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The Cytology of Neurons

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THE CELLS OF THE NERVOUS system vary more than those in any other part of the body. Nevertheless, all neurons have common features that distinguish them from cells in other tissues. For example, they typically are highly polarized. Furthermore, cell functions are compartmentalized, an arrangement that contributes significantly to the processing of electrical signals. The chief functional compartments of neurons—the cell body, dendrites, axons, and terminals—are usually separated by considerable distances, a feature that accounts for the functional polarization discussed in Chapter 2. In most neurons the cell body, which contains the nucleus and the organelles for making RNA and protein, contains less than a tenth of the cell's total volume. The dendrites and axon that originate from the cell body make up the remainder. As discussed in Chapter 2, dendrites are thin processes that branch several times and are specially shaped to receive synaptic input from other neurons. The cell body usually gives off a single axon, another thin process that propagates electrical impulses, often over considerable distances, to the neuron's synaptic terminals on other nerve cells or on target organs.

Neurons also differ from most other cells in being excitable. Rapid shifts in electrical potential are made possible by specialized protein structures (ion channels and pumps) in the cell membrane that control the instantaneous flow of ions into and out of the cells. Polarization and electrical excitability are not unique to neurons, however. Epithelial cells and other nonneuronal secretory cells also are polarized, with basolateral and apical surfaces that differ in structure and function. Some nonneural cells, notably muscle, are excitable, and like nerve cells their excitability depends on special protein molecules that allow ions to pass across the plasma membrane. In neurons, however, polarity and excitability are developed to a higher degree, permitting signals to be received, processed, and conducted over long distances.

Although built on a common plan, neurons are quite diverse—over 50 distinct types have been described. This cytological diversity, which results from developmental differentiation, is also apparent on a molecular level. Each neuron expresses a combination of general and specific molecules. The kinds of proteins a cell synthesizes depends on the genes expressed in the cell; each type of cell synthesizes certain macromolecules (enzymes, struc

tural proteins, membrane constituents, and secretory products) and not others. In essence each cell is the macromolecules that it makes. Many of these molecules are common to all cells in the body; some are characteristic of all neurons, others of large classes of neurons, and still others are restricted to only a few nerve cells.

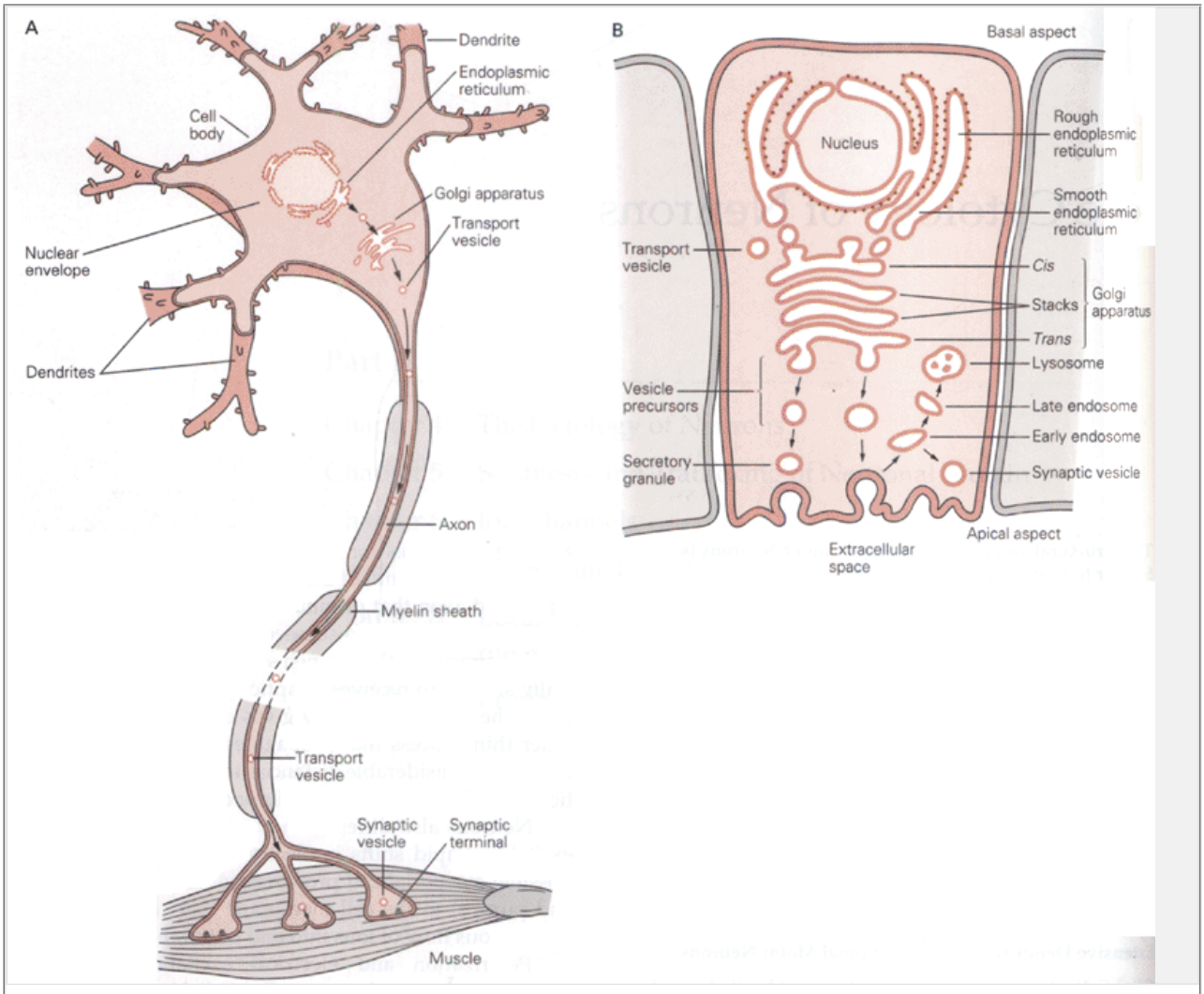

Figure 4-1 The epithelial blueprint of a neuron.

A. This diagram of a spinal motor neuron shows the cell body and the nucleus surrounded by the nuclear envelope, which is continuous with the rough and smooth endoplasmic reticulum. The space between the two membranes that constitute the nuclear envelope is continuous with the extracellular space. Dendrites emerge from the basal aspect of the neuron, the axon from the apical aspect. (Adapted from Williams et al. 1989.) **B**. This diagram of an epithelial cell shows a membrane system called the *vacuolar apparatus*, which includes all the major or- ganelles found in the neuron. Vesicles, which bud off the endoplasmic reticulum, shuttle to the cis face of the Golgi complex.

This chapter begins with an overview of the neuron, describing traits common to all neuronal types. We then discuss the differences among nerve cells. We have chosen to illustrate neuronal diversity with a detailed description of only three types of neurons: the sensory neurons of the dorsal root ganglion, the motor neurons of the spinal cord, and the pyramidal cells of the hippocampus. Neuronal structure can be readily illustrated by comparing the sensory and motor neurons in the spinal cord that mediate the stretch reflex, responsible for the classic kneejerk reflex. The distinctive features of the two neurons in this simple reflex circuit nicely illustrate the relationship between anatomy and function. The specialized features of nerve cells in complex neuronal circuits in the brain are illustrated by examining the pyramidal neurons of the CA3 and CA1 regions of the hippocampus. These cortical neurons belong to circuits thought to be responsible for memory storage (Chapters 62 and 63) and to be affected in certain forms of epilepsy (Chapter 46).

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The Structural and Functional Blueprint of Neurons Is Similar to Epithelial Cells

Neurons develop from epithelial cells and retain fundamental epithelial features. For example, both cell types have distinctive poles: the epithelial cell's basolateral surface corresponds to the aspect of the neuron's cell body from which dendrites arise, while the apical surface corresponds to the aspect of the neuron from which the axon arises (Figure 4-1A).

The boundaries of the neuron are defined by the external cell membrane, or *plasmalemma*. Nerve cell membranes have the general asymmetric bilayer structure of all biological membranes and represent a hydrophobic barrier impermeable to most water-soluble substances. The cytoplasm has two main components: the cytosol (including the cytoskeletal matrix) and the membranous organelles.

The cytosol is the aqueous phase of the cytoplasm. In this phase only a very few proteins are freely soluble, mostly enzymes that catalyze various metabolic reactions. Many cytosolic proteins have general housekeeping functions and are common to all neurons. Others have specific roles in particular types of neurons; for example, the enzymes involved in the synthesis and degradation of the particular substance used as a neuro-transmitter. Moreover, some cytosolic proteins are distributed unevenly in the cell because they interact to form aggregates, particles, or matrices. Many cytosolic proteins involved in signaling are concentrated at the cell's periphery in the cytoskeletal matrix immediately adjacent to the plasmalemma.

Membranous Organelles Are Selectively Distributed Throughout the Neuron

The membranous organelles of the cytoplasm include the mitochondria and peroxisomes as well as a complex system of tubules, vesicles, and cisternae (the vacuolar apparatus) that consists of the rough endoplasmic reticulum, the smooth endoplasmic reticulum, the Golgi complex, secretory vesicles, endosomes, lysosomes, and a multiplicity of transport vesicles that functionally interconnect these various compartments (Figures 4-1B and 4-2).

Membranes of the vacuolar apparatus are thought to be derived from deep invaginations of the cell's external membrane that become discrete organelles. Their lumen corresponds topologically to the outside of the cell; consequently the inner leaflet of their lipid bilayer corresponds to the outer leaflet of the plasmalemma (Figure 4-1B). Even though the major subcompartments of this system are anatomically discontinuous, membranous and lumenal material are moved from one compartment to another with great efficiency and specificity by means of transport vesicles. For example, proteins and phospholipids synthesized in the rough endoplasmic reticulum are transported to the Golgi complex and then to secretory vesicles destined to fuse with the plasmalemma by exocytosis (the secretory pathway). Conversely, membrane taken into the cell in the form of en-docytic vesicles is incorporated into early endosomes, which are sorting compartments concentrated at the cell's periphery; the membrane is then either shuttled

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back to the plasmalemma by vesicle recycling or directed to late endosomes and eventually to lysosomes for degradation (the endocytic pathway).

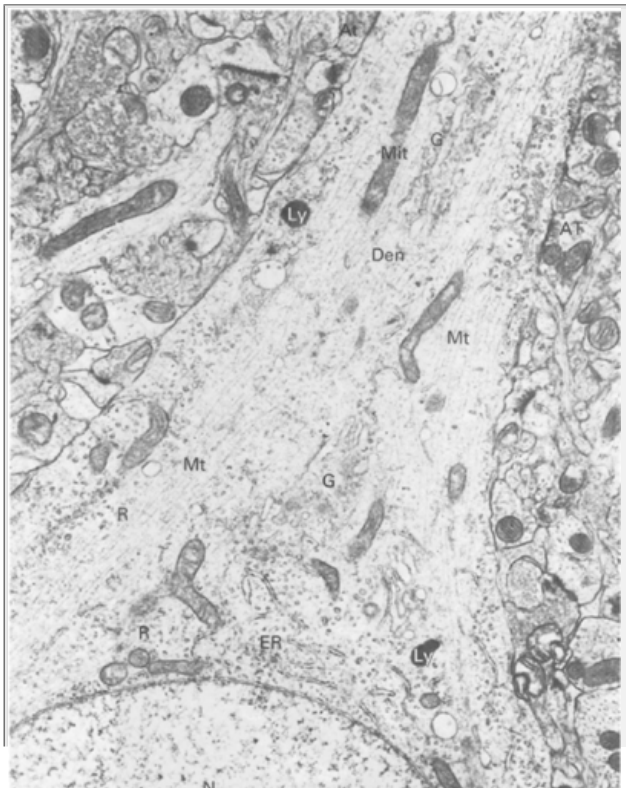


Figure 4-2 Endoplasmic reticulum in a pyramidal cell. This micrograph of the basal pole of a pyramidal neuron's cell body, from which a single dendrite emerges, reveals therough and smooth endoplasmic reticulum (**ER**) above the nucleus (**N**). A portion of the Golgi complex (**G**) appears at the base of the dendrite (**Den**); some Golgi cisternae have entered the dendrite, as have mitochondria (**Mit**), lysosomes (**Ly**), and ribo-somes (**R**). Microtubules (**Mt**) are the prominent cytoskeletal filaments seen in the cytosol. Axon terminals (**AT**) are seen synapsing on the neuron. (From Peters et al. 1991.)

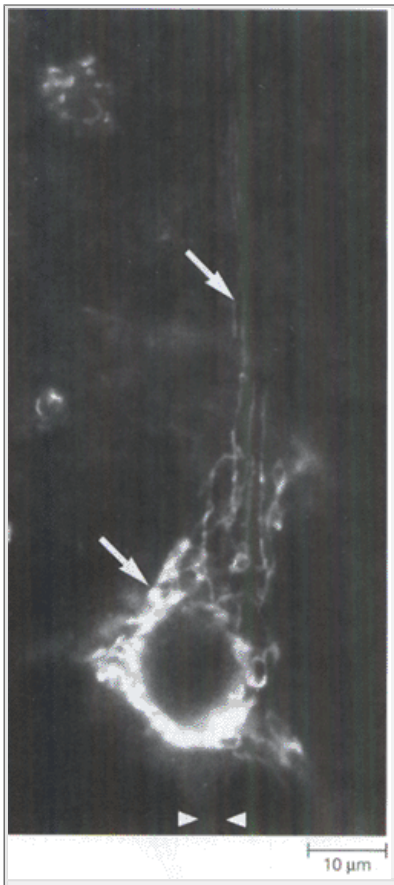


Figure 4-3 Under the light microscope the Golgi complex appears as a network of filaments that extend into dendrites (arrows), but not into the axon. The **arrowheads** at the bottom indicate the axon hillock. The Golgi complex in this micrograph is in a large neuron of the brain stem immuno-stained with antibodies specifically directed against this or- ganelle. (From De Camilli et al. 1986.)

A specialized portion of the rough endoplasmic reticulum forms a spherical flattened cisterna called the nuclear envelope, which surrounds the chromosomal DNAand its associated proteins and defines the nucleus (see Figure 4-1). This cisterna is continuous with other portions of the rough endoplasmic reticulum. Because of this continuity, the nuclear envelope is presumed to have evolved to ensheathe the chromosomes by an in-vagination of the plasmalemma. The nuclear envelope is interrupted by the nuclear pores, where fusion of the inner and outer membrane of the nuclear envelope results in the formation of hydrophilic channels through which proteins and RNA are exchanged between the cytoplasm proper and the nuclear cytoplasm. Thus the nucleoplasm and cytoplasm can be considered functionally continuous domains of the cytosol.

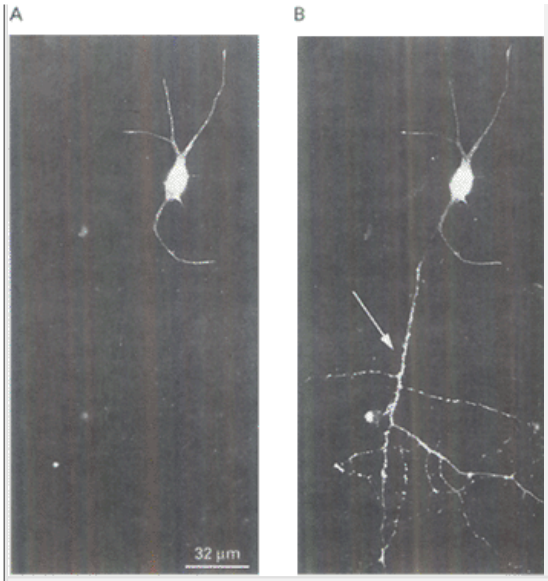
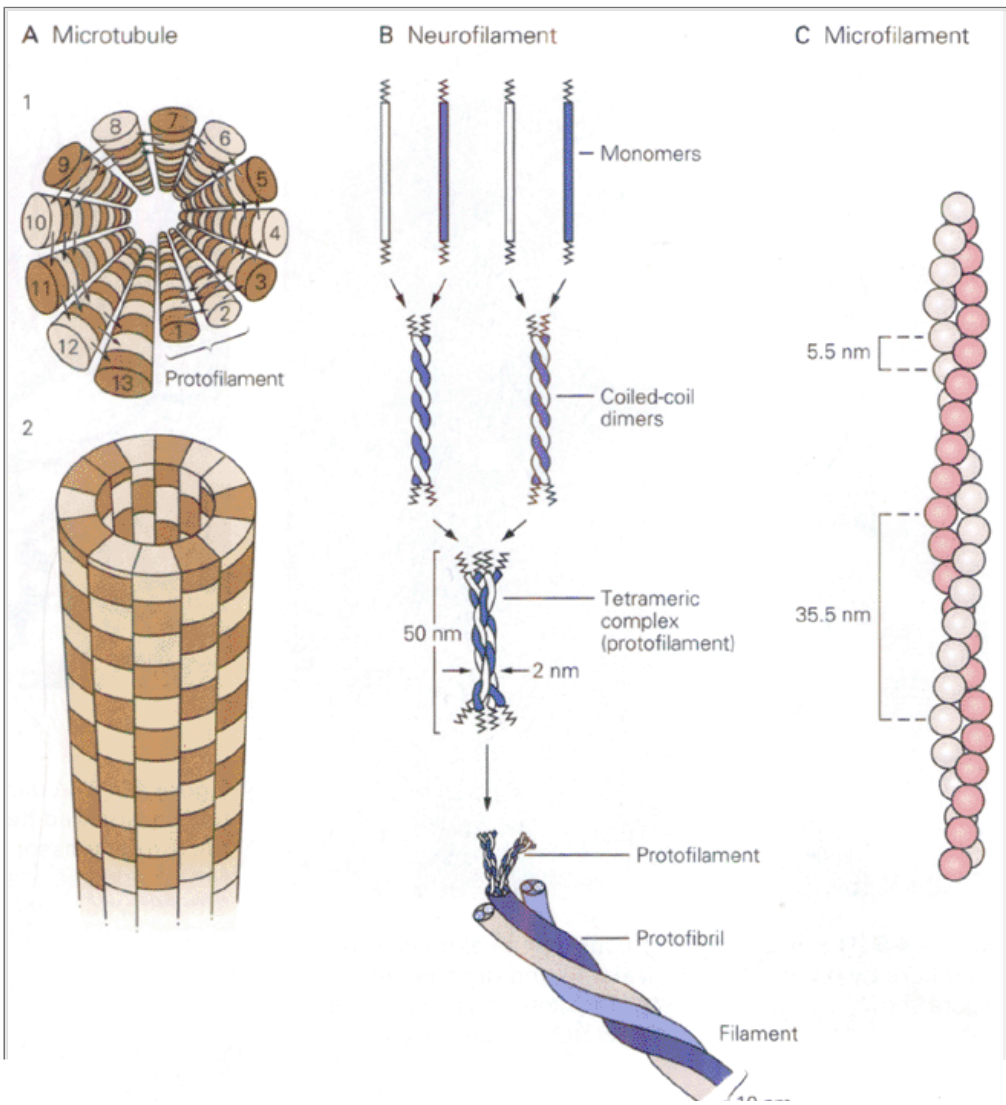


Figure 4-4 Neurons develop two distinct types of processes, dendrites and axons, even when grown in isolation. The figure shows a hippocampal neuron grown in isolation in primary culture and stained by double immunofluorescence for the synaptic vesicle protein synaptophysin and the transferrin receptor, a protein involved in iron uptake. When photographed through an appropriate filter, immunofluorescence corresponding to the transferrin receptor is seen only in dendrites (**A**). When photographed for synapsin, synaptic vesicles are selectively concentrated in the axon (**arrow**) as revealed by synapsin immunofluorescence (**B**). (From Cameron et al. 1991.)

Mitochondria and peroxisomes make use of molecular oxygen. Mitochondria generate ATP, the major molecule by which cellular energy is transferred or spent. Peroxisomes engage in detoxification through peroxidation reactions and also prevent the accumulation of the strong oxidizing agent hydrogen peroxide. These two organelles, which are thought to be derived from symbi

otic organisms that invaded eukaryotic cells early in evolution, are not functionally continuous with the vacuolar apparatus of the cell.



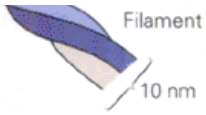


Figure 4-5 Atlas of fibrillary structures.

A. Microtubules, the largest-diameter fibers (25 nm), are helical cylinders composed of 13 protofilaments each 5 nm in width. Protofilaments are linearly arranged pairs of alternating α- and β-tubulin subunits (each subunit has a molecular weight of about 50,000). A tubulin molecule is a heterodimer consisting of one α- and one β-tubulin subunit. **1**. In this exploded view up a microtubule the arrows indicate the direction of the right-handed helix. **2**. A side-view of a micro-tubule shows the alternating α- and β-subunits.

B. Neurofilaments are built with fibers that twist around each other to produce coils of increasing thickness. The thinnest units are monomers that form coiled-coil heterodimers. These dimers form a tetrameric complex that becomes the protofilament. Two protofilaments become a protofibril, and three protofibrils are helically twisted to form the 10 nm neurofilament. (Adapted from Bershadsky and Vasiliev 1988.)

C. Microfilaments, the smallest-diameter fibers (about 7 nm), are composed of two strands of polymerized globular (G) actin monomers arranged in a helix. Several isoforms of G-actin are encoded by families of actin genes. In mammals there are at least six different (but closely related) actins. Each variant is encoded by a separate gene. Microfilaments are polar structures; the globular monomers actually are asymmetric. The monomers look like arrowheads, with a pointed tip and chevron-shaped (barbed) end, and polymerize tip to tail.

The cytoplasm of the cell body extends into the den-dritic tree without any functional boundary. Generally, all organelles present in the cytoplasm of the cell body are also present in dendrites, although the concentrations of some organelles, such as the rough endoplasmic reticulum, the Golgi complex, and lysosomes, progressively diminish with distance from the cell body. In contrast, a sharp functional boundary exists at the axon hillock, the point of emergence of the axon. For example, ribosomes, the rough endoplasmic reticulum, and the Golgi complex—the organelles that represent the main protein biosynthetic machinery of the neuron—for the most part are excluded from axons (Figure 4-3). Lysosomes and certain proteins, which in epithelial cells are selectively targeted to the basolateral surface of the cell, also are excluded from axons. Axons are, however, rich in synaptic vesicles, synaptic vesicle precursor membranes, and endocytic intermediates involved in synaptic vesicle traffic (Figures 4-1 and 4-4).

Mitochondria and the smooth endoplasmic reticulum are present in all neuronal compartments, including the axon. The smooth endoplasmic reticulum is anatomically continuous with the rough endoplasmic reticulum. One of its functions is to act as a regulated Ca2store throughout the neuronal cytoplasm. It also performs a variety of enzymatic reactions and is involved in lipid metabolism.

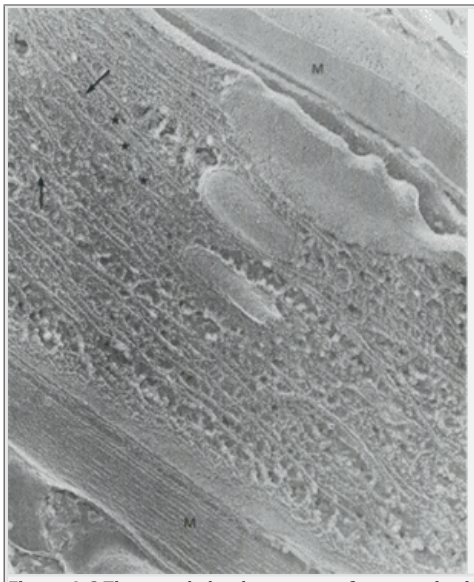


Figure 4-6 The cytoskeletal structure of an axon is visualized here by means of quick freezing and deep etching. The figure shows the dense packing of microtubules and neurofilaments linked by cross-bridges. Microtubules are indicated by **stars**. The arrows bracket the microtubule-rich domain of the axon through which organelles are transported both in the an-terograde and the retrograde direction. **M** = myelin sheath. × 105,000. (Courtesy of B. Schnapp and T. Reese.)

The Cytoskeleton Determines the Shape of the Neuron

The cytoskeleton is the major intrinsic determinant of the shape of a neuron and is responsible for the asymmetric distribution of organelles within the cytoplasm. It contains three main filamentous structures: micro-tubules, neurofilaments (called intermediate filaments in nonneuronal cells), and actin microfilaments (Figures 4-5 and 4-6). These filaments and their associated proteins account for about 25% of the total protein of the neuron.

Microtubules form long scaffolds that extend the full length of the neuron and play a key role in developing and maintaining the neuron's processes. Asingle micro-tubule can be as long as 0.1 mm. Microtubules are constructed of 13 protofilaments in a tubular array with an outside diameter of 25–28 nm (Figure 4-5A). Each protofilament consists of several pairs of α- and β-tubulin subunits arranged linearly. The polar structure of the tubulin dimer creates a plus and a minus end of the polymer. The tubulins are encoded by a multigene family; at least six genes code for both the - and -subunits. More than 20 isoforms of tubulin are present in the brain because of the expression of different genes as well as post-translational modifications.

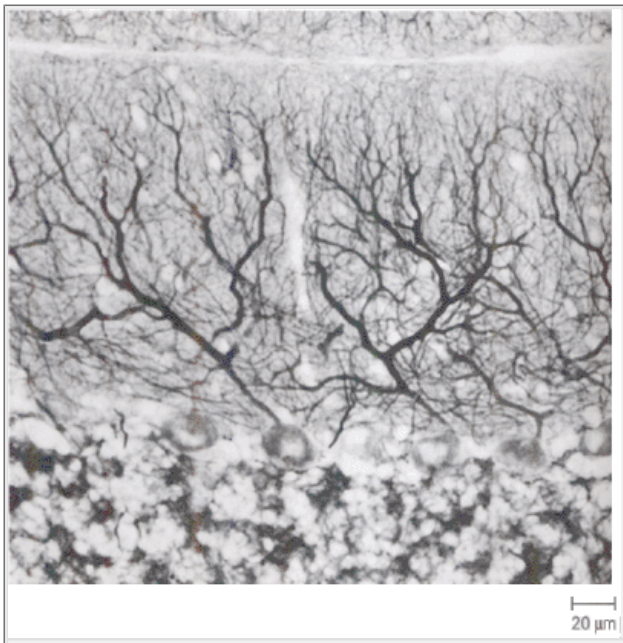


Figure 4-7 The dendritic architecture in the cerebellar cortex is visualized here by immunoperoxidase staining for the microtubule-associated protein MAP2, a dendrite-specific MAP. Dendrites of all classes of neurons are stained. The field is dominated by the dendrites of Purkinje cells. (Courtesy of P. De Camilli.)

Tubulin is a GTPase and microtubules grow by the addition of GTP-bound tubulin dimers at their plus end. Shortly after polymerization GTPis hydrolyzed to GDP. When a microtubule stops growing its plus end becomes capped by GDP-bound tubulin. Given the low affinity of the GDP-bound tubulin for the polymer, this would lead to rapid catastrophic depolymerization unless the microtubule were stabilized by interaction with other proteins. In fact, microtubules undergo rapid cycles of polymerization and depolymerization in dividing cells, but they are much more stable in mature dendrites and axons. This stability is due to microtubule-associated proteins (MAPs), which promote the oriented polymerization and assembly of the microtubules. The MAPs in the axons differ from those in the dendrites. For example, MAP2 is present in dendrites but

absent from axons (Figure 4-7), while tau and MAP3 are present in the axon.

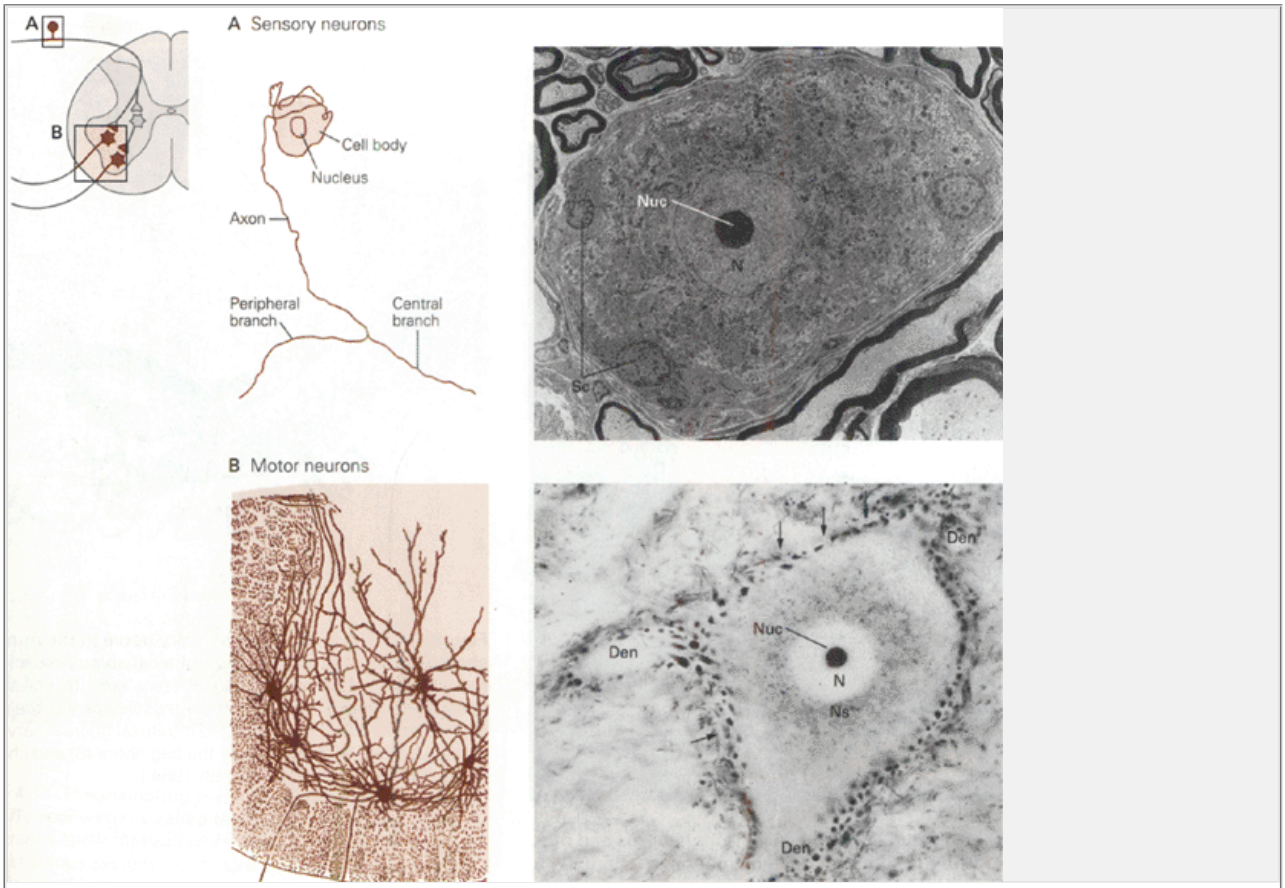


Figure 4-8 A sensory (dorsal root ganglion) cell and a spinal motor neuron form a monosynaptic circuit that controls the knee-jerk stretch reflex.

A. Sensory neuron. **Left**: The axon of the primary sensory neuron is typically quite convoluted before it bifurcates into a central and a peripheral branch. The cell body contains a prominent nucleus. (From Dogiel 1908.) **Right**: Low-power electron micrograph shows the cell body of a large dorsal root ganglion cell. **A** prominent nucleolus (**Nuc**) can be seen within the nucleus (**N**). The cell body of the neuron is surrounded by Schwann cells (**Sc**), the type of glial cells found in the peripheral nervous system. (Courtesy of R. E. Coggeshall and F. Mandriota.)

B. Motor neuron. **Left**: Many dendrites typically branch from the cell bodies of spinal motor neurons, as shown by five spinal motor neurons in the ventral horn of a kitten. (From Ramón y Cajal 1909.) **Right**: Detail of the cell body of a motor neuron is shown in this photomicrograph. An enormous number of nerve endings from presynaptic neurons (**arrows**) are visible. These terminals, called synaptic boutons, appear as knob-like enlargements on the cell membrane. The synaptic boutons are prominent in this micrograph because the tissue is specially impregnated with silver. Three dendrites (**Den**) are also shown. The nucleus and its nucleolus are surrounded by Nissl substance (**Ns**), clumps of ribosomes associated with the membrane of the endoplasmic reticulum. (Courtesy of G. L. Rasmussen.)

Neurofilaments, 10 nm in diameter, are the bones of the cytoskeleton (see Figure 4-5B). They are the most abundant fibrillar components of the axon. (On average, there are 3-10 times more neurofilaments than microtubules in an axon.) Neurofilaments are related to the intermediate filaments of other cell types, all of which belong to a family of proteins called cytokeratins. (Other cytokeratins include vimentin, glial fibrillary acidic protein, desmin, and keratin.) Unlike microtubules, neuro-filaments are very stable and almost totally polymerized

in the cell. In Alzheimer's disease and some other degenerative disorders they become modified and form a characteristic lesion called the neurofibrillary tangle (see Chapter 58).

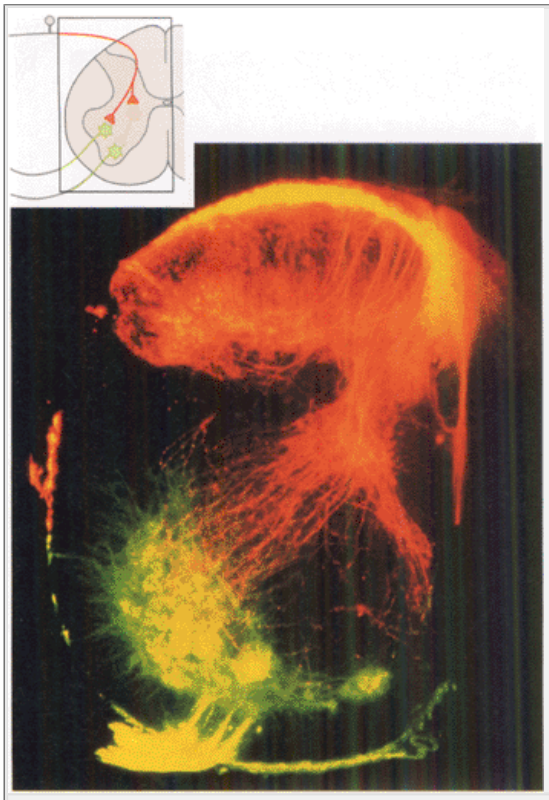


Figure 4-9 Connections between sensory neurons and motor neurons in the spinal cord of an embryonic rat are shown in this micrograph. The sensory axons (orange) enter the spinal cord through the dorsal root and then run longitudinally in the dorsal column. Collaterals descend from the dorsal column to the spinal gray matter, where they arborize and make synaptic contact with the dendrites of motor neurons (**green**). (Courtesy of W. Snider.)

Microfilaments, 3-5 nm in diameter, are the thinnest of the three main types of fibers that make up the cy-toskeleton (see Figure 4-5C). Like the thin filaments of muscle, microfilaments are polar polymers of globular actin monomers (each bearing an ATP or ADP) wound into a double-stranded helix. Actin is a major constituent of all cells, perhaps the most abundant animal protein in nature. Several closely related molecular forms of actin, each encoded by a different gene, have been identified: the actin of skeletal muscle, and at least two other molecular forms, β and γ. Neural actin is a mixture of the β and γ species, which differ from muscle actin at a few amino acid residues. Most of the actin molecule is highly conserved, not only in different cells of an animal but also in organisms as distantly related as humans and protozoa.

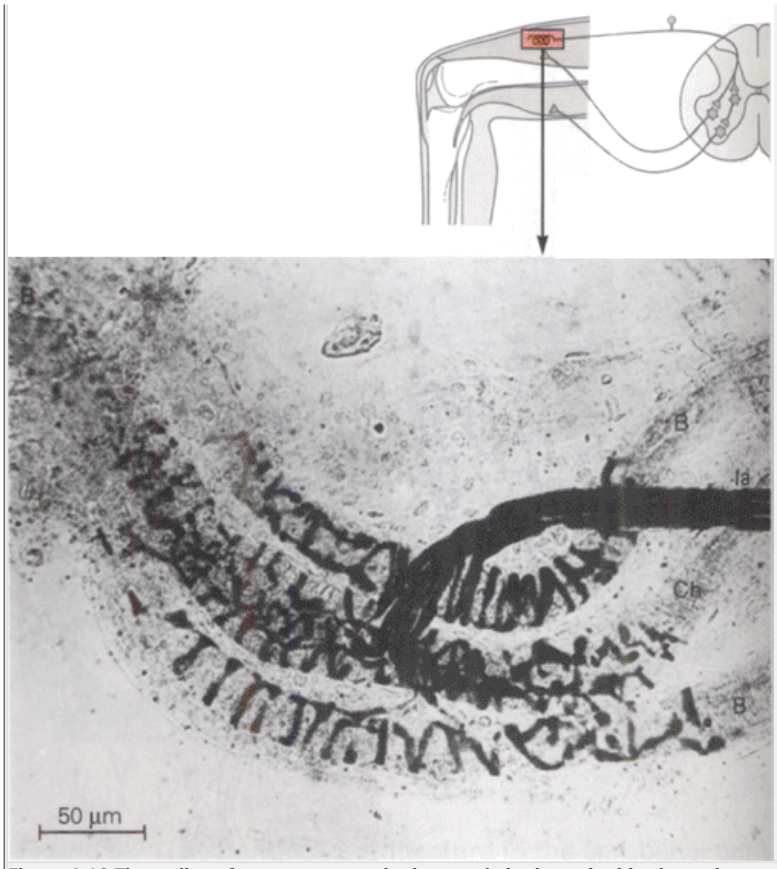


Figure 4-10 The ending of a sensory nerve in the muscle is shown in this photomicrograph of a cat soleus muscle. Numerous fibers of a single primary afferent axon (Ia) coil around specialized muscle fibers within the muscle spindle, the sensory organ for stretch. Specialized intrafusal fibers innervated by the IA afferent fibers include the bag fibers (**B**) and chain fibers (**Ch**). (From Boyd and Smith 1984.)

Unlike the microtubules and neurofilaments, actin filaments form short polymers: they are concentrated at the cell's periphery in the cortical cytoplasm lying just underneath the plasmalemma, where, together with a very large number of actin-binding proteins (for example, spectrin-fodrin, ankyrin, talin, and actinin), they form a dense network. This matrix plays a key role in the dynamic function of the cell's periphery, such as the motility of growth cones during development, generation of specialized microdomains on the cell surface, and the formation of pre- and postsynaptic morphologic specializations.

Like microtubules, microfilaments are in a dynamic

state and undergo cycles of polymerization and depoly-merization. At any one time about half the total actin in neurons can exist as unpolymerized monomers. The state of actin within the cell is controlled by binding proteins. These proteins facilitate assembly and block changes in polymer length by capping the rapidly growing end of the filament or by severing it. Other binding proteins cross-link or bundle microfilaments. The dynamic state of microtubules and microfilaments permit the mature neuron to retract old processes and extend new ones.

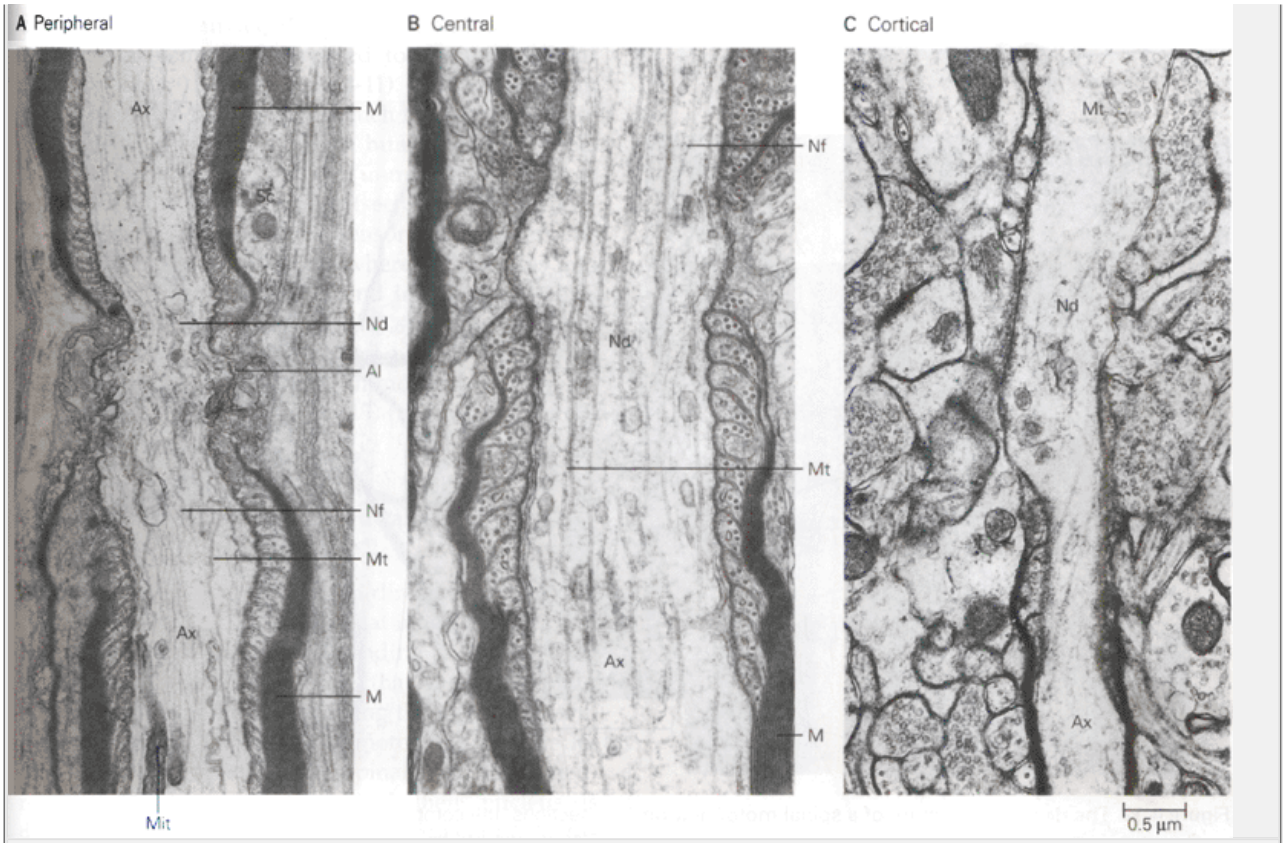


Figure 4-11 The insulating myelin sheath of the axon has regularly spaced gaps called the nodes of Ranvier. Electron micrographs show the region of nodes in axons from the peripheral nervous system, spinal cord, and cerebral cortex. The axon (**Ax**) runs from the top to the bottom in all three micrographs. The axon is coated with many layers of myelin (**M**), which is lacking at the nodes (**Nd**), where the axolemma (**Al**) is exposed. (In the peripheral nervous system the support cell responsible for myelination is called a Schwann cell (**Sc**), and in the central nervous system it is an oligodendrocyte.) The elements of the cytoskeleton that can be seen within the axon are microtubules (**Mt**) and neurofilaments (**Nf**). Mitochondria (**Mit**) are also seen. (From Peters et al. 1991.)

In addition to serving as cytoskeleton, microtubules and actin filaments act as tracks along which other or-ganelles and proteins are driven by molecular motors. Since these filamentous polymers are polar, each motor drives its organelle cargo in one direction only. In the axon all microtubules are arranged in parallel, with the plus end pointing away from the cell body and the minus end facing the cell body. This regular orientation permits the orderly movement of distinct classes of or-ganelles along the axon, thus maintaining the special distribution of organelles throughout the cell. In dendrites, however, microtubules with opposite polarities are mixed, and this explains why the organelles of the cell body and dendrites are similar. Actin motors, called *myosins*, mediate other types of cell motility, including extension of the cell's processes. Myosin is also thought to translocate membranous organelles within the cortical cytoplasm. Actomyosin in muscle is responsible for contraction (Chapter 34).

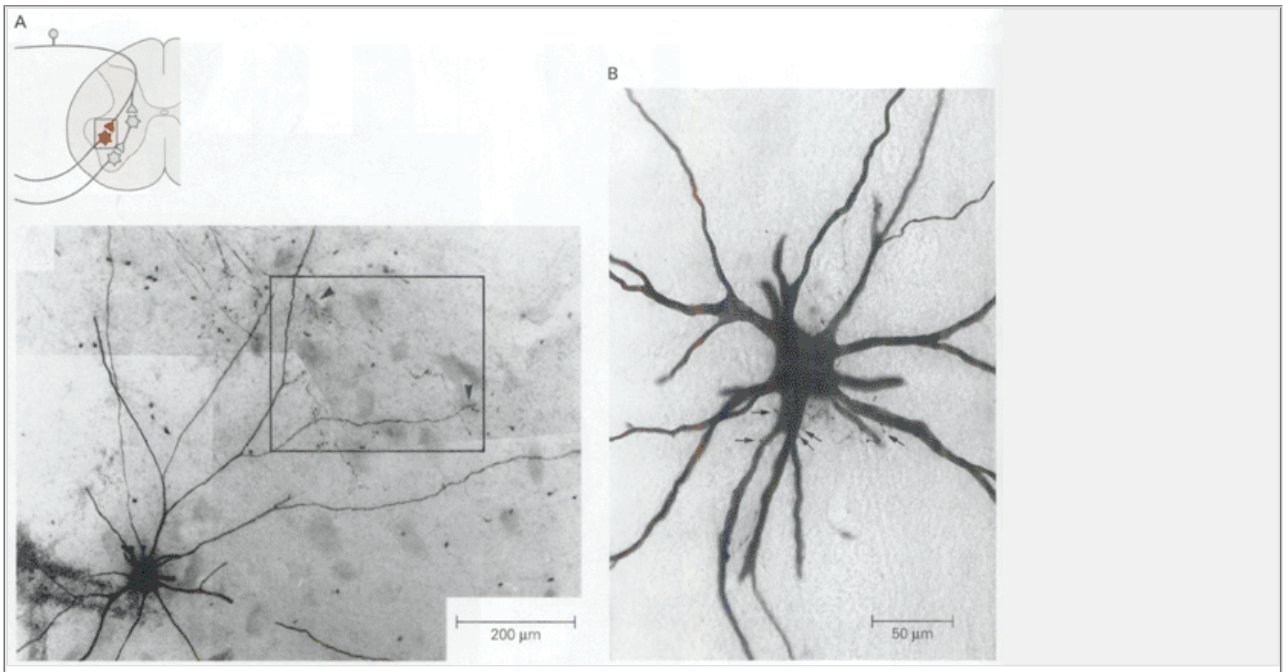


Figure 4-12 The dendritic structure of a spinal motor neuron.

A. Light micrograph of a motor neuron in the lumbosacral region of a cat's spinal cord. The cell body is shown in the lower left of the picture. The boxed area shows distal dendritic branches receiving contacts (**arrows**) from sensory (Ia afferent) neurons. Both sensory and motor neurons were identified by injection of the enzyme horseradish peroxidase, which serves as an intracellular marker. Because this is one of a set of serial sections, the complete dendritic branching pattern of this motor neuron can be reconstructed. The upper arrowhead identifies a presynaptic contact on a fifth-order dendritic branch, and the **lower arrowhead** points to a contact on a third-order branch. (From Brown and Fyffe 1981.)

B. Presynaptic contacts (**arrows**) on primary dendrites within 45 m of the cell body of the motor neuron shown in **A.** (From Brown and Fyffe 1984.)

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The Neurons That Mediate the Stretch Reflex Differ in Morphology and Transmitter Substance

The relationship between neuronal structure and functions can be seen by comparing the sensory and motor neurons that mediate the stretch reflex. As described in Chapter 2, the monosynaptic component of the stretch reflex is a simple two-neuron circuit consisting of large sensory neurons that receive information from muscle cells and motor neurons that cause the skeletal muscles of the limb to contract (see Figure 2-5).

The Sensory Neuron Conducts Information From the Periphery to the Central Nervous System

Sensory neurons for the stretch reflex convey information about the state of muscle contraction. Their cell bodies are round with large diameters (60-120 µm) and are located in dorsal root ganglia situated immediately adjacent to the spinal cord. At maturity these neurons possess a single axonal process that bifurcates into two branches a short distance from the cell body (Figure 4-8). The peripheral branch projects to muscle and the central branch to the spinal cord, where it forms synapses on the cell bodies and dendrites of motor neurons (Figure 4-9).

The peripheral branch of the sensory axon coils around a fine, specialized muscle fiber within the muscle spindle, a sensory receptor sensitive to stretch (Figure 4-10). The peripheral branch is 14-18 µm in diameter and is coated with an insulating sheath of myelin 8-10 µm thick. (Myelination is discussed in some detail later in the chapter.) The myelin sheath is regularly interrupted along the length of the axon. At these gaps,

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called nodes of Ranvier, the plasma membrane of the axon (the axolemma) is exposed to the extracellular space for about 0.5 µm (Figure 4-11). This arrangement greatly increases the speed at which the nerve impulse is conducted along the axon (in humans, 80 m/s) because the signal jumps from one unmyelinated node to the next by saltatory conduction (see Chapters 8 and 9).

The central branch of the sensory axon enters the spinal cord in the dorsal horn, where it bifurcates into branches that ascend and descend in the spinal cord. Collateral fibers from the axon form synapses on motor neurons in the ventral horn. When excited, the sensory neuron releases the excitatory amino acid neurotrans-mitter L-glutamate (see Chapter 15) that depolarizes the motor neurons.

The Motor Neuron Conveys Central Motor Commands to the Muscle Fiber

The axon of each sensory neuron directly contacts two classes of motor neurons: those that innervate the muscle within which the sensory ending is located (*the homonymous muscle*) and those that innervate other muscles that cooperate in stretching the knee joint (*synergistic muscles*). Both types of motor neurons are located in the ventral horn of the spinal cord. Motor neurons have large cell bodies, and their nucleus is distinctive because of its large and prominent nucleolus (see Figure 4-8B).

Unlike dorsal root ganglion cells, which have no dendrites, motor neurons have several dendritic trees that arise directly from the cell body. Each dendritic tree is complex, generated by extensive branching of primary dendrites (Figure 4-12). The total number of terminal dendritic branches per cell is often more than 100. The average length of a dendrite from the motor neuron's cell body to its end is about 20 cell-body diameters (1 mm), but some branches are twice as long. The branches project radially, so that the entire dendritic structure of a single motor neuron can extend within the spinal cord over an area about 2 to 3 mm in diameter. Such extensive dendritic structures are characteristic of central neurons, whose firing is regulated by input from many neurons. Short specialized dendritic extensions called *spines* serve to increase the area of the neuron available for synaptic inputs. Dendritic spines provide a biochemical and electrical compartment where incoming signals are initially received and processed; their morphology is discussed later in this chapter.

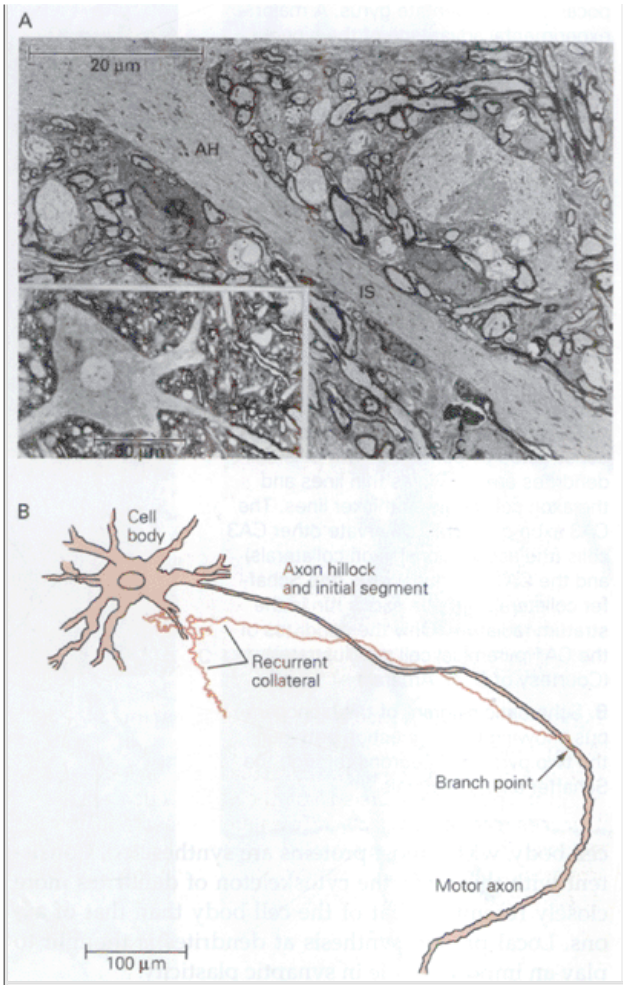

Figure 4-13 The axon of a spinal motor neuron has branches that make synaptic contact with several interneurons and, rarely, a recurrent (feedback) connection on the motor neuron.

A. An electron micrograph of a cat's spinal motor neuron shows the cell body, axon hillock (**AH**), initial segment (**IS**), and the first part of the myelinated portion of the axon. Glial cells surround the initial part of the axon. A cross-section of a capillary (**C**) is also visible. The inset shows two dendrites emerging from opposite sides of the cell body. (From Conradi 1969.)

B. The axons of motor neurons typically give off from one to five recurrent branches that usually make synaptic contact with inhibitory interneurons. In rare instances an axonal branch (a recurrent collateral) makes direct contact with its own cell body. (Courtesy of R. E. Burke.)

Messenger RNAis transported along dendrites and appears to be concentrated at the base of dendritic spines. Some protein synthesis occurs in dendrites, indicating that the dendrites are functional extensions of the

cell body, where most proteins are synthesized. Consistent with this view, the cytoskeleton of dendrites more closely resembles that of the cell body than that of axons. Local protein synthesis at dendrites is thought to play an important role in synaptic plasticity.

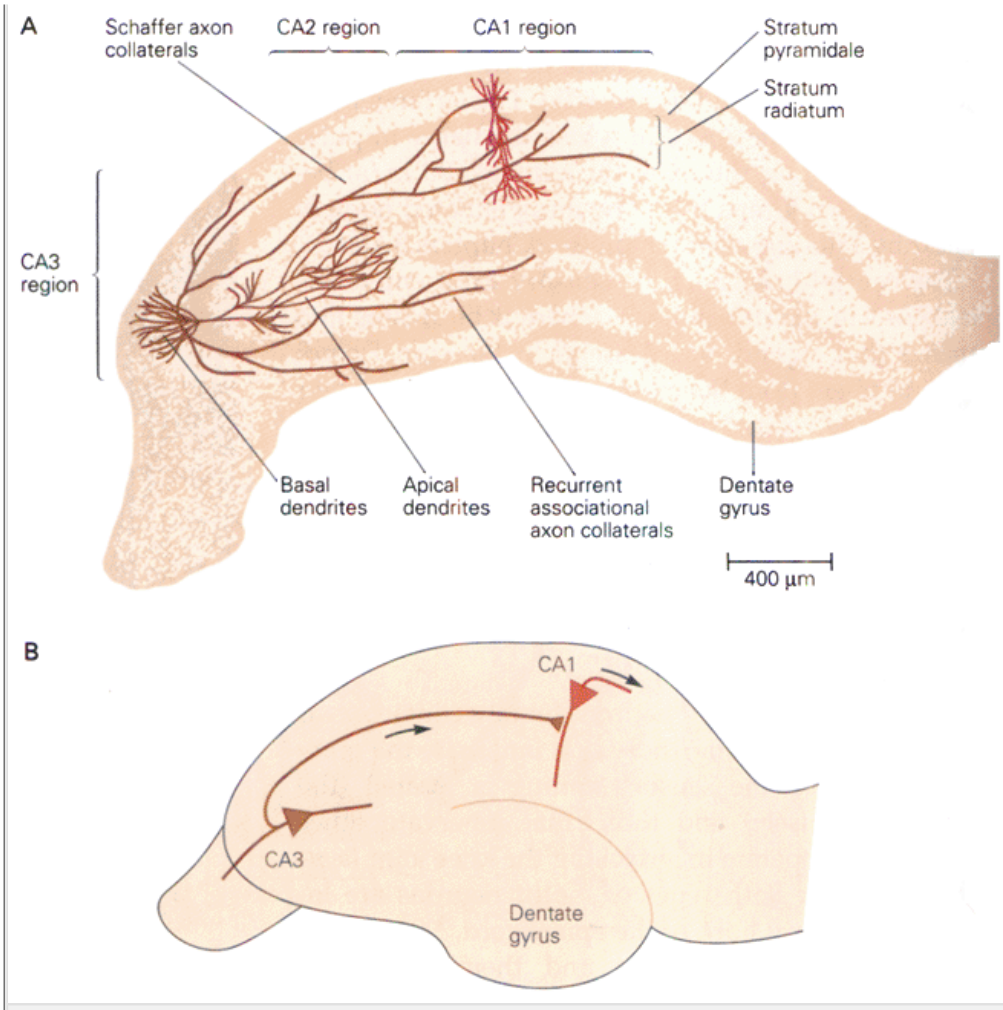

Figure 4-14 Pyramidal cells in the CA1 and CA3 regions of the hippocampus.

A. A composite illustration of the rat hippocampus and dentate gyrus. A major experimental advantage of the hippocampus for neuroscience research is its highly laminar organization. A Nisslstained section shows dark bands representing accumulations of neuronal cellbodies in the pyramidal cell layer (stratum pyramidale) of the hippocampus. The hippocampus can be divided into three separate regions—CA1, CA2, CA3—based on the size and connections of the resident pyramidal cells. Typical CA3 and CA1 pyramidal cells are drawn on the Nissl-stained section. Each cell has been traced with an intracellular marker (horseradish peroxidase or *Phaseolus vulgaris* leukoagglutinin) through adjacent 400 µm slices and reconstructed by computer. The CA3 cell dendrites are shown as thin lines and the axon collaterals as thicker lines. The CA3 axon collaterals innervate other CA3 cells (the associational axon collaterals) and the CA1 pyramidal cells (the Schaffer collaterals). These axons run in the stratum radiatum. Only the dendrites of the CA1 pyramidal cell are illustrated. (Courtesy of D. G. Amaral.)

B. Schematic diagram of the hippocampus showing the connection between the two pyramidal neurons through the Schaffer axon collaterals.

Each motor neuron gives rise to only one axon, about 20 µ m in diameter, from a specialized region of the cell body called the *axon hillock*. The axon hillock and the initial (unmyelinated) segment of the axon extend the length of about one cell-body diameter (Figure 4-13). About half the surface area of the axon hillock and cell body and three-quarters of the dendritic membrane are covered by synaptic boutons, the knob-like terminals of the axons of presynaptic neurons (see Figure 4-8B). The axon hillock and the initial segment of the axon function as a *trigger zone*, the site at which the many incoming signals from other neurons are integrated and the action potential, the output signal of the neuron, is generated (see Chapter 9).

Close to the cell body the axon gives off several *recurrent collateral* branches (Figure 4-13). These branches are called recurrent because many of them project back to the motor neuron and modify the activity of the cell. More often, however, recurrent collaterals form synapses on a particular type of interneuron in the spinal cord, the Renshaw cell. These interneurons hyperpolarize the motor neurons, using the neurotransmitter L-glycine, and thus inhibit firing in the motor neurons.

In addition, motor neurons receive recurrent excitatory inputs from other motor neurons, and both excitatory and inhibitory inputs from interneurons driven by descending fibers from the brain that control and coordinate movement. These synaptic inputs, together with the excitatory input from the primary sensory neurons and inhibitory input from Renshaw cells, are integrated by mechanisms that are described in Chapter 12.

A Single Motor Neuron Forms Synapses With Several Muscle Cells

One striking difference between motor and sensory neurons is the location of their synaptic inputs. The sensory neuron has few if any boutons on its cell body or

along the peripheral branch of its axon. Its primary input is from sensory receptors at the terminal of the peripheral axon. In contrast, the motor neuron receives primary and modifying inputs throughout its dendrites and cell body. (Almost all presynaptic boutons on motor neurons are located on the dendritic branches; only 5% are located on the cell body.) The synapses on the motor neuron are distributed in a functional pattern. Most inhibitory synapses are on the cell body or close to it, whereas excitatory ones are located farther out along the dendrites. Inhibitory inputs are strategically placed close to the trigger zone to have maximal influence on the final tally of inputs to the neuron (see Chapter 12).

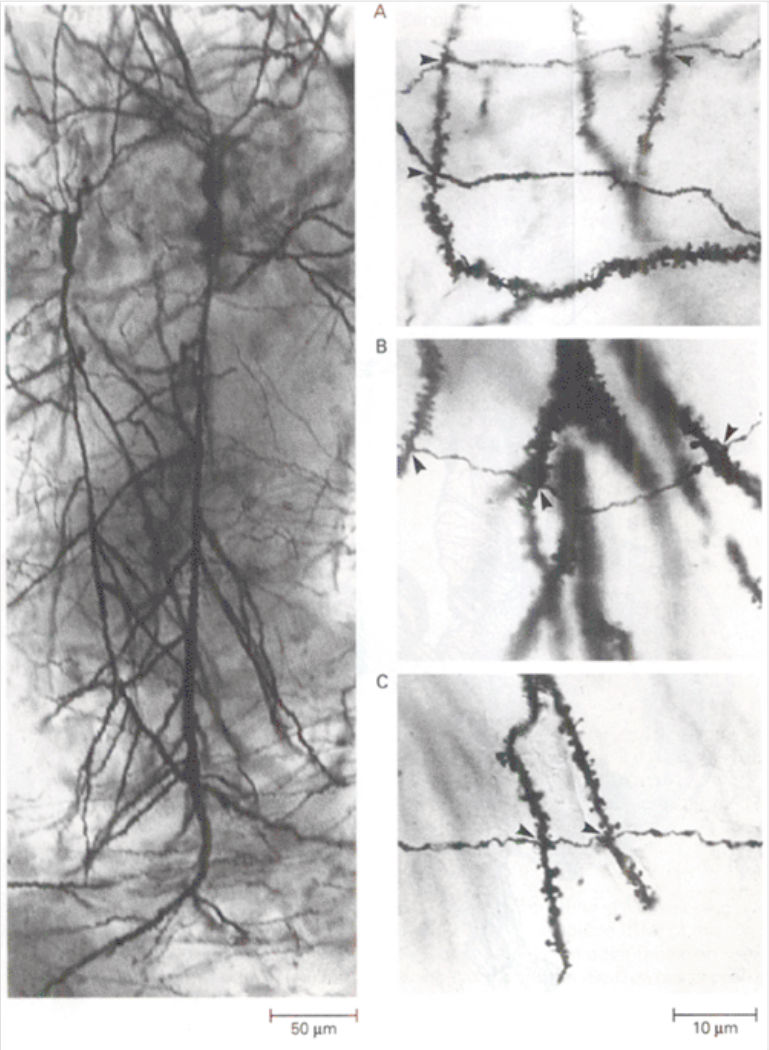

Figure 4-15 Pyramidal cells in the CA3 region of the hippocampus form synapses on the dendrites of CA1 cells in the stratum radiatum.

Left: Micrograph of a Golgi-stained CA1 pyramidal cell is shown with dendrites extending downward 350 µm into the stratum radiatum.

Right: Three micrographs show synapses formed on this CA1 cell by CA3 cells. **A.** Axons of two CA3 neurons form synapses on a dendrite 50 µm from the CA1 neuron's cell body. **B.** A single CA3 axon forms synapses on dendrites 259 µm from the cell body. **C.** A single CA3 axon forms synapses on two dendrites 263 µm from the cell body. (From Sorra and Harris 1993.)

The information flow from sensory neurons to motor neurons is both divergent and convergent. Each sensory neuron contacts 500–1000 motor neurons and typically forms two to six synapses on a single motor neuron (divergence of information). At the same time each motor neuron receives input from many sensory neurons (convergence of information); inputs from more than 100 sensory neurons are needed for a motor neuron to reach the threshold for firing.

The axons that mediate the stretch reflex in the leg leave the lumbosacral region of the spinal cord and join the femoral nerve. (The motor axons and sensory fibers travel along the same peripheral path to the muscle.)

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When the motor neuron enters the muscle it ramifies into many unmyelinated branches, each with a diameter of only a few micrometers. These terminal fibers run along the surface of a muscle fiber and form many synaptic contacts called *neuromuscular junctions*. These synapses are the most completely characterized and best understood of all synapses in the nervous system (see Chapter 11).

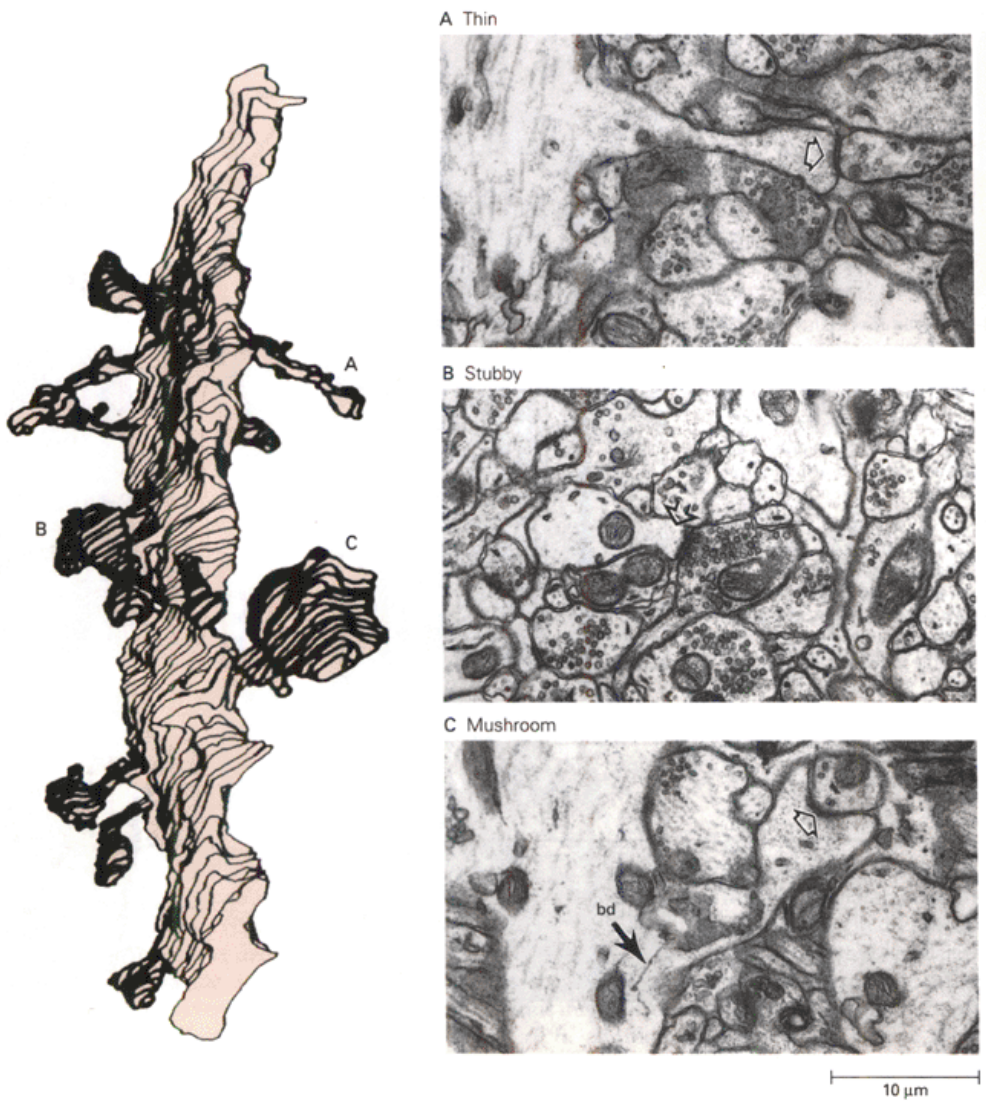

Figure 4-16 The dendrites of pyramidal cells in the CA1 region of the hippocampus bear a variety of spines.

Left: The diversity of dendritic spine shapes is evident along even a short segment of the mature dendrite in this three-dimensional reconstruction from a series of electron micro-graphs. (From Harris and Stevens 1989.)

Right: Three micrographs illustrate the details of different types of dendritic spines. **A.** A thin dendritic spine from the postnatal day-15 rat hippocampus. The postsynaptic density shows as the thickened receptive surface (**open arrow**) located across from the presynaptic axon, which has round clear vesicles. **B.** Stubby spines containing postsynaptic densities (**open arrow**) are both small and rare in the mature hippocampus. Their larger counterparts (not shown) predominate in the immature brain. **C.** Mushroom-shaped spines have a larger head. These spines are present by day 15 as shown here. The immature spines contain flat cisternae of smooth endoplasmic reticulum, some with a beaded appearance (**bd**). Synapse with postsynaptic density is indicated by the **open arrow**. Branched spines did not occur in this dendritic segment. (From Harris et al. 1992.)

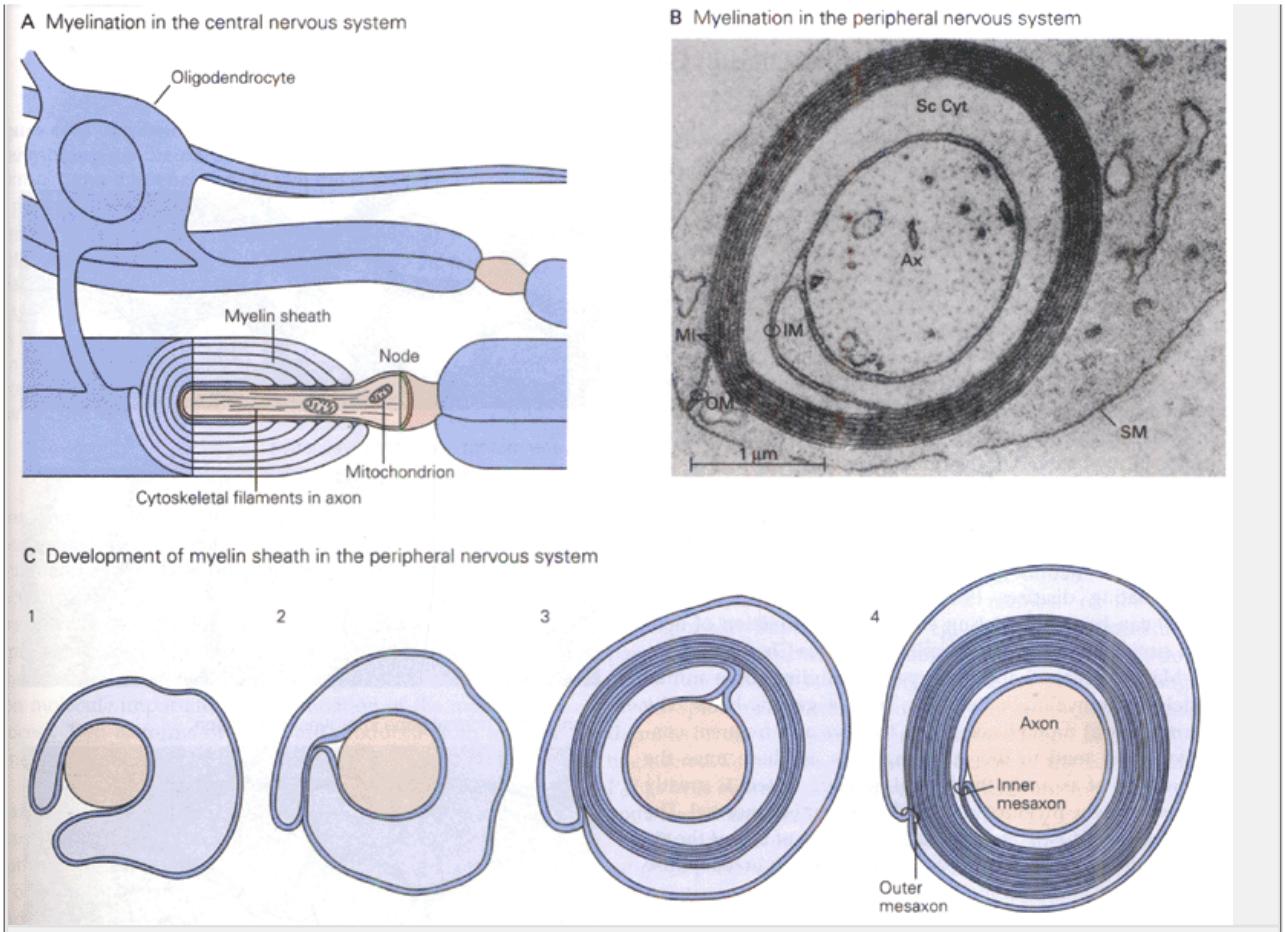

Figure 4-17 The axons of both central and peripheral neurons are insulated by a myelin sheath.

A. An axon in the central nervous system receives its myelin sheath from an oligodendrocyte. (Adapted from Bunge 1968.)

B. An electron micrograph of a transverse section through an axon (**Ax**) in the sciatic nerve of a mouse. The spiraling lamellae of the myelin sheath (**MI**) start at a structure called the inner mesaxon (**IM;** circled). The spiraling sheath is still developing and is seen arising from the surface membrane (**SM**) of the Schwann cell, which is continuous with the outer mesaxon (**OM;** circled). The Schwann cell cytoplasm (**Sc Cyt**) is still present, next to the axon; eventually it is squeezed out and the sheath becomes compact. (From Dyck et al. 1984.)

C. A peripheral nerve fiber is myelinated by a Schwann cell. (Adapted from Williams et al. 1989.)

Each muscle fiber is contacted by only a single axon, but a single motor axon innervates several muscle fibers. The axon and the muscle fibers it innervates constitute a *motor unit*. The muscle fibers innervated by any one motor axon are widely spread, overlapping muscle fibers of other motor units. The number of muscle fibers innervated by a single motor axon varies throughout the body, depending on the mass of the body part to be moved. Thus, in the leg a single motor axon innervates more than 1000 muscle fibers, while in the eye an axon contacts fewer than 100 muscle fibers. A lower innervation ratio permits greater precision of movement control.

The sensory and motor neurons that mediate the stretch reflex differ in appearance, location in the nervous system, the distribution of their axons and dendrites, and the inputs they receive. All of these cytological

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features have important behavioral consequences. In addition, the two types of cells differ biochemically because they use different neurotransmitters (although both transmitters are excitatory). For example, the motor neuron, which uses acetylcholine as a transmitter, requires a set of macromolecules that includes the biosynthetic enzyme choline acetyltransferase and a specific membrane transporter for choline, an essential precursor in the synthesis of acetylcholine (Chapter 15).

Box 4-1 Defects in Myelin Proteins Disrupt Conduction of Nerve Signals

Because normal conduction of the nerve impulse depends on the insulating properties of the myelin sheath surrounding the axon, defective myelin can result in severe disturbances of motor and sensory function. Myelin in both the central and peripheral nervous systems contains a major class of proteins, myelin basic proteins (MBP), which have an important role in myelin compaction. At least seven related proteins are produced from a single MBPgene by alternative RNA splicing.

Myelin basic proteins are capable of eliciting a strong immune response. When injected into animals they cause experimental allergic encephalomyelitis, a syndrome characterized by local inflammation and by destruction of the myelin sheaths (*demyelination*) in the central nervous system. This experimental disease has been used as a model for multiple sclerosis, a common demyelinating disease in humans. Because demyelination slows down conduction of the action potential in the affected neurons' processes, multiple sclerosis and other demyelinating diseases (for example, Guillain-Barré syndrome) can have devastating effects on the function of neuronal circuits in the brain and spinal cord (see Chapter 35).

Many diseases that affect myelin, including some animal models of demyelinating disease, have a genetic basis. The *shiverer* (or *shi*) mutant mice have tremors and frequent convulsions and tend to die at young ages. In these mice the myelination of axons in the central nervous system is greatly deficient and the myelination that does occur is abnormal. The mutation that causes this disease is a deletion of five of the six exons of the gene for myelin basic protein, which in the mouse is located on chromosome 18. The mutation is recessive; a mouse will develop the disease only if it has inherited the defective gene from both parents. *Shiverer* mice that inherit both defective genes have only about 10% of the myelin basic protein found in normal mice.

When the wild-type gene is injected into fertilized eggs of the *shiverer* mutant with the aim of rescuing the mutant, the resulting transgenic mice express the wild-type gene but produce only 20% of the normal amounts of myelin basic proteins. Nevertheless, myelination of central neurons in the transgenic mice is much improved. Although they still have occasional tremors, the transgenic mice do not have convulsions and live a normal life span (Figure 4-18).

Central and peripheral myelin also contain a distinct protein termed myelin-associated glycoprotein (MAG). MAG belongs to a superfamily that is related to the immunoglobulins and includes several important cell surface proteins thought to be involved in cell-to-cell recognition (for example, the major histocompatibility complex of antigens, T-cell surface antigens, and the neural cell adhesion molecule or NCAM). MAG is expressed by Schwann cells early during peripheral myeli-nation and eventually becomes a component of mature (compact) myelin. It is situated primarily at the margin of the mature myelin sheath just adjacent to the axon. Its early expression, subcellular location, and structural similarity to other surface recognition proteins suggest that it is an adhesion molecule important for the initiation of the myelination process. Two isoforms of MAG are produced from a single gene through alternative RNA splicing.

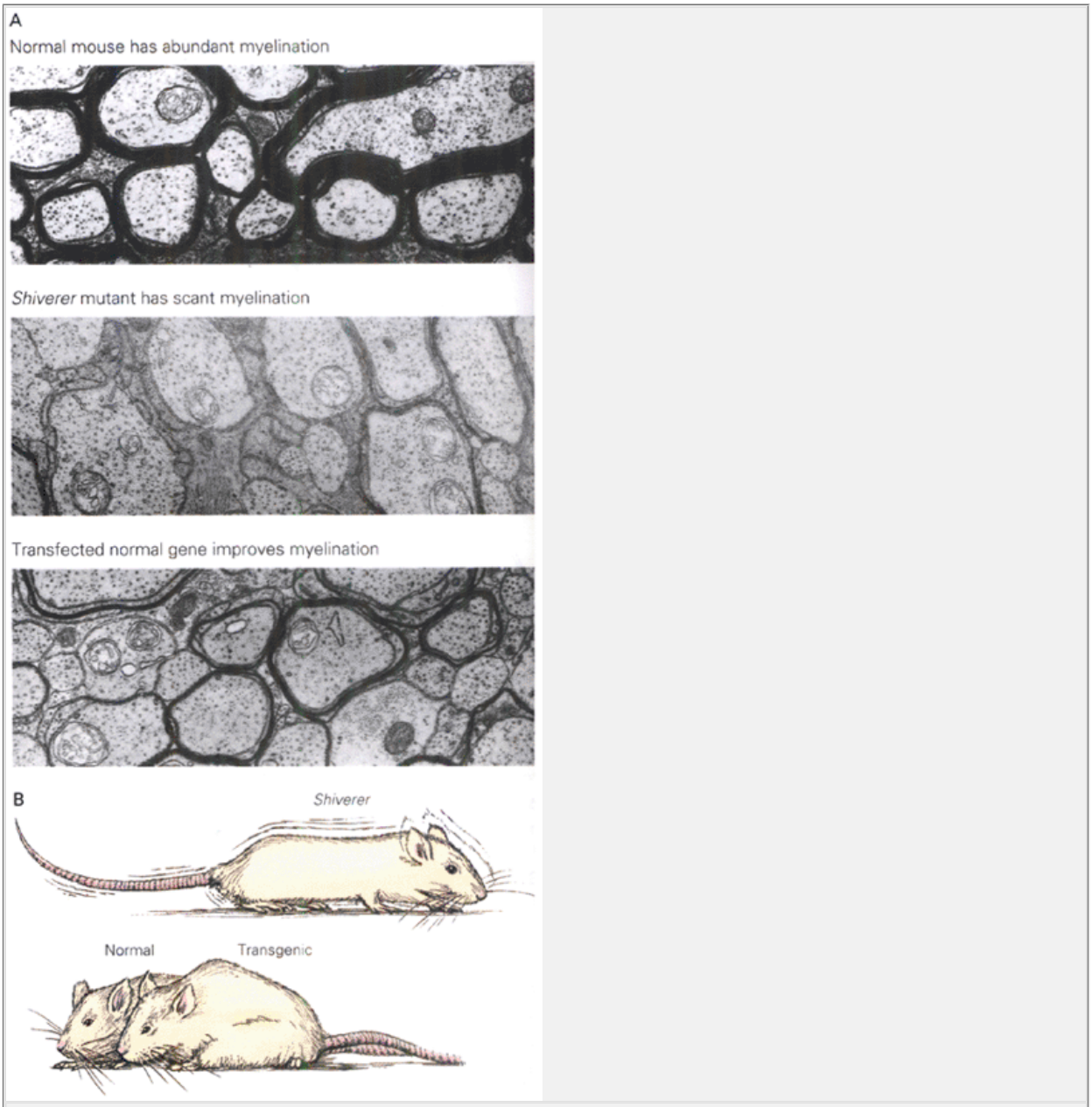

Figure 4-18 A genetic disorder of myelination in mice (*shiverer* mutant) can be partially cured by transfection of the normal gene that encodes myelin basic protein.

A. Electron micrographs show the state of myelination in the optic nerve of a normal mouse, a *shiverer* mutant, and a mutant transfected with the gene for myelin basic protein. (From Readhead et al. 1987.)

B. Myelination is incomplete in the *shiverer* mutant. As a result, the *shiverer* mutant exhibits poor posture and weakness. Injection of the wild-type gene into the fertilized egg of the mutant improves myelination. A normal mouse and a transfected *shiverer* mutant look perky.

More than half of the total protein in central myelin is a characteristic proteolipid, PLP, which has five membrane-spanning domains. Proteolipids differ from lipoproteins in that they are insoluble in water. Proteolipids are soluble only in organic solvents because they contain long chains of fatty acids that are covalently linked to amino acid residues throughout the proteolipid molecule. In contrast, lipoproteins are noncovalent complexes of proteins with lipids so structured that many serve as soluble carriers of the lipid moiety in the blood.

Many mutations of the proteolipid PLPare known, in humans as well as in other mammals (for example, the *jimpy* mouse). Pelizaeus-Merzbacher disease, a heterogeneous X-linked disease in humans, results from a PLP mutation. Almost all of these mutations occur in a membrane-spanning domain of the molecule. All of these mutant animals have reduced amounts of the mutated protein and show hy-pomyelination and degeneration and death of oligodendro-cytes. These observations suggest that the proteolipid is involved in the compaction of myelin.

The major protein in mature peripheral myelin, myelin protein zero (MPZ or P_0), spans the plasmalemma of the Schwann cell. It has a basic intracellular domain and, like myelin-associated glycoprotein, is a member of the immunoglobulin superfamily. The glycosylated extracellular part of the protein, which contains the immunoglobulin domain, functions as a homophilic adhesion protein during myelin spiraling and compaction by interacting with identical domainsonthesurfaceoftheopposedmembrane.Genetically engineered P_0 mice in which the function of myelin protein P_0 has been eliminated have poor motor coordination, tremors, and occasional convulsions.

Observation of *trembler* mouse mutants led to the identification of peripheral myelin protein 22 (PMP22). This Schwann cell protein spans the membrane four times and is normally present in compact myelin. PMP22 is altered by a single amino acid. Asimilar protein is found in humans, encoded by a gene on chromosome 17.

Although several hereditary peripheral neuropathies result from mutations of the PMP22 gene on chromosome 17, one form of Charcot-Marie-Tooth disease is caused by the DNA duplication of this gene (Figure 4-19). Charcot-Marie-Tooth disease, the most common inherited peripheral neuropathy, is characterized by progressive muscle weakness, greatly decreased conduction in peripheral nerves, and cycles of demyelination and remyelination. Since both duplicated genes are active, the disease results from *increased* production of PMP22 (a two- to three-fold increase in gene dosage) rather than from a reduction in a mutant protein.

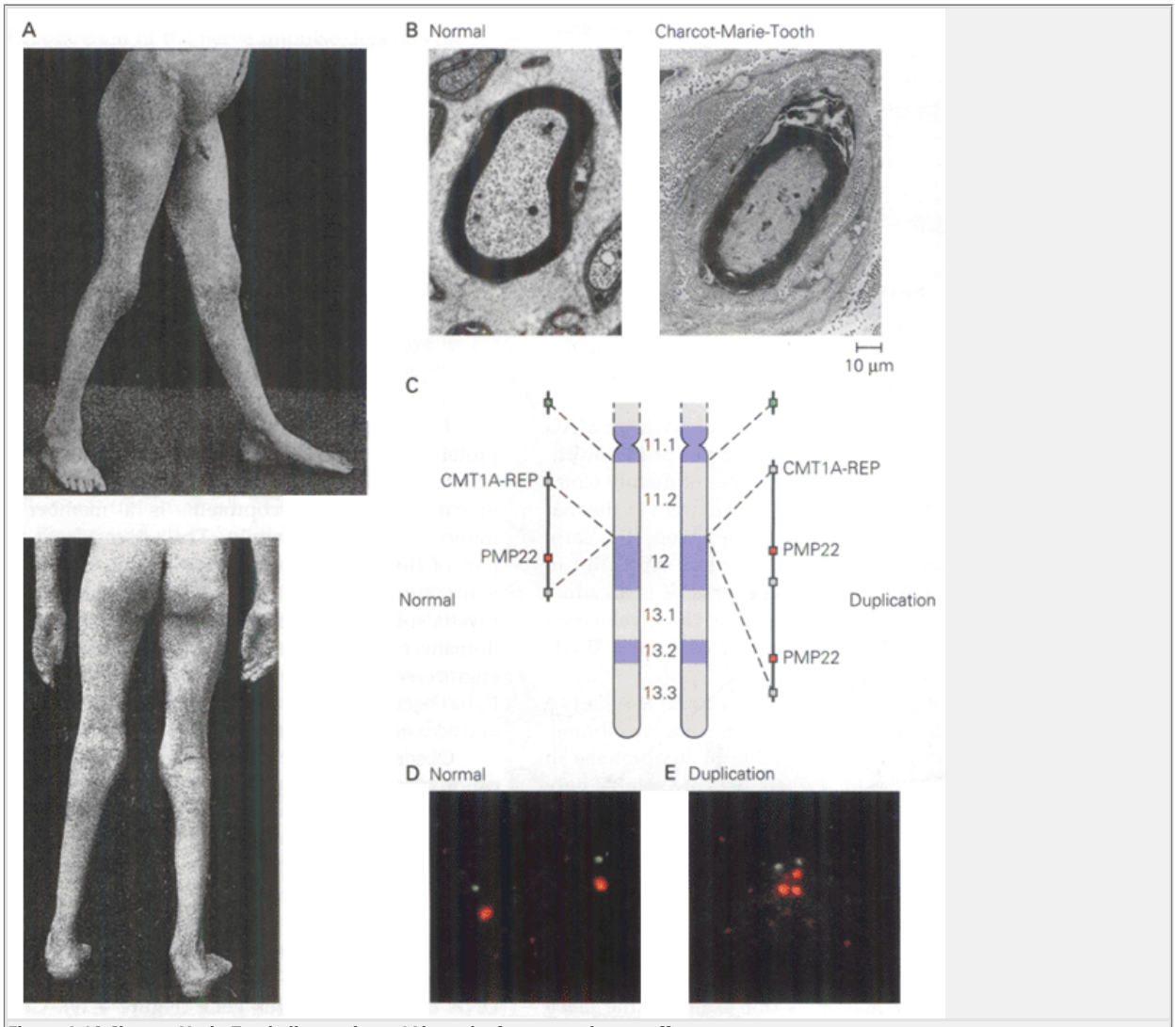

Figure 4-19 Charcot-Marie-Tooth disease (type 1A) results from gene dosage effects.

A. A patient with Charcot-Marie-Tooth shows impaired gait and deformities (from Charcot's original description of the disease, 1886).

B. Sural nerve biopsies from a normal individual (from AP Hays, Columbia University) and from a patient with Charcot-Marie-Tooth (from Lupski and Garcia 1993).

C. The disordered myelination in Charcot-Marie-Tooth disease results from the increased production of the peripheral myelin protein PMP22. The increase is caused by a duplication of a normal 1.5 megabase region of the DNA on the short arm of chromosome 17 at 17p11.2-p12. The PMP22 gene is flanked by two similar repeat sequences, as shown in the representation of a normal chromosome 17. Normal individuals have two normal chromosomes. In patients with the disease the duplication results in two functiong PMP22 genes, each flanked by the repeat sequence. The normal and duplicated regions are shown in the expanded diagrams indicated by the dashed lines. (The repeats are thought to have given rise to the original duplication, which was then inherited. The presence of two similar flanking sequences with homology to a transposable element is believed to increase the frequency of unequal crossing-over in this region of chromosome 17 because the repeats enhance the probability of mispairing of the two parental chromosomes in a fertilized egg.)

D-E. Although a large duplication, 3 megabases cannot be detected in routine examination of chromosomes in the light microscope, but microscopic evidence for the duplication can be obtained using fluorescence *in situ* hybridization. With this technique, the PMP22 gene is detected with an oligonucleotide probe tagged with the dye Texas Red. An oligonucleotiede probe tagged with fluoroscein, a green fluorescent dye that hybridizes with DNA from region 11.2 (indicated in green closer to the centromere), is used for in situ hybridization on the same sample. A nucleus from a normal individual (D)

shows a pair of chromosomes, each with one red site (PMP22 gene) for each green site. In a nucleus from a patient with the disease (E) there is one extra red site, indicating that one chromosome has one PMP22 gene and the other has two PMP22 genes.

Pyramidal Neurons in the Cerebral Cortex Have More Extensive Dendritic Trees Than Spinal Motor Neurons

Whereas motor neurons are the major excitatory projection neurons of the spinal cord, pyramidal cells are the excitatory projection neurons in the cerebral cortex. Pyramidal cells in different cortical regions are morphologically similar and use L-glutamate as a transmitter. We shall focus here on the pyramidal cells of the hippocampus, a structure important for memory storage.

The hippocampus is divided into two major regions, CA3 and CA1. In both regions the cell bodies of pyramidal cells are situated in a single continuous layer, the stratum pyramidale (Figure 4-14). In contrast to the motor neurons of the spinal cord, pyramidal cells have not one but two dendritic trees, and these emerge from opposite sides of the cell body: the basal dendrites arise from the side that gives rise to the axon, and the apical dendrites arise from the opposite side of the cell body.

Excitatory input to CA1 pyramidal neurons is extensive. About 5000 CA3 pyramidal cell axons—comprising the Schaffer collateral pathway—converge on a single CA1 cell. These Schaffer collaterals form synapses at all levels of the CA1 cell's dendritic tree close to the cell body and at more distant levels (Figure 4-15). The connections formed by the Schaffer collaterals are called *en passant* synapses because CA3 axons continue to pass through the stratum radiatum, making contact with the dendrites of many other CA1 pyramidal cells.

Most of the synapses are made on dendritic spines. In many parts of the brain, spines have two inputs, one excitatory and the other inhibitory. In area CA1, however, each pyramidal cell spine has only one synapse, which is excitatory. These spines have four principal shapes: thin, mushroom, branched, and stubby (Figure 4-16). The neck of the spine restricts diffusion between the head of the spine and the rest of the dendrite. Thus, each spine may function as a separate biochemical region. As we shall see later, this compartmentalization may be important for selectively altering the strength of synaptic connections during learning and memory.

Glial Cells Produce the Insulating Myelin Sheath Around Signal-Conducting Axons

The signal-conducting axons of both sensory and motor neurons are ensheathed in myelin along most of their length (see Figure 4-11). Acting as insulation, myelin speeds transmission along axons and thus is critical for quick reflex movements like the knee jerk. The myelin sheath is arranged in concentric bimolecular layers of lipids interspersed between protein layers (Figure 4-17). Biochemical analysis shows that myelin has a composition similar to that of plasma membranes, consisting of 70% lipid and 30% protein, with a high concentration of cholesterol and phospholipid.

Both the regular lamellar structure and biochemical composition of the myelin sheath are consequences of how myelin is formed from plasma membrane. In the development of the peripheral nervous system, before myelination takes place, the sensory cell axon lies along a peripheral nerve in a trough formed by a class of glia called Schwann cells. Schwann cells line up along the axon at intervals that will eventually become the nodes of Ranvier. The external cell membrane of each Schwann cell surrounds a single axon and forms a double-membrane structure called the *mesaxon*, which elongates and spirals around the axon in concentric layers (Figure 4-17C). The cytoplasm of the Schwann cell appears to be squeezed out during the ensheathing process when the Schwann cell's processes condense into the compact lamellae of the mature myelin sheath.

In the femoral nerve, which carries the sensory and motor axons that mediate the stretch reflex, the primary sensory axon is about 0.5 m long and the internodal distance is 1-1.5 mm; thus approximately 300-500 nodes of Ranvier occur along a primary afferent fiber between the thigh muscle and the dorsal root ganglion, where the cell body lies. Since each internodal segment is formed by a single Schwann cell, as many as 500 Schwann cells participate in the myelination of a single peripheral sensory axon.

In the central nervous system myelination of the central branch of dorsal root ganglion cell axons and the axons of motor neurons differs somewhat from myelination in the peripheral system. The glial cell responsible for elaborating central myelin is the *oligodendrocyte*, which typically ensheathes several axon processes. Schwann cells and oligodendrocytes differ developmentally and biochemically. The expression of myelin genes by Schwann cells in the peripheral nervous system is regulated by the contact between the axon and the myelinating Schwann cell. In contrast, the expression of myelin genes by oligodendrocytes in the central nervous system appears to depend on the presence of

astrocytes, the other major type of glial cell in the central nervous system.

Specific diseases can arise from dysfunction of the specialized properties of neurons. In particular, defective myelination of the axon produces severe disturbances of motor and sensory function. Thus, understanding the biochemistry of myelin formation provides important insight into the basis of certain neurological diseases (Box 4-1).

An Overall View

Nerve cells have four distinctive compartments: dendrites, for receiving signals from other neurons; the cell body, which contains the DNA encoding neuronal proteins and the complex apparatus for synthesizing them; the axon, which projects over long distances to target cells (for example, other neurons or muscle); and nerve terminals, for release of neurotransmitters at synapses with targets.

In this chapter we have illustrated this basic cellular plan by describing three types of neurons. Although all of these cells conform to a basic plan, each type differs considerably, most obviously by location in the nervous system—peripheral or central, spinal cord, or brain. They also differ in the location of synaptic inputs on the cell and in the types of target cells to which they project. Furthermore, they differ in cell body size and shape, distribution of their dendritic trees and number of axon branches, and in their degree of myelination. Biochemically, they differ most obviously in transmitter type, and, as we shall see throughout this book, in many other constituents (for example, in the enzymes that synthesize neurotransmitters, the pumps that exchange ions or recapture neurotransmitter substances, and the receptors that transduce physical or biochemical inputs).

The functional significance of many morphological differences is plainly evident. For example, the dorsal root sensory neuron must extend a process in the peripheral nervous system, as must the spinal motor neuron. It also is clear why the motor neuron has a more complex dendritic tree than the sensory neuron: Even simple reflex activity requires coordination of inputs, both excitatory and inhibitory, to regulate specific motor units, and purposeful movements need still more integration because of inputs from the brain.

The functional significance of some other cytological differences is not so obvious, but can be understood in the context of the electrophysiological activities of the particular neurons. Thus the large number of dendrites and axonal branches in cortical pyramidal neurons must contribute to the complexity of information processing in the brain.

Selected Readings

Baldissera F, Hultborn H, Illert M. 1981. Integration in spinal neuronal systems. In: VB Brooks (ed). *Handbook of Physiology: A Critical, Comprehensive Presentation of Physiological Knowledge and Concepts.* Sect. 1, The *Nervous System.* Vol. 2, *Motor Control*, pp. 509-595. Bethesda, MD: American Physiological Society.

Burke RE. 1990. Spinal cord: ventral horn. In: GM Shepherd (ed). *The Synaptic Organization of the Brain*, 3rd ed., pp. 88-132. New York: Oxford University Press.

Dyck PJ, Thomas PK, Griffin JW, Low PA, Poduslo JF (eds). 1993. *Peripheral Neuropathy*, 3rd ed. Philadelphia: Saunders.

Lemke G. 1992. Myelin and myelination. In: Z Hall (ed). *An Introduction to Molecular Neurobiology*, pp. 281-312. Sunderland, MA: Sinauer.

Peters A, Palay SL, Webster H deF. 1991. *The Fine Structure of the Nervous System: Neurons and Their Supporting Cells*, 3rd ed. New York: Oxford Univ. Press.

Rothwell J. 1994. *Control of Human Voluntary Movement*, 2nd ed. London: Chapman & Hall.

Siegel GJ, Agranoff BW, Albers RW, Molinoff PB (eds). 1999. *Basic Neurochemistry: Molecular, Cellular, and Medical Aspects*, 6th ed. Philadelphia: Lippincott-Raven.

References

Amaral DG, Ishizuka N, Claiborne B. 1990. Neurons, numbers and the hippocampal network. Prog Brain Res 83:1–11.

Amaral DG. 1993. Emerging principles of intrinsic hippocampal organization. Curr Opin Neurobiol 3:225–229.

Bershadsky AD, Vasiliev JM. 1988. *Cytoskeleton*. New York: Plenum.

Boyd IA, Smith RS. 1984. The muscle spindle. In: PJ Dyck, PK Thomas, EH Lambert, R Bunge (eds). *Peripheral Neuropathy*, 2nd ed., 1:171-202. Philadelphia: Saunders.

Brown AG, Fyffe RE. 1981. Direct observations on the contacts made between Ia afferent fibres and -motoneu rones in the cat's lumbosacral spinal cord. J Physiol (Lond) 313:121–140.

Brown AG, Fyffe REW. 1984. *Intracellular Staining of Mammalian Neurones*. London: Academic.

Bunge RP. 1968. Glial cells and the central myelin sheath. Physiol Rev 48:197–251.

Burke RE. 1981. Motor units: anatomy, physiology, and functional organization. In: VB Brooks (ed). *Handbook of Physiology: ACritical, Comprehensive Presentation of Physiological Knowledge and Concepts*. Sect. 1, *The Nervous System*. Vol. 2, Motor Control, pp. 345-422. Bethesda, MD: American Physiological Society.

Burke RE, Dum RP, Fleshman JW, Glenn LL, Lev-Tov A, O'Donovan MJ, Pinter MJ. 1982. An HRP study of the relation between cell size and motor unit type in cat ankle extensor motoneurons. J Comp Neurol 209:17–28.

Cameron PL, Sudhof TC, Jahn R, De Camilli P. 1991. Colocalization of synaptophysin with transferrin receptors: implications for synaptic vesicle biogenesis. J Cell Biol 115:151–164.

Charcot J-M, Marie P. 1886. Sur une forme particulière d'atrophie musculaire progressive, souvent familiale, débutant par les pieds et les jambes et atteignant plus tard les mains. Rev Med 6:97–138.

Conradi S. 1969. Ultrastructure and distribution of neuronal and glial elements on the motoneuron surface in the lumbosacral spinal cord of the adult cat. Acta Physiol Scand 332:5-48 (Suppl.).

De Camilli P, Moretti M, Donini SD, Walter U, Lohmann SM. 1986. Heterogeneous distribution of the cAMP receptor protein RII in the nervous system: evidence for its intracellular accumulation on microtubules, microtubule-organizing centers, and in the area of the Golgi complex. J Cell Biol 103:189–203.

Dogiel AS. 1908. *Der Bau der Spinalganglien des Menschen und der Säugetiere*. Jena: Fischer.

Dyck PJ, Thomas PK, Lambert EH, Bunge R (eds). 1984. *Peripheral Neuropathy*, 2nd ed. Vols. 1, 2. Philadelphia: Saunders.

Gulyas AI, Miles R, Hájos N, Freund TF. 1993. Precision and variability in postsynaptic target selection of inhibitory cells in the hippocampal CA3 region. Eur J Neurosci 5:1729–1751.

Harris KM, Stevens JK. 1989. Dendritic spines of CA1 pyramidal cells in the rat hippocampus: serial electron microscopy with reference to their biophysical characteristics. J Neurosci 9:2982–2997.

Harris KM, Jensen FE, Tsao B. 1992. Three-dimensional structure of dendritic spines and synapses in rat hippocampus (CA1) at postnatal day 15 and adult ages: implications for the maturation of synaptic physiology and long-term potentiation. J Neurosci 12:2685–2705.

Ishizuka N, Weber J, Amaral DG. 1990. Organization of intrahippocampal projections originating from CA3 pyramidal cells in the rat. J Comp Neurol 295:580-623. Lemke G. 1988. Unwrapping the genes of myelin. Neuron 1:535–543.

Lemke G. 1993. The molecular genetics of myelination: an update. Glia 7:263–271.

Lorente de Nó R. 1934. Studies on the structure of the cerebral cortex. II. Continuation of the study of the ammonic system. J Psychol Neurol 46:113–177.

Lupski JR, Garcia CA. 1992. Molecular genetics and neuropathology of Charcot-Marie-Tooth disease type 1A. Brain Pathol 2:337–349.

Lupski JR, de Oca-Luna RM, Slaugenhaupt S, Pentao L, Guzzetta V, Trask BJ, Saucedo-Cardenas O, Barker DF, Killian JM, Garcia CA, Chakravarti A, Patel PI. 1991. DNA duplication associated with Charcot-Marie-Tooth disease type 1A. Cell 66:219–232.

Ramón y Cajal S. [1901] 1988. Studies on the human cerebral cortex. IV. Structure of the olfactory cerebral cortex of man and mammals. In: J DeFelipe, EG Jones (eds, transl). *Cajál on the Cerebral Cortex*, pp. 289-362. New York: Oxford Univ. Press.

Ramón y Cajal S. [1909] 1995. *Histology of the Nervous System of Man and Vertebrates*. N Swanson, LW Swanson (transl). Vols. 1, 2. New York: Oxford Univ. Press.

Readhead C, Popko B, Takahashi N, Shine HD, Saavedra RA, Sidman RL, Hood L. 1987. Expression of a myelin basic protein gene in transgenic Shiverer mice: correction of the dysmyelinating phenotype. Cell 48:703–712.

Roa BB, Lupski JR. 1994. Molecular genetics of Charcot-Marie-Tooth neuropathy. Adv Human Genet 22:117-152. Sorra KE, Harris KM. 1993. Occurrence and three-dimensional structure of multiple synapses between individual radiatum axons and their target pyramidal cells in hippocampal area CA1. J Neurosci 13:3736–3748.

Ulfhake B, Kellerth J-O. 1981. A quantitative light microscopic study of the dendrites of cat spinal α-motoneurons after intracellular staining with horseradish peroxidase. J Comp Neurol 202:571–583.

Williams PL, Warwick R, Dyson M, Bannister LH (eds). 1989. *Gray's Anatomy*, 37th ed, pp. 859-919. Edinburgh: Churchill Livingstone.