properties that allow it to release neurotransmitters at synapses. Fourth, this system for rapid signaling over the long distances between the cell body and its terminals is enabled by a cytoskeletal structure that mediates, on a slower time scale, efficient transport of various proteins, mRNAs, and organelles between the two compartments.

In this part of the book, we shall be concerned with the distinctive cell biological properties that allow neurons and glia to fulfill their various specialized functions. A major emphasis will be on properties of ion channels that endow neurons with the ability to generate and propagate electrical signals in the form of action potentials. We begin the discussion of neurons by considering general properties shared by ion channels—the ability to select and conduct ions, and to gate between open and closed conformations. Neurons use four major classes of channels for signaling: (1) resting channels generate the resting potential and underlie the passive electrical properties of neurons that determine the time course of synaptic potentials, their spread along dendrites, and the threshold for firing an action potential; (2) sensory receptor channels respond to certain sensory stimuli to generate local receptor potentials; (3) ligand-gated channels open in response to neurotransmitters, generating local synaptic potentials; and (4) voltage-gated channels produce the currents that generate self-propagating action potentials. In this part, we focus mainly on resting and voltage-gated channels. In Part III, we consider in more detail ligand-gated channels, and the neurotransmitters and second messengers that control their activity. The channels that are activated by sensory stimuli will be examined in Part IV.

Part Editors: John D. Koester and Steven A. Siegelbaum

Part II

7

The Cells of the Nervous System

The cells of the nervous system— neurons and glia—share many characteristics with cells in general. However, neurons are specially endowed with the ability to communicate precisely and rapidly with other cells at distant sites in the body. Two features give neurons this ability.

First, they have a high degree of morphological and functional asymmetry: Neurons have receptive dendrites at one end and a transmitting axon at the other. This arrangement is the structural basis for unidirectional neuronal signaling.

Second, neurons are both electrically and chemically excitable. The cell membrane of neurons contains specialized proteins—ion channels and receptors—that facilitate the flow of specific inorganic ions, thereby redistributing charge and creating electrical currents that alter the voltage across the membrane. These changes in charge can produce a wave of depolarization in the form of action potentials along the axon, the usual way a signal travels within the neuron. Glia are less excitable, but their membranes contain transporter proteins that facilitate the uptake of ions as well as proteins that remove neurotransmitter molecules from the extracellular space, thus regulating neuronal function.

There are hundreds of distinct types of neurons depending on their dendritic morphology, pattern of axonal projections, and electrophysiological properties. This structural and functional diversity is largely specified by the genes expressed by each neuronal cell type. Although neurons all inherit the same complement of genes, each expresses a restricted set and thus produces only certain molecules—enzymes, structural proteins, membrane constituents, and secretory products—and not others. In large part, this expression depends on the cell's developmental history. In essence, each cell *is* the set of molecules it expresses.

There are also many kinds of glial cells that can be identified based on their unique morphological,

physiological, and biochemical features. The diverse morphologies of glial cells suggest that glia are probably as heterogeneous as neurons. Nonetheless, glia in the vertebrate nervous system can be divided into two major classes: macroglia and microglia. There are three main types of macroglia: oligodendrocytes, Schwann cells, and astrocytes. In the human brain, about 90% of all glial cells are macroglia. Of these, approximately half are myelin-producing cells (oligodendrocytes and Schwann cells) and half are astrocytes. *Oligodendrocytes* provide the insulating myelin sheaths of the axons of some neurons in the central nervous system (CNS) (Figure 7–1A). *Schwann cells* myelinate the axon of neurons in the peripheral nervous system (Figure 7–1B); nonmyelinating Schwann cells have other functions, including promoting development, maintenance, and repair at the neuromuscular synapse. *Astrocytes* owe their name to their irregular, roughly star-shaped cell bodies and large numbers of processes; they support neurons and modulate neuronal signaling in several ways (Figure 7–1C). *Microglia* are the brain's resident immune cells and phagocytes, but also have homeostatic functions in the healthy brain.

Neurons and Glia Share Many Structural and Molecular Characteristics

Neurons and glia develop from common neuroepithelial progenitors of the embryonic nervous system and share many structural characteristics (Figure 7–2). The boundaries of these cells are defined by the cell membrane or *plasmalemma,* which has the asymmetric bilayer structure of all biological membranes and provides a hydrophobic barrier impermeable to most water-soluble substances. Cytoplasm has two main components: cytosol and membranous organelles.

Cytosol is the aqueous phase of cytoplasm. In this phase, only a few proteins are actually free in solution. With the exception of some enzymes that catalyze metabolic reactions, most proteins are organized into functional complexes. A recent subdiscipline called *proteomics* has determined that these complexes can consist of many distinct proteins, none of which are covalently linked to another. For example, the cytoplasmic tail of the *N*-methyl-D-aspartate (NMDA)-type glutamate receptor, a membrane-associated protein that mediates excitatory synaptic transmission in the

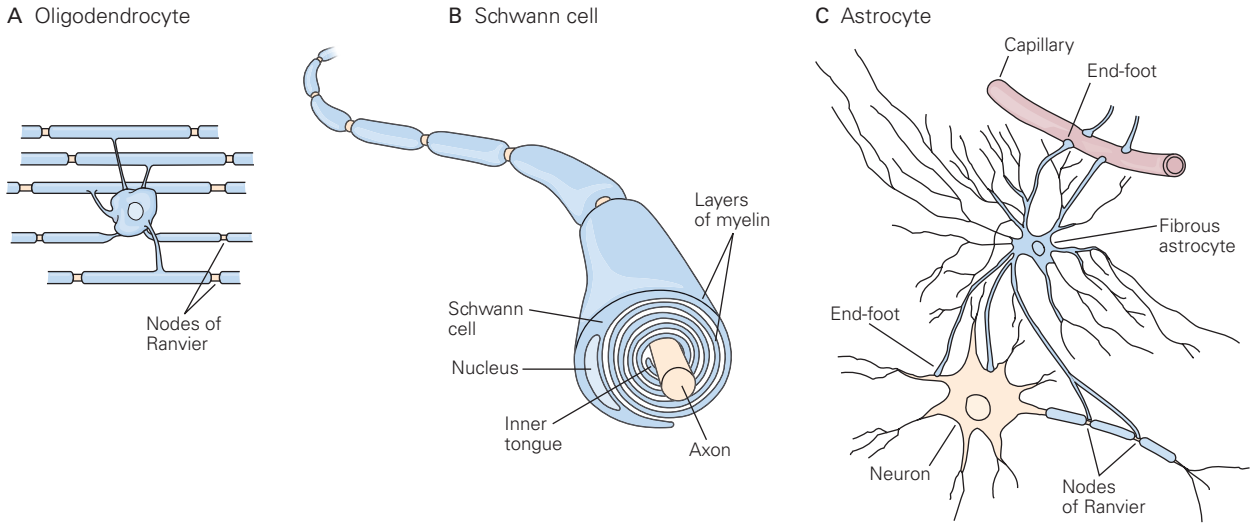

Figure 7–1 The principal types of glial cells are oligodendrocytes and astrocytes in the central nervous system and Schwann cells in the peripheral nervous system.

A. Oligodendrocytes are small cells with relatively few processes. In the white matter of the brain, as shown here, they provide the myelin sheaths that insulate axons. A single oligodendrocyte can wrap its membranous processes around many axons. In the gray matter, perineural oligodendrocytes surround and support the cell bodies of neurons.

B. Schwann cells furnish the myelin sheaths for axons in the peripheral nervous system. During development, several Schwann cells are positioned along the length of a single axon. Each cell forms a myelin sheath approximately 1 mm long between two nodes of Ranvier. The sheath is formed as the inner tongue of the Schwann cell turns around the axon several times, wrapping the axon in layers of membrane. In actuality, the layers of myelin are more compact than what is shown here. (Adapted from Alberts et al. 2002.)

C. Astrocytes, a major class of glial cells in the central nervous system, are characterized by their star-like shape and the broad end-feet on their processes. Because these end-feet put the astrocyte into contact with both capillaries and neurons, astrocytes are thought to have a nutritive function. Astrocytes also play an important role in maintaining the blood–brain barrier (described later in the chapter).

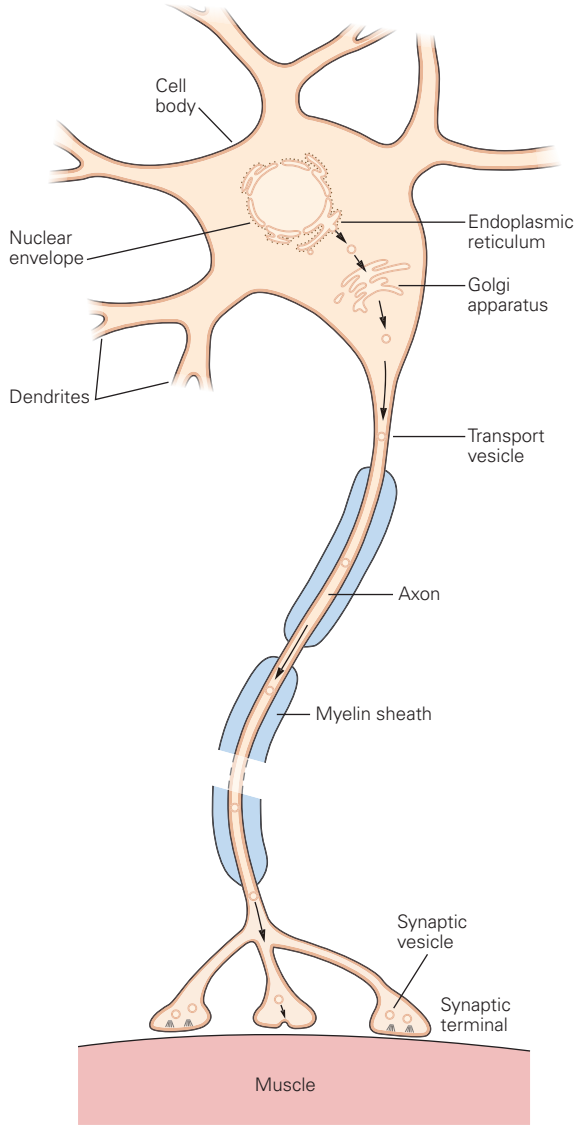

Figure 7–2 The structure of a neuron. The cell body and nucleus of a spinal motor neuron are surrounded by a double-layered membrane, the nuclear envelope, which is continuous with the endoplasmic reticulum. The space between the two membrane layers that constitutes the nuclear envelope is continuous with the lumen of the endoplasmic reticulum. Dendrites emerge from the basal aspect of the neuron, the axon from the apical aspect. (Adapted, with permission, from Williams et al. 1989.)

CNS, is anchored in a large complex of more than 100 scaffold proteins and protein-modifying enzymes. (Many cytosolic proteins involved in second-messenger signaling, discussed in later chapters, are embedded in the cytoskeletal matrix immediately below the plasmalemma.) *Ribosomes*, the organelle on which messenger RNA (mRNA) molecules are translated, are made up of several protein subunits. *Proteasomes*, large multi-enzyme organelles that degrade ubiquitinated proteins (a process described later in this chapter), are also present throughout the cytosol of neurons and glia.

Membranous organelles, the second main component of cytoplasm, include mitochondria and peroxisomes as well as a complex system of tubules, vesicles, and cisternae called the *vacuolar apparatus*. Mitochondria and peroxisomes process molecular oxygen. Mitochondria generate adenosine triphosphate (ATP), the major molecule by which cellular energy is transferred or spent, whereas peroxisomes prevent accumulation of the strong oxidizing agent hydrogen peroxide. Mitochondria, which are derived from symbiotic archeobacteria that invaded eukaryotic cells early in evolution, are not functionally continuous with the vacuolar apparatus. Mitochondria also play other essential roles in Ca^{2+} homeostasis and lipid biogenesis.

The vacuolar apparatus includes the smooth endoplasmic reticulum, the rough endoplasmic reticulum, the Golgi complex, secretory vesicles, endosomes, lysosomes, and a multiplicity of transport vesicles that interconnect these various compartments (Figure 7–3). 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.

The major subcompartments of this system are anatomically discontinuous but functionally connected because membranous and lumenal material is moved from one compartment to another by means of transport vesicles. For example, proteins and phospholipids synthesized in the rough endoplasmic reticulum (the portion of the reticulum studded with ribosomes) and the smooth endoplasmic reticulum are transported to the Golgi complex and then to secretory vesicles, which empty their contents when the vesicle membrane fuses with the plasmalemma (a process called *exocytosis*). This secretory pathway adds membranous components to the plasmalemma and also releases the contents of these secretory vesicles into the extracellular space.

Conversely, components of cell membrane are taken into the cell through endocytic vesicles (*endocytosis*). These are incorporated into early endosomes, sorting compartments that are concentrated at the cell's periphery. The endocytosed membrane, which typically contains specific proteins such as transmembrane receptors, can be either directed back to the plasma membrane by maturing into recycling endosomes or can mature into late endosomes which are targeted for degradation by fusion with lysosomes. (Exocytosis and endocytosis are discussed in detail later in this

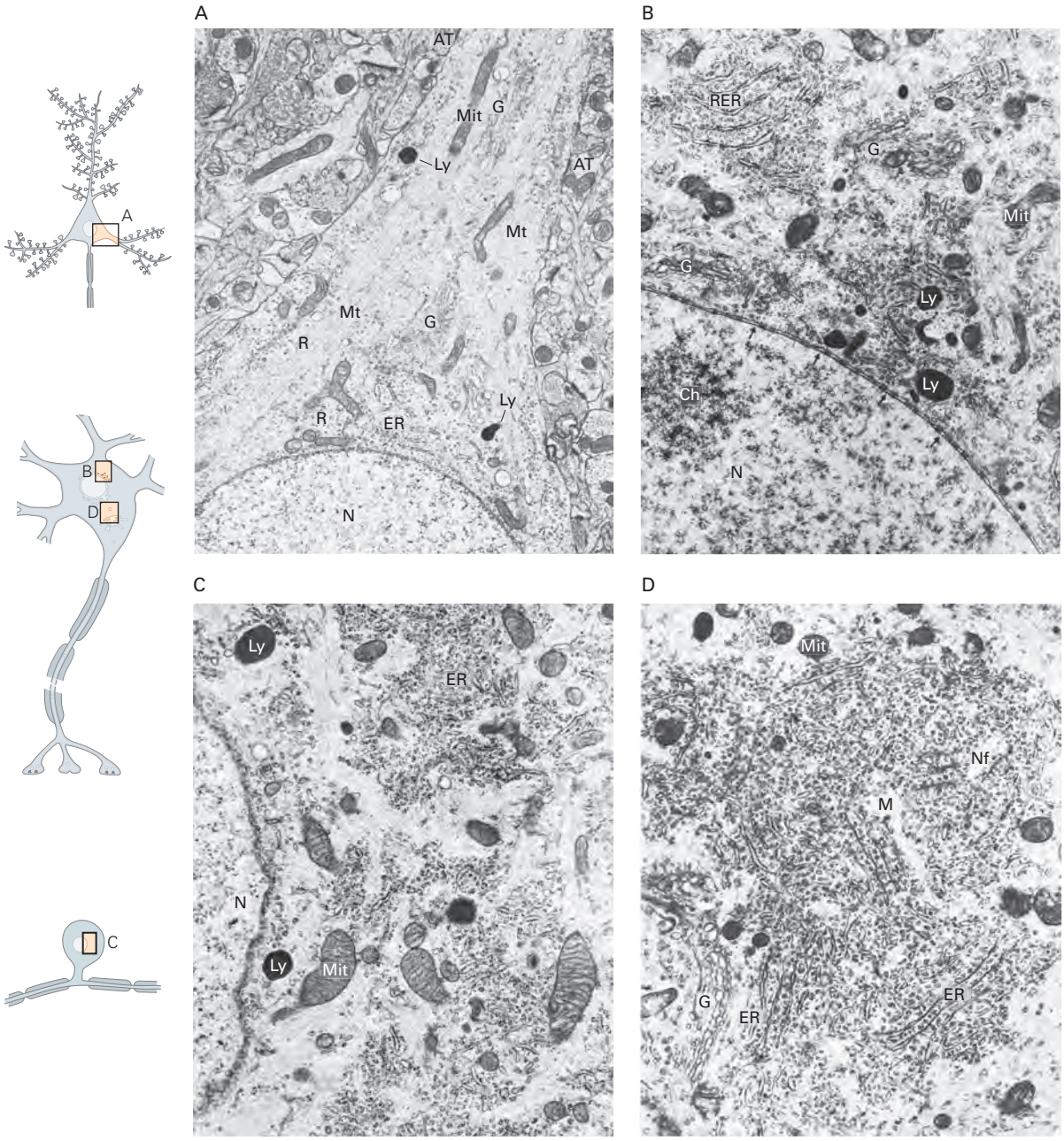

Figure 7–3 Organelles of the neuron. Electron micrographs show cytoplasm in four different regions of the neuron. (Adapted, with permission, from Peters et al. 1991.)

A. A dendrite emerges from a pyramidal neuron's cell body, which includes the endoplasmic reticulum (**ER**) above the nucleus (**N**) and a portion of the Golgi complex (**G**) nearby. Some Golgi cisternae have entered the dendrite, as have mitochondria (**Mit**), lysosomes (**Ly**), and ribosomes (**R**). Microtubules (**Mt**) are prominent cytoskeletal filaments in the cytosol. Axon terminals (**AT**) making contact with the dendrite are seen at the top and right.

B. Some components of a spinal motor neuron that participate in the synthesis of macromolecules. The nucleus (**N**) contains masses of chromatin (**Ch**) and is bounded by the nuclear envelope, which contains many nuclear pores (**arrows**). The mRNA leaves the nucleus through these pores and attaches to ribosomes that either remain free in the cytoplasm or attach to the membranes of the endoplasmic reticulum to form the rough endoplasmic reticulum (**RER**). Regulatory proteins synthesized in the cytoplasm are imported into the nucleus through the pores. Several parts of the Golgi apparatus (**G**) are seen, as are lysosomes (**Ly**) and mitochondria (**Mit**).

C, D. Micrographs of a dorsal root ganglion cell (**C**) and a motor neuron (**D**) show the organelles in the cell body that are chiefly responsible for synthesis and processing of proteins. The mRNA enters the cytoplasm through the nuclear envelope and is translated into proteins. Free polysomes, strings of ribosomes attached to a single mRNA, generate cytosolic proteins and proteins to be imported into mitochondria (**Mit**) and peroxisomes. Proteins destined for the endoplasmic reticulum are formed after the polysomes attach to the membrane of the endoplasmic reticulum (**ER**). The particular region of the motor neuron shown here also includes membranes of the Golgi apparatus (**G**), in which membrane and secretory proteins are further processed. Some of the newly synthesized proteins leave the Golgi apparatus in vesicles that move down the axon to synapses; other membrane proteins are incorporated into lysosomes (**Ly**) and other membranous organelles. The microtubules (**M**) and neurofilaments (**Nf**) are components of the cytoskeleton.

chapter.) The smooth endoplasmic reticulum also acts as a regulated internal Ca^{2+} store throughout the neuronal cytoplasm (see the discussion of Ca^{2+} release in Chapter 14).

A specialized portion of the rough endoplasmic reticulum forms the *nuclear envelope*, a spherical flattened cisterna that surrounds chromosomal DNA and its associated proteins (histones, transcription factors, polymerases, and isomerases) and defines the nucleus (Figure 7–3). Because the nuclear envelope is continuous with other portions of the endoplasmic reticulum and other membranes of the vacuolar apparatus, it is presumed to have evolved as an invagination of the plasmalemma to ensheathe eukaryotic chromosomes. The nuclear envelope is interrupted by nuclear pores, where fusion of the inner and outer membranes of the envelope results in the formation of hydrophilic channels through which proteins and RNA are exchanged between the cytoplasm proper and the nuclear cytoplasm.

Even though nucleoplasm and cytoplasm are continuous domains of cytosol, only molecules with molecular weights less than 5,000 can pass through the nuclear pores freely by diffusion. Larger molecules need help. Some proteins have special nuclear localization signals, domains that are composed of a sequence of basic amino acids (arginine and lysine) that are recognized by soluble proteins called *nuclear import receptors* (importins). At a nuclear pore, this complex is guided into the nucleus by another group of proteins called *nucleoporins.*

The cytoplasm of the nerve cell body extends into the dendritic tree without functional differentiation. Generally, all organelles in the cytoplasm of the cell body are also present in dendrites, although the densities of the rough endoplasmic reticulum, Golgi complex, and lysosomes rapidly diminish with distance from the cell body. In dendrites, the smooth endoplasmic reticulum is prominent at the base of thin processes called *spines* (Figures 7–4 and 7–5), the receptive portion of excitatory synapses. Concentrations of polyribosomes in dendritic spines mediate local protein synthesis (see below).

In contrast to the continuity of the cell body and dendrites, a sharp functional boundary exists between the cell body at the axon hillock, where the axon emerges. The organelles that compose the main biosynthetic machinery for proteins in the

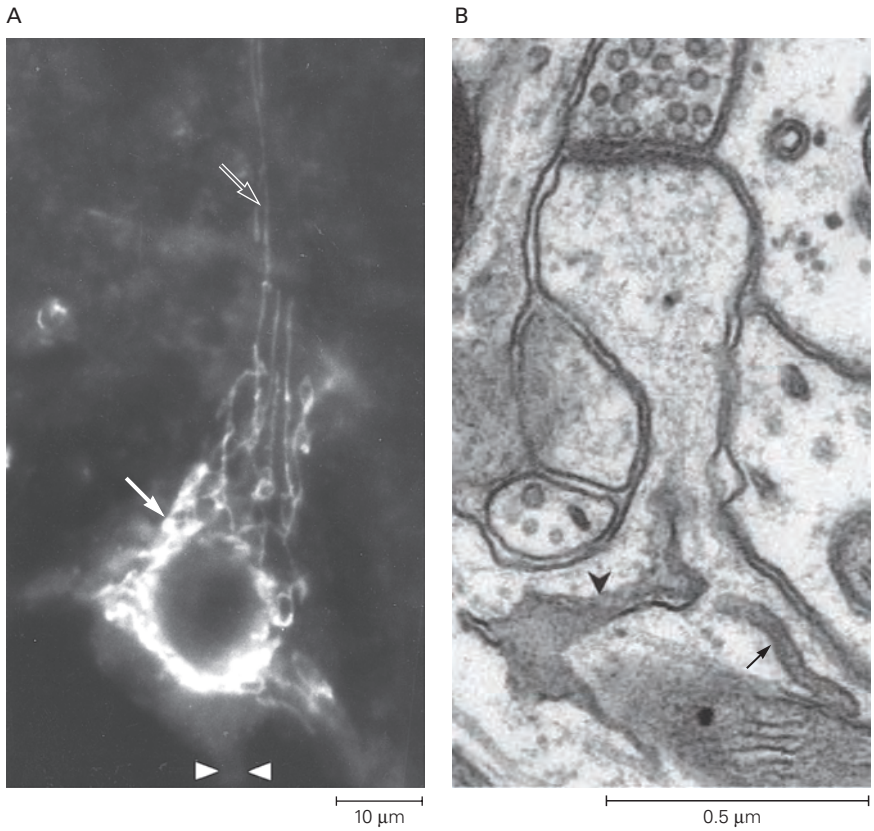

Figure 7–4 Golgi and endoplasmic reticulum membranes extend from the cell body into dendrites.

A. The Golgi complex (**solid arrow**) appears under the light microscope as several filaments that extend into the dendrites (**open arrow**) but not into the axon. The **arrowheads** at the bottom indicate the axon hillock. For this micrograph, a large neuron of the brain stem was immunostained with antibodies specifically directed against the Golgi complex. (Reproduced, with permission, from De Camilli et al. 1986. Copyright © 1986 Rockefeller University Press.)

B. Smooth endoplasmic reticulum (**arrowhead**) extends into the neck of a dendritic spine, while another membrane compartment sits at the origin of the spine (**arrow**). (Reproduced, with permission, from Cooney et al. 2002. Copyright © 2002 Society for Neuroscience.)

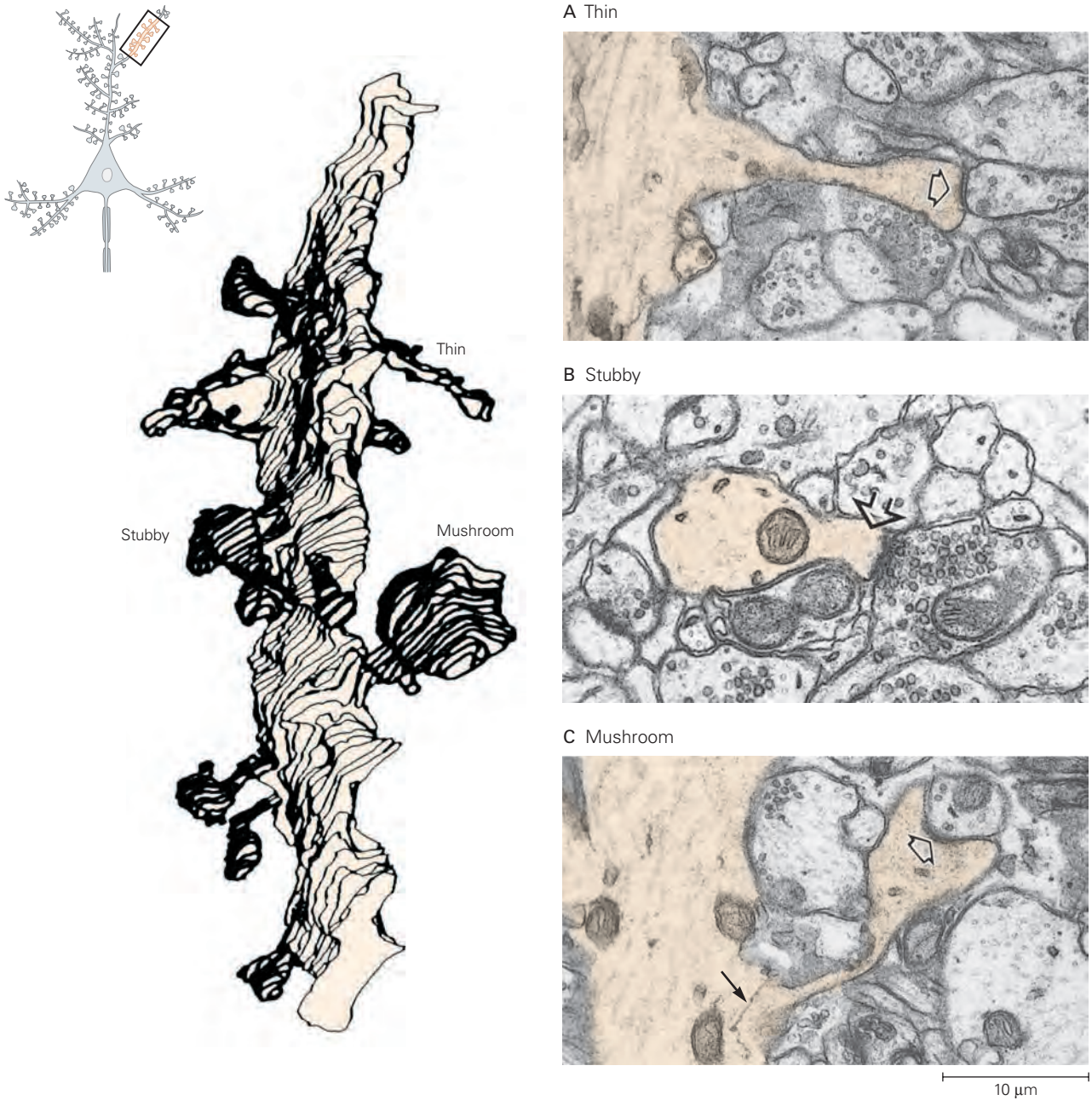

Figure 7–5 Types of dendritic spines. Three types of dendritic spine shapes are shown in a mature dendrite in a pyramidal cell in the CA1 region of the hippocampus. The drawing at left is based on a series of electron micrographs. (Drawing reproduced, with permission, from Harris and Stevens 1989; A, B, and C are reproduced, with permission, from Sorra and Harris 1993. Copyright © 1993 Society for Neuroscience.)

A. In this thin dendritic spine, the thickened receptive surface (**arrow**), located across from the presynaptic axon, contains synaptic receptors. The tissue shown here and in **B** and **C** is from the hippocampus of a postnatal day-15 rat brain.

B. Stubby spines containing postsynaptic densities (**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. The immature spine shown here contains flat cisternae of smooth endoplasmic reticulum, some with a beaded appearance (**solid arrow**). The postsynaptic density is indicated by the **open arrow**.

neuron—ribosomes, rough endoplasmic reticulum, and the Golgi complex—are generally excluded from axons (Figure 7–4), as are lysosomes and certain proteins. However, axons are rich in smooth endoplasmic reticulum, individual synaptic vesicles, and their precursor membranes.

The Cytoskeleton Determines Cell Shape

The cytoskeleton determines the shape of a cell and is responsible for the asymmetric distribution of organelles within the cytoplasm. It includes three filamentous structures: microtubules, neurofilaments, and microfilaments. These filaments and associated proteins account for approximately a quarter of the total protein in the cell.

Microtubules form long scaffolds that extend from one end of a neuron to the other and play a key role in developing and maintaining cell shape. A single microtubule can be as long as 0.1 mm. Microtubules consist of protofilaments, each of which consists of multiple pairs of *α- and β-tubulin* subunits arranged longitudinally along the microtubule (Figure 7–6A). Tubulin subunits bind to neighboring subunits along the protofilament and also laterally between adjacent protofilaments. Microtubules are polarized with a plus end (or growing end) and a minus end (where microtubules can be depolymerized). Interestingly, microtubule orientations differ between axons and dendrites. In the axon, microtubules display a single orientation with the plus end directed away from the cell body. In proximal dendrites, microtubules can be oriented both ways, with a plus end oriented toward or away from the cell body.

Microtubules grow by addition of guanosine triphosphate (GTP)-bound tubulin dimers at their plus end. Shortly after polymerization, the GTP is hydrolyzed to guanosine diphosphate (GDP). When a microtubule stops growing, its positive end is capped by a GDP-bound tubulin monomer. The low affinity of the GDP-bound tubulin for the polymer would lead to catastrophic depolymerization, were not for the fact that the microtubules are stabilized by interaction with other proteins.

In fact, while microtubules undergo rapid cycles of polymerization and depolymerization in dividing cells, a phenomenon referred to as *dynamic instability*, in mature dendrites and axons, they are more stable. This stability is thought to be caused by *microtubule-associated proteins* (MAPs) that promote the oriented polymerization and assembly of the tubulin polymers. MAPs in axons differ from those in dendrites. For example, MAP2 is present in dendrites but not in axons, where tau proteins (see Box 7–1) and MAP1b are present. Furthermore, microtubule stability is also tightly regulated by many different types of reversible tubulin posttranslational modifications such as acetylation, detyrosination, and polyglutamylation. In Alzheimer disease and some other degenerative disorders, tau proteins are modified and abnormally polymerized, forming a characteristic lesion called the *neurofibrillary tangle* (Box 7–1).

Tubulins are encoded by a multigene family. At least six genes code the α- and β-subunits. Because of the expression of the different genes or posttranscriptional modifications, more than 20 isoforms of tubulin are present in the brain.

Neurofilaments, 10 nm in diameter, are the bones of the cytoskeleton (Figure 7–6B). Neurofilaments are related to intermediate filaments of other cell types, including the cytokeratins of epithelial cells (hair and nails), glial fibrillary acidic protein in astrocytes, and desmin in muscle. Unlike microtubules, neurofilaments are stable and almost totally polymerized in the cell.

At 3 to 7 nm in diameter, *microfilaments* are the thinnest of the three main types of fibers that make up the cytoskeleton (Figure 7–6C). Like thin filaments of muscle, microfilaments are made up of two strands of polymerized globular actin monomers, each bearing an ATP or adenosine diphosphate (ADP), wound into a double-stranded helix. Actin is a major constituent of all cells, perhaps the most abundant animal protein in nature. There are several closely related molecular forms: the α actin of skeletal muscle and at least two other molecular forms, β and γ. Each is encoded by a different gene. Neural actin in higher vertebrates is a mixture of the β and γ species, which differ from muscle actin by a few amino acid residues. Most actin molecules are highly conserved, not only in different cell types of a species but also in organisms as distantly related as humans and protozoa.

Unlike microtubules and neurofilaments, actin filaments are short. They are concentrated at the cell's periphery in the cortical cytoplasm just beneath the plasmalemma, where they form a dense network with many actin-binding proteins (eg, spectrin-fodrin, ankyrin, talin, and actinin). This matrix plays a key role in the dynamic function of the cell's periphery, such as the motility of growth cones (the growing tips of axons) during development, generation of specialized microdomains at the cell surface, and the formation of pre- and postsynaptic morphological specializations.

Like microtubules, microfilaments undergo cycles of polymerization and depolymerization. At any one

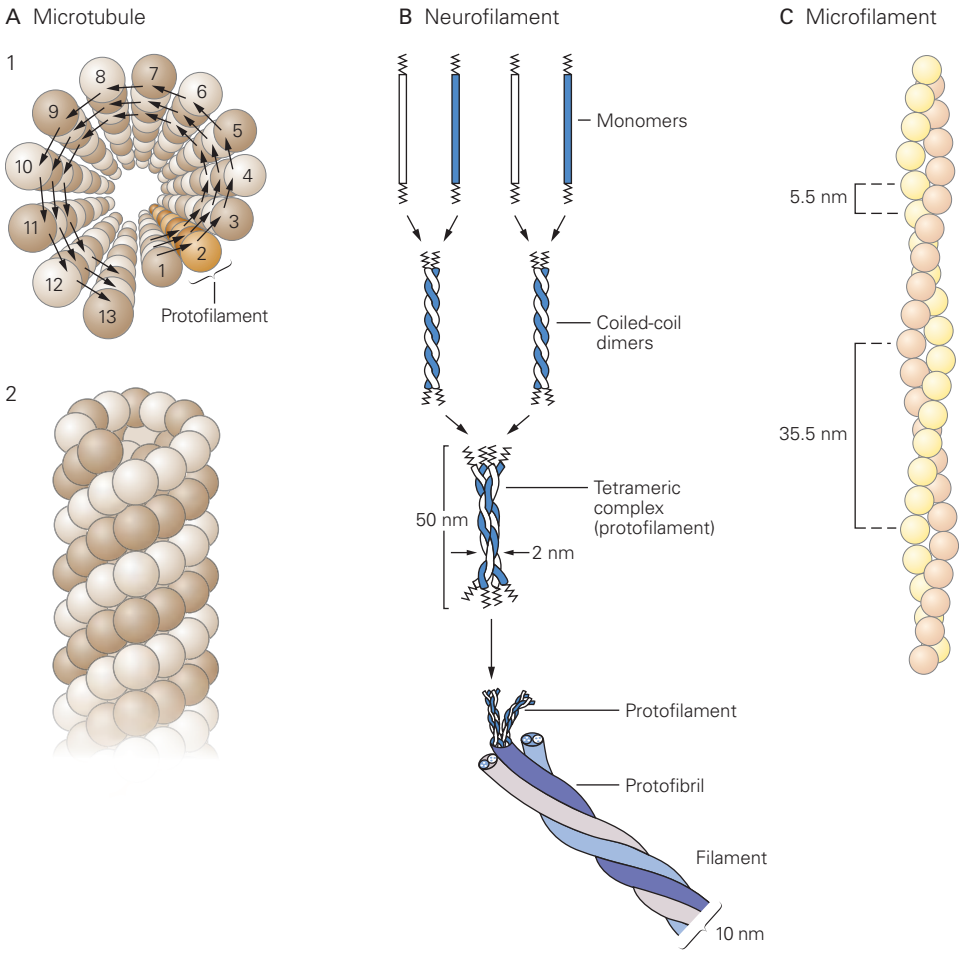

Figure 7–6 Atlas of fibrillary structures.

A. Microtubules, the largest-diameter fibers (25 nm), are helical cylinders composed of 13 protofilaments, each 5 nm in width. Each protofilament is made up of a column of alternating α- and β-tubulin subunits; each subunit has a molecular weight of approximately 50,000 Da. Adjacent subunits bind to each other along the longitudinal protofilaments and laterally between subunits of adjacent protofilaments.

A tubulin molecule is a heterodimer consisting of one α- and one β-tubulin subunit. **1.** View of a microtubule. The **arrows** indicate the direction of the right-handed helix. **2.** A side view of a microtubule 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 diameter neurofilament. (Adapted, with permission, from Bershadsky and Vasiliev 1988.)

C. Microfilaments, the smallest-diameter fibers (approximately 7 nm), are composed of two strands of polymerized globular actin (G-actin) monomers arranged in a helix. At least six different (but closely related) actins are found in mammals; each variant is encoded by a separate gene. Microfilaments are polar structures because the globular monomers are asymmetric.

time, approximately half of the total actin in a cell can exist as unpolymerized monomers. The state of actin is controlled by binding proteins, which facilitate assembly and limit polymer length by capping the rapidly growing end of the filament or by severing it. Other binding proteins crosslink or bundle actin filaments. The dynamic state of microtubules and microfilaments permits a mature neuron to retract old axons and dendrites and extend new ones. This structural plasticity is thought to be a major factor in changes of synaptic connections and efficacy and, therefore, cellular mechanisms of long-term memory and learning.