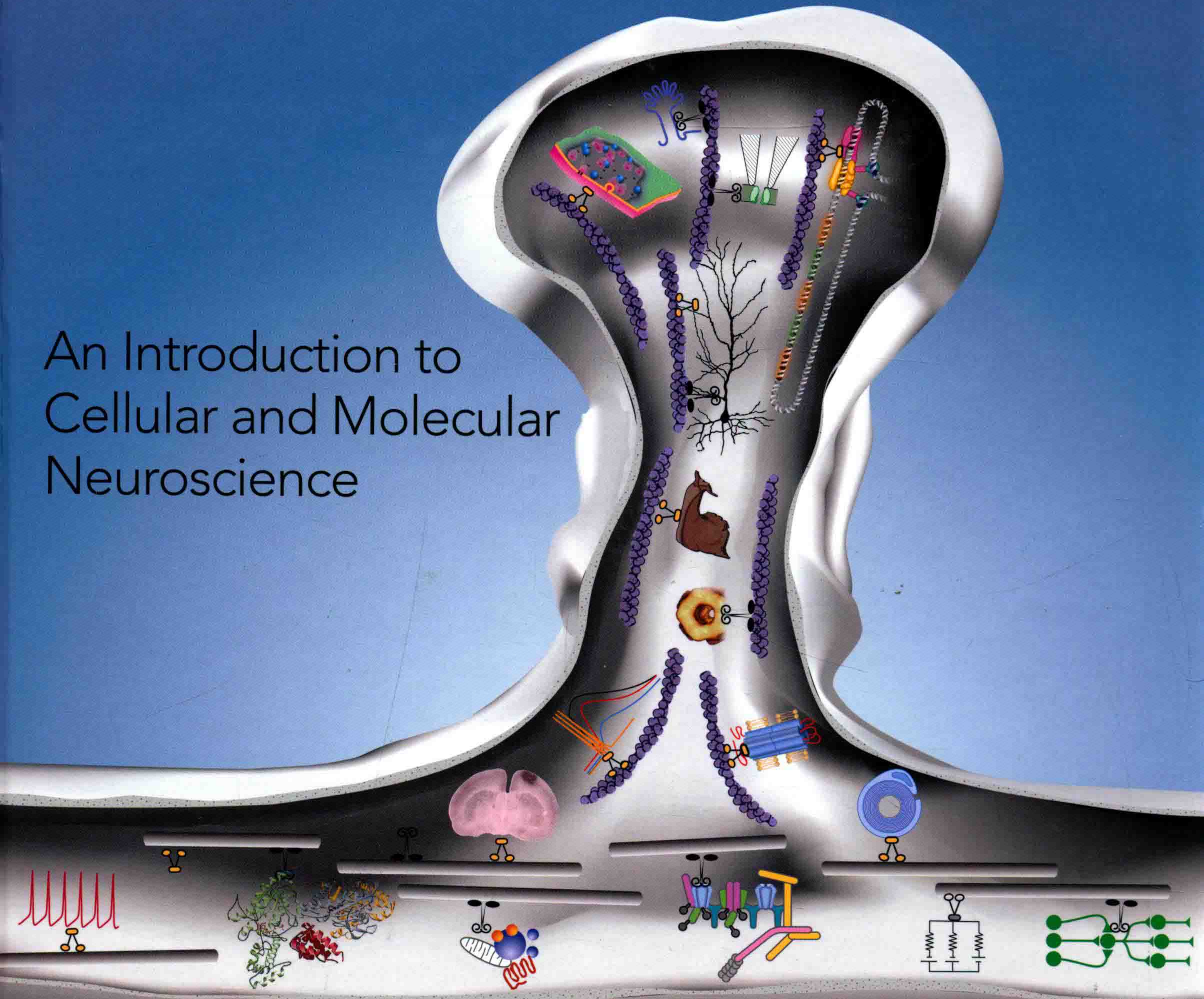
Third Edition

From Molecules to Networks

An Introduction to Cellular and Molecular Neuroscience



Edited by
John H. Byrne | Ruth Heidelberger | M. Neal Waxham

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John H. Byrne
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FROM MOLECULES TO NETWORKS

Preface to the Third Edition

The third edition brings many changes from the second. All chapters have been updated to include recent developments in the field, and major revisions have been made to the chapters on *Regulation of Neuronal Gene Expression and Protein Synthesis*, *Molecular Properties of Ion Channels*, *Cable Properties and Information Processing in Dendrites*, and *Molecular Mechanisms of Neurological Disease*. In addition, this edition features two new chapters, *Biophysics of Voltage-Gated Ion Channels* and *Synaptic Plasticity*. Finally, the order of the chapters has been rearranged and organized into three major sections to link more closely related material.

We are extremely grateful to Mica Haley at Elsevier for her support and encouragement throughout the project. Thanks also to Kristi Anderson, Laura Jackson, and members of the production staff. Special thanks to Lorenzo Morales, the graphic artist who did an outstanding job of creating and restyling the illustrations for consistency among chapters on the second edition and who has continued to do so with this new edition. He also helped to design the cover illustration.

Most importantly, we are indebted to Jim Roberts for his enormous contributions as co-editor of the first two editions. The success of the book would not have been possible without his insight, enthusiasm and hard work. We are delighted that he continues to co-author one of the chapters.

John H. Byrne
Ruth Heidelberger
M. Neal Waxham

Preface to the Second Edition

The second edition contains substantial improvements over the first edition. All chapters have been updated to include recent developments in the field, and major revisions have been done on the chapters on *Energy Metabolism in the Brain, Molecular Properties of Ion Channels, Gap Junctions,* and *Learning and Memory*. In addition, this edition features two new chapters, *Information Processing in Neural Networks* and *Molecular and Cellular Mechanisms of Neurodegenerative Disease*. Although the first edition covered biochemical and gene networks in significant detail, little was included on neural networks. It is the neural networks in the brain that collect and process information about the external world and about the internal state of the body and generate motor commands. Therefore, an understanding of these networks is essential to understanding the brain and also helps to put the cellular and molecular processes in perspective. However, discussing all of the brain systems is beyond the scope of a textbook on cellular and molecular neuroscience. Rather, our goal is to describe the principles of operation of neural networks and the key circuit motifs that are common to many networks. The second new chapter reports on the progress in the last 20 years on elucidating the cellular and molecular mechanisms underlying brain disorders. This chapter focuses specifically on amyotrophic lateral sclerosis (ALS), Parkinson's disease, and Alzheimer's disease, and the progress that has been made and the strategies that have been used to study and treat the disorders. The fact that all three diseases are associated with neuronal loss, albeit in different brain regions and with different neurotransmitter groups, suggests that there may be common aspects to the degenerative process.

We are once again extremely grateful to Johannes Menzel at Elsevier for his unfading support and encouragement throughout the project. Thanks also to Clare Caruana, Meg Day, Kristi Gomez, Kirsten Funk, Megan Wickline, and members of the production staff. Special thanks to Lorenzo Morales, the graphic artist on the project, who did an outstanding job of creating many of the illustrations in the second edition and restyling all the illustrations for consistency among chapters. He also designed the cover illustration.

John H. Byrne
James L. Roberts

Preface to the First Edition

The past 20 years have witnessed an exponential increase in the understanding of the nervous system at all levels of analyses. Perhaps the most striking developments have been in the understanding of the cell and molecular biology of the neuron. The field has moved from treating the neuron as a simple black box that added up impinging synaptic input to fire an action potential to one in which the function of nerve cells involves a host of biochemical and biophysical processes that act synergistically to process, transmit and store information. In this book, we have attempted to provide a comprehensive summary of current knowledge of the morphological, biochemical, and biophysical properties of nerve cells. The book is intended for graduate students, advanced undergraduate students, and professionals. The chapters are highly referenced so that readers can pursue topics of interest in greater detail. We have also included material on mathematical modeling approaches to analyze the complex synergistic processes underlying the operation and regulation of nerve cells. These modeling approaches are becoming increasingly important to facilitate the understanding of membrane excitability, synaptic transmission, as well gene and protein networks. The final chapter in the book illustrates the ways in which the great strides in understanding the biochemical and biophysical properties of nerve cells have led to fundamental insights into an important aspect of cognition, memory.

We are extremely grateful to the many authors who have contributed to the book, and the support and encouragement during the two past years of Jasna Markovac and Johannes Menzel of Academic Press. We would also like to thank Evangelos Antzoulatos, Evyatar Av-Ron, Diasinou Fioravanti, Yoshihisa Kubota, Rong-Yu Liu, Fred Lorenzetii, Riccardo Mozzachiodi, Gregg Phares, Travis Rodkey, and Fredy Reyes for help with editing the chapters.

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SECTION I

CELLULAR AND MOLECULAR

CHAPTER

1

Cellular Components of Nervous Tissue

Patrick R. Hof, Grahame Kidd, Javier DeFelipe, Jean de Vellis, Miguel A. Gama Sosa, Gregory A. Elder and Bruce D. Trapp

Several types of cellular elements are integrated to constitute normally functioning brain tissue. The neuron is the communicating cell, and many neuronal subtypes are connected to one another via complex circuitries, usually involving multiple synaptic connections. Neuronal physiology is supported and maintained by neuroglial cells, which have highly diverse functions. These include myelination, secretion of trophic factors, maintenance of the extracellular milieu, and scavenging of molecular and cellular debris. Neuroglial cells also participate in the formation and maintenance of the blood–brain barrier, a multicomponent structure that is interposed between the circulatory system and the brain substance and that serves as the molecular gateway to brain tissue.

NEURONS

The neuron is a highly specialized cell type and is the essential cellular element in the CNS (central nervous system). All neurological processes are dependent on complex cell–cell interactions among single neurons as well as groups of related neurons. Neurons can be categorized according to their size, shape, neurochemical characteristics, location, and connectivity, which determine their particular functional role in the brain. More importantly, neurons form circuits, and these circuits constitute the structural basis for brain function. *Macrocircuits* involve a population of neurons projecting from one brain region to another region, and *microcircuits* reflect the local cell–cell interactions within a brain region. The detailed analysis of these macro- and microcircuits is an essential step in understanding the neuronal basis of a given cortical function in the healthy and the diseased brain. Thus, these cellular characteristics allow us to appreciate the special structural and biochemical qualities of a neuron in relation to its neighbors and to place it in the context of a specific neuronal subset, circuit, or function.

Broadly speaking, therefore, there are five general categories of neurons: inhibitory neurons that make local contacts (e.g., GABAergic interneurons in the cerebral and cerebellar cortex), inhibitory neurons that make distant contacts (e.g., medium spiny neurons of the basal ganglia or Purkinje cells of the cerebellar cortex), excitatory neurons that make local contacts (e.g., spiny stellate cells of the cerebral cortex), excitatory neurons that make distant contacts (e.g., pyramidal neurons in the cerebral cortex), and neuromodulatory neurons that influence neurotransmission, often at large distances. Within these general classes, careful analyses of the structural variation of the anatomic features of neurons have led to various categorizations and to the development of the concept of cell type. The grouping of neurons into descriptive cell types (such as chandelier, double bouquet, or bipolar cells) allows the analysis of populations of neurons and the linking of specified cellular characteristics with certain functional roles.

General Features of Neuronal Morphology

Neurons are highly polarized cells, meaning that they develop distinct subcellular domains that subserve different functions. Morphologically, in a typical neuron, three major regions can be defined: (1) the cell body (*soma* or *perikaryon*), which contains the nucleus and the major cytoplasmic organelles; (2) a variable number of dendrites, which emanate from the perikaryon and ramify over a certain volume of gray matter and which differ in size and shape, depending on the neuronal type; and (3) a single axon, which extends, in

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most cases, much farther from the cell body than the dendritic arbor (Fig. 1.1). Dendrites may be spiny (as in pyramidal cells) or non-spiny (as in most interneurons), whereas the axon is generally smooth and emits a variable number of branches (collaterals). In vertebrates, many axons are surrounded by an insulating myelin sheath, which facilitates rapid impulse conduction. The axon terminal region, where contacts with other cells are made, displays a wide range of morphological specializations, depending on its target area in the central or peripheral nervous system.

The cell body and dendrites are the two major domains of the cell that receive inputs, and dendrites play a critically important role in providing a massive receptive area on the neuronal surface (see also Chapters 16 and 17). In addition, there is a characteristic shape for each dendritic arbor, which can be used to classify neurons into morphological types. Both the structure of the dendritic arbor and the distribution of axonal terminal ramifications confer a high level of subcellular specificity in the localization of particular synaptic contacts on a given neuron. The three-dimensional distribution of dendritic arborization is also important with respect to the type of information transferred to the neuron. A neuron with a dendritic tree restricted to a particular cortical layer typically receives a very limited pool of afferents, whereas the widely expanded dendritic arborization of a large pyramidal neuron receives highly diversified inputs (Fig. 1.2) (Mountcastle, 1978). The structure of the dendritic tree is maintained by surface interactions between adhesion molecules and, intracellularly, by an array of cytoskeletal components (microtubules, neurofilaments, and associated proteins), which also take part in the movement of organelles within the dendritic cytoplasm.

An important specialization of the dendritic arbor of certain neurons is the presence of large numbers of dendritic spines, which are membranous protrusions. They are abundant in large pyramidal neurons and are much sparser on the dendrites of interneurons (see below).

The perikaryon contains the nucleus and a variety of cytoplasmic organelles. Stacks of rough endoplasmic reticulum are conspicuous in large neurons and, when interposed with arrays of free polyribosomes, are referred to as *Nissl substance*. Another feature of the perikaryal cytoplasm is the presence of a rich cytoskeleton composed primarily of neurofilaments and microtubules. These cytoskeletal elements are dispersed in bundles that extend from the soma into the axon and dendrites.

Whereas dendrites and the cell body are the domains of the neuron that receive afferents, the axon, at the other pole of the neuron, is responsible for

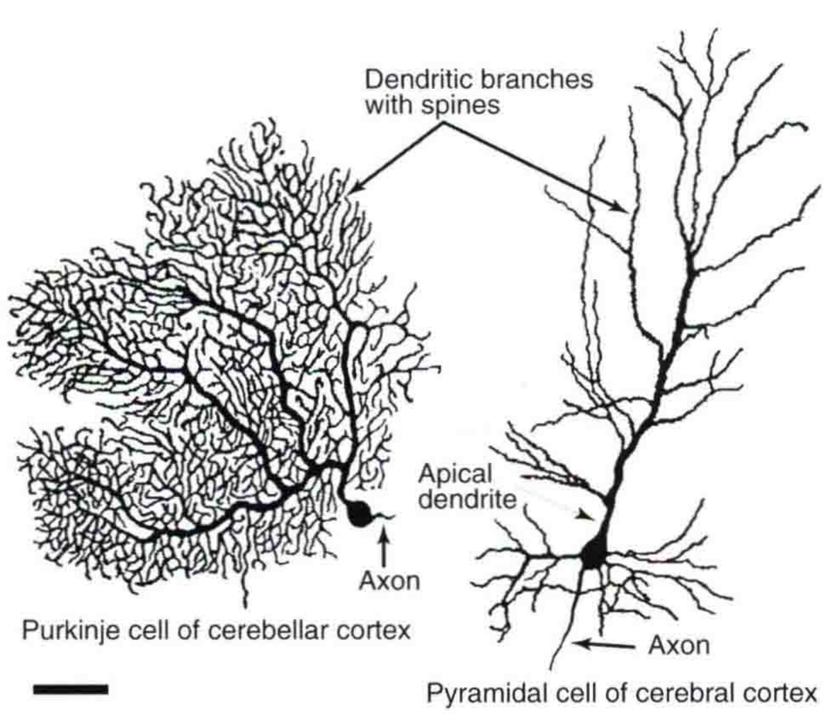

FIGURE 1.1 **Typical morphology of projection neurons.** (Left) A Purkinje cell of the cerebellar cortex and (right) a pyramidal neuron of the neocortex. These neurons are highly polarized. Each has an extensively branched, spiny apical dendrite, shorter basal dendrites, and a single axon emerging from the basal pole of the cell.

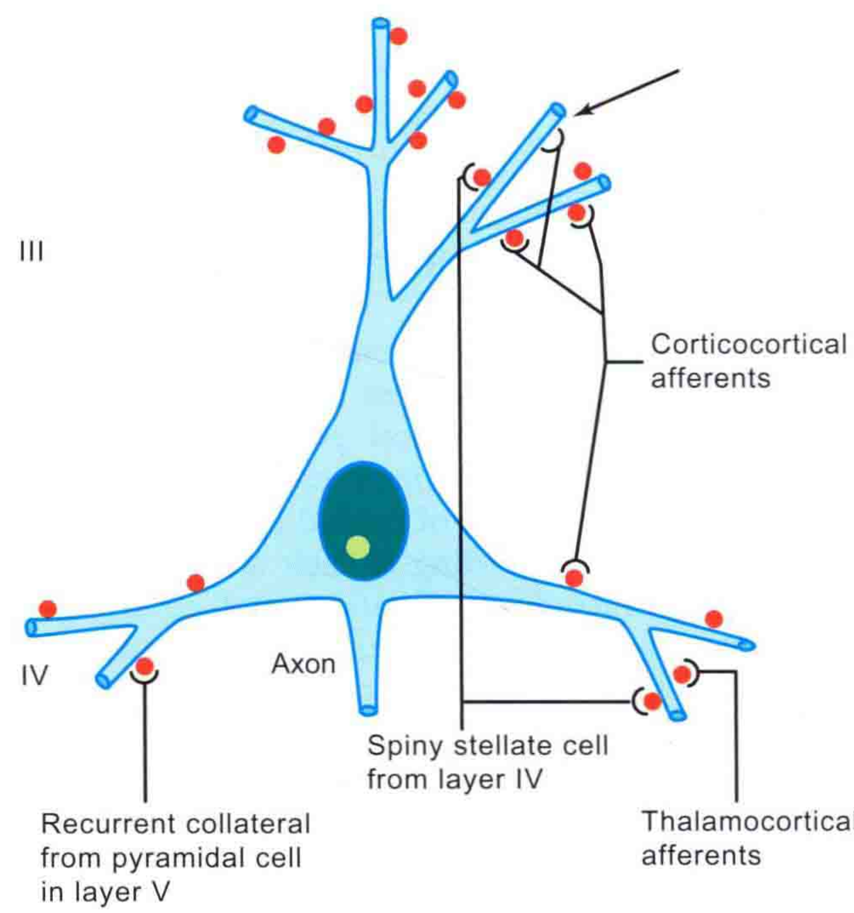

FIGURE 1.2 **Schematic representation of the spatial distribution of four major excitatory inputs to pyramidal neurons.** A pyramidal neuron in layer III is shown as an example. Note the preferential distribution of synaptic contacts on spines. Spines are indicated in red. Arrow shows a contact directly on the dendritic shaft.

transmitting neural information. This information may be primary, in the case of a sensory receptor, or processed information that has already been modified through a series of integrative steps. The morphology of the axon and its course through the nervous system are correlated with the type of information processed by the particular neuron and by its connectivity patterns with other neurons. The axon leaves the cell body from a small swelling called the *axon hillock*. This structure is particularly apparent in large pyramidal neurons; in other cell types, the axon sometimes emerges from one of the main dendrites. At the axon hillock, microtubules are packed into bundles that enter the axon as parallel fascicles. The axon hillock is the part of the neuron where the action potential is generated (see Chapter 12). The axon is generally unmyelinated in local circuit neurons (such as inhibitory interneurons), but it is myelinated in neurons that furnish connections between different parts of the nervous system. Axons usually have higher numbers of neurofilaments than dendrites, although this distinction can be difficult to make in small elements that contain fewer neurofilaments. In addition, the axon may show extensive, spatially constrained ramifications, as in certain local circuit neurons; it may give out a large number of recurrent collaterals, as in neurons connecting different cortical regions; or it may be relatively straight in the case of projections to subcortical centers, as in cortical motor neurons that send their very long axons to the ventral horn of the spinal cord. At the interface of axon terminals with target cells are the synapses, which represent specialized zones of contact consisting of a presynaptic (axonal) element, a narrow synaptic cleft, and a postsynaptic element on a dendrite or perikaryon.

Synapses and Spines

Synapses

Each synapse is a complex of several components: (1) a *presynaptic element*, (2) a *cleft*, and (3) a *postsynaptic element*. The presynaptic element is a specialized part of the presynaptic neuron's axon, the postsynaptic element is a specialized part of the postsynaptic somatodendritic membrane, and the space between these two closely apposed elements is the cleft. The portion of the axon that participates in the axon is the *bouton*, and it is identified by the presence of synaptic vesicles and a presynaptic thickening at the active zone (Fig. 1.3). The postsynaptic element is marked by a postsynaptic thickening opposite the presynaptic thickening. When both sides are equally thick, the synapse is referred to as *symmetric*. When the postsynaptic thickening is greater, the synapse is *asymmetric*. Edward George Gray noticed this difference, and divided synapses into two types: *Gray's type 1* synapses are asymmetric, and have clear, round vesicles; *Gray's type 2* synapses are symmetric, and have variably shaped, or pleomorphic, vesicles. The significance of this distinction is that research has shown that, in general, Gray's type 1 synapses tend to be excitatory, whereas Gray's type 2 synapses tend to be inhibitory. This correlation greatly enhanced the usefulness of electron microscopy in neuroscience.

In cross-section on electron micrographs, a synapse looks like two parallel lines separated by a very narrow space (Fig. 1.3). Viewed from the inside of the axon or dendrite, it looks like a patch of variable shape. Some synapses are a simple patch, or *macule*. Macular synapses can grow fairly large, reaching diameters over 1 μm. The largest synapses have discontinuities or holes within the macule, and are called *perforated synapses* (Fig. 1.3). In cross-section, a perforated synapse may resemble a simple macular synapse, or several closely spaced smaller macules.

The portion of the presynaptic element that is apposed to the postsynaptic element is the *active zone*. This is the region where the synaptic vesicles are concentrated, and where, at any time, a small number of vesicles are docked and presumably ready for fusion with the presynaptic membrane to release their contents. The active zone is also enriched with voltage gated calcium channels, which are necessary to permit activity-dependent fusion and neurotransmitter release by rapidly increasing calcium concentration (see also Chapter 15).

The synaptic cleft is truly a space, but its properties are essential. The width of the cleft (~20 nm) is critical because it defines the volume in which each vesicle releases its contents, and therefore, the peak concentration of neurotransmitter upon release. The synaptic cleft is spanned by adhesion molecules, particularly on the flanks of the synapse, which is believed to stabilize the cleft.

The postsynaptic element may be a portion of a soma or a dendrite, or, rarely, part of an axon. In the cerebral cortex, most Gray's type 1 synapses are located on dendritic spines, which are specialized protrusions of the dendrite, and most Gray's type 2 synapses are located on somata or dendritic shafts. A similar segregation is seen in cerebellar cortex. In non-spiny neurons, symmetric and asymmetric synapses are often less well separated. Irrespective of location, a postsynaptic thickening marks the postsynaptic element. In Gray's type 1 synapses, the postsynaptic thickening (or postsynaptic density, PSD) is greatly enhanced. Among the molecules that are associated with the PSD are neurotransmitter receptors (e.g., *N*-methyl-D-aspartate receptors) and molecules with less obvious function, such as PSD-95.