)*, and if that summation is at or above threshold they fire an action potential. If the sum is below threshold, no action potential is initiated. This is a process called *synaptic integration*. Initially, two action potentials in the green neuron produced summating EPSPs that fired an action potential in the blue neuron. But, if an IPSP from the inhibitory neuron occurs just before two action potentials in the excitatory neuron, the summation of the one IPSP and the two EPSPs is below threshold and no action potential is elicited in the postsynaptic cell. The inhibitory neuron (and inhibition in general) is a way of gating or regulating the ability of an excitatory signal to fire a postsynaptic cell. As was referred to earlier in the chapter, a neuron can receive contacts from up to 10,000 presynaptic neurons, and, in turn, any one neuron can contact up to 10,000 postsynaptic neurons. This combinatorial possibility can give rise to enormously complex neuronal circuits, which currently are very difficult for neuroscientist to understand. But despite this potential vast complexity, much can be learned about the functioning of neuronal circuits by examining the properties of a subset of simple circuit

configurations. Although simple, they can do much of what needs to be done by a nervous system.

The concept of *feedforward excitation*, allows one neuron to relay information to its neighbor. Long chains of these can be used to propagate information through the nervous system. The concept of f*eedforward inhibition*, involves a presynaptic cell which excites an inhibitory interneuron (an interneuron is a neuron interposed between two neurons) and that inhibitory interneuron then inhibits the next following cell. This is a way of shutting down or limiting excitation in a downstream neuron in a neural circuit. *Convergence/Divergence* is when one postsynaptic cell receives convergent input from a number of different presynaptic cells and any individual neuron can make divergent connections to many different postsynaptic cells. Divergence allows one neuron to communicate with many other neurons in a network. Convergence allows a neuron to receive input from many neurons in a network. *Lateral inhibition* involves a presynaptic cell that excites inhibitory interneurons and they inhibit neighboring cells in the network. This type of circuit is often used in sensory systems to provide edge enhancement. *Feedback/recurrent inhibition* occurs when a presynaptic cell connects to a postsynaptic cell, and the postsynaptic cell in turn connects to an interneuron, which then inhibits the presynaptic cell. This circuit can limit excitation in a pathway. Each neuron in the closed chain inhibits the neuron to which it is connected. This circuit would at first appear to do nothing, but, it can lead to the generation of complex patterns of spike activity. In f*eedback/recurrent excitation*, a presynaptic neuron excites a postsynaptic neuron and that postsynaptic neuron excites the presynaptic neuron. This type of circuit can serve a switch-like function because once the presynaptic cell is activated that activation could be perpetuated. Activation of the presynaptic neuron could switch this network on and it could stay on. These simple designs are ubiquitous components of many neural circuits.

One of the best understood microcircuits is the circuit that mediates simple reflex behaviors. Consider the “knee jerk” or stretch reflex (Figure 1.4). A neurologist will strike the knee of a patient with a rubber hammer, which elicits an extension of the leg. This test is used as a simple way to examine the integrity of some of the sensory and motor pathways in the spinal cord. The tap of hammer stretches the muscle and leads to the initiation of action potentials in *sensory neurons* within the muscle that are sensitive to stretch. The action potentials are initiated in an all-or-none fashion and propagate into the spinal cord where the axon splits into two branches. The action potential in the sensory neuron invades the synaptic

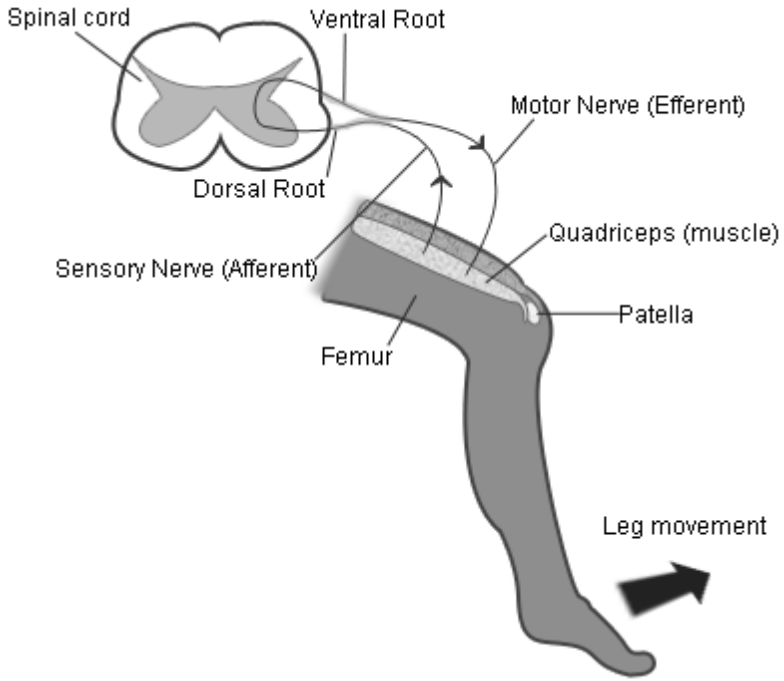

Figure 1.4 The patellar reflex, a classic example of a microcircuit.

terminal of the sensory neuron causing the release of transmitter and subsequent excitation of the motor neuron. The stretch to the muscle leads to an action potential in the motor neuron, which then propagates out the peripheral nerve to invade the synapse at the muscle, causing the release of transmitter and an action potential in the muscle. The action potential in the muscle cell leads to a contraction of the muscle and an extension of the limb. So, here we have a simple feedforward excitation circuit that mediates a behavior. The action potential in the sensory neuron invades the synaptic terminal of the sensory neuron causing the release of transmitter, and subsequent excitation of the postsynaptic interneuron. This neuron is called an *interneuron* because it is interposed between one neuron and another neuron. The excitation of the interneuron leads to the initiation of an action and the subsequent release of transmitter from the presynaptic terminal of the interneuron, but for this branch of the circuit, the transmitter leads to an IPSP in the postsynaptic flexor motor neuron. The functional consequences of this feedforward inhibition it is to

decrease the probability of the flexor motor neuron becoming active and producing an inappropriate flexion of the leg.

The most numerous cellular constituents of the central nervous system are non-neuronal, neuroglial ("nerve glue") cells that occupy the space between neurons. It has been estimated that there are roughly 360 billion glial cells, which comprise 80-90% of the cells in the CNS. Neuroglia differ from neurons in several general ways in that they:

1. Do not form synapses
2. Have principally only one type of process
3. Retain the ability to divide
4. Are less electrically excitable than neurons

Neuroglia are classified based on size and shape for their nucleus and distinguished from neurons, at the light microscopic level. Alkaline (basic) dyes are used to show nuclear morphology. In addition, several metal stains are used show the shape of the cell and cytoplasmic architecture. Characteristics of nuclei, including size, shape, staining intensity, and distribution of chromatin, are used to distinguish cell types in pathological material. Cell body characteristics, including size, shape, location, branching pattern, and density of processes, are also commonly used. Neuroglia are divided into two major categories based on size; macroglia and the microglia. The macroglia are of ectodermal origin and consist of astrocytes, oligodendrocytes and ependymal cells. Microglia cells are almost certainly of mesodermal origin. A comparison of the various neuroglial types is shown in Figure 1.5.

There are three types of macroglia: oligodendroglia, ependyma, and astrocytes. This section also discusses the two types of astrocytes: protoplasmic and fibrous. Protoplasmic astrocytes are found primarily in gray matter. With silver or glial specific stains, their cell bodies and processes are very irregular. The processes may be large or very fine, sometimes forming sheets that run between axons and dendrites, and may even surround synapses. These fine sheet-like processes give the protoplasmic astrocyte cell body a "fuzzy" or murky appearance under the light microscope. Bundles of fine fibrils may be seen within the cytoplasm. The nucleus of a protoplasmic astrocyte is ellipsoid or bean-shaped with characteristic flecks of chromatin. Specific types of intercellular junctions have been noted between the processes of protoplasmic astrocytes. These possibly mediate ion exchange between cells. Fibrous astrocytes are found primarily in white matter, have a smoother cell body contour than do protoplasmic astrocytes as seen with

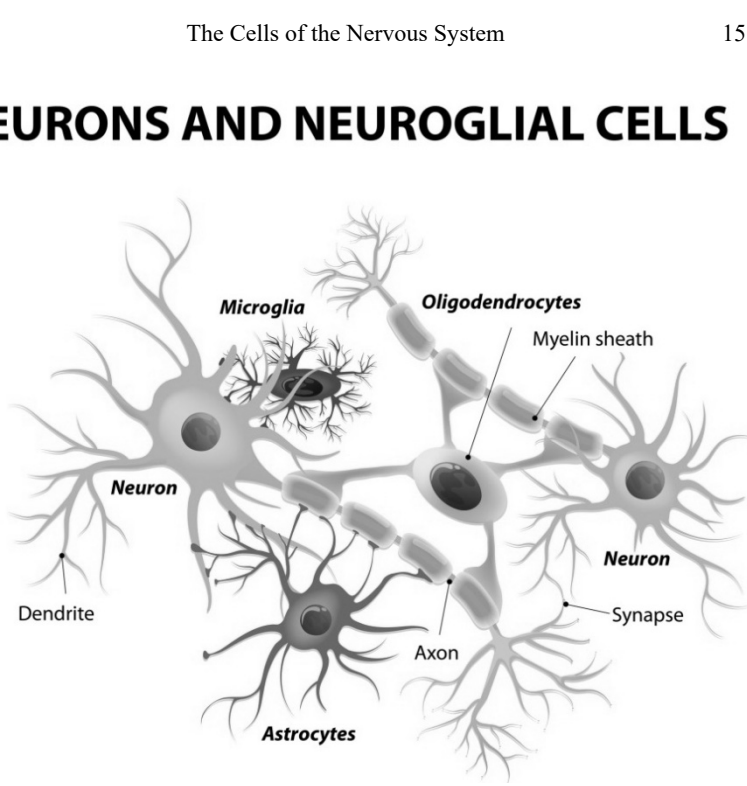

Figure 1.5 Types of glial cells (neuroglia) typically found in the nervous system.

glial-specific stains, and have processes that tend to emerge from the cell body radially. These processes are narrower and branch to form end feet on blood vessels, ependyma, and pia. Consequently, the processes of fibrous astrocytes do not form sheets and do not tend to conform to the shape of the surrounding neurons or vascular elements. The major distinguishing feature of fibrous astrocytes, as the name suggests, is an abundance of glial fibrils arranged in parallel arrays in the cytoplasm and extending into the processes. In Nissl stains, the fibrous astrocytes have a nucleus essentially the same as that of the protoplasmic type with a flecked appearance. Intercellular adherences have also been observed between fibrous astrocytes. Both types of astrocytes function to support the neurons in their immediate vicinity. They provide a physical barrier between cells, maintain the ionic and pH equilibrium of the extracellular space around neurons, and continually modify the chemical environment of the neighboring cells. During development, they form scaffolding along which nerve cells migrate to achieve their mature structure. During injury, the astrocytes proliferate and phagocytize dead cells. This often leads to the

formation of glial scar. In addition to these general functions, astrocytes also act in more specialized ways to facilitate neuron function. They metabolize neurotransmitters by removing them from the synaptic cleft.

Oligodendrocytes are also located in both gray and white matter. They are the predominant cell type in white matter where they are often located as rows of cells between groups of neuronal processes. These are termed interfascicular oligodendroglia and are involved in the formation and maintenance of the myelin surrounding the neuronal processes nearby. In gray matter, oligodendroglia are usually located near neurons and, therefore, are known as perineuronal satellite cells. Cell bodies of oligodendroglia are often located near capillaries, but they lack the definite perivascular end feet characteristic of astrocytes. The role of oligodendroglia in the central nervous system, particularly of the interfascicular oligodendrocytes, is the formation and maintenance of myelin. Myelin wraps the neuronal axon. A single oligodendrocyte contributes to the myelination of several adjacent nerve processes. Moreover, more than one oligodendrocyte contributes to the myelination of a single internode of an axon. The lamellae of myelin membranes result from the spiral wrapping of the axon by cytoplasmic processes of interfascicular oligodendroglia. Also, the oligodendrocyte forming a particular myelin internode (the myelin between two nodes) is seldom seen directly adjacent to the myelin-wrapped process. This is because thin cytoplasmic bridges connect the region of the oligodendrocyte cell body to the external wrap of myelin. It is important to note that the region of the axon exposed at the *node of Ranvier* is not bare. It may be the site of branching of the axon, the site of synaptic contacts, or it may be covered with various glial processes. The axon in the nodal region usually contains concentrations of organelles, especially mitochondria. In the peripheral nervous system (PNS), Schwann cells are responsible for the myelin formation. These cells myelinate axons differently than the interfascicular oligodendroglia. They migrate around the axon, laying a membrane covering around the axon by squeezing out the cytoplasm of the Schwann cell. Also, every internode of a PNS axon represents a single Schwann cell. In addition unmyelinated axons in the PNS are also enclosed by membranes formed by Schwann cells.

Ependymal cells are derived from the early germinal epithelium lining the lumen of the neural tube and thus are also ectodermal derivatives (along with neurons, astrocytes, and oligodendrocytes). Ependymal cells line the ventricles of the brain and the central canal of the spinal cord. They are arranged in a single-layered columnar epithelium, and have many of the histological characteristics of simple epithelium, which vary from squamous to cuboidal depending upon their location. The ependyma

forming the ventricular lining do not connect to a basal lamina, but rest directly upon underlying nervous tissue.

Microglia, in contrast to the other types of glial cells, originate from embryonic mesoderm. They are present throughout the central nervous system, but tend to be inconspicuous in mature normal tissue and are difficult to identify with the light or electron microscope. They are more abundant in gray matter, and may compromise up to 5-10% of the neuroglia in the cerebral cortex. The general appearance of microglia is similar to oligodendrocytes, although they are smaller and have undulating processes with spine-like projections. Microglial nuclei are elongated or triangular and stain deeply with alkaline dyes. Following damage to nervous tissue, microglia proliferate and migrate to the site of injury where they clear cellular debris by phagocytosis. The reacting microglia have a swollen form with shortened processes and are difficult to discriminate from phagocytes from the periphery or migrating perivascular cells. It is estimated that at least one third of the phagocytes appearing in the area of a lesion are of CNS origin.