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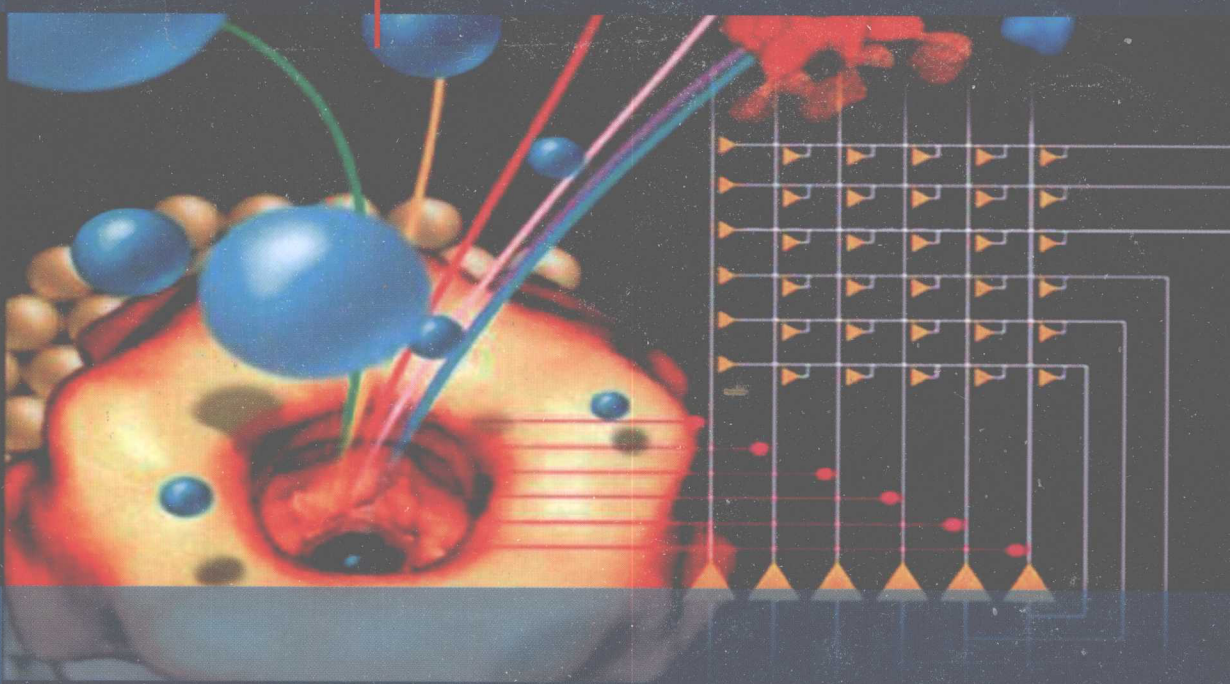
From Molecules to Networks

An Introduction to Cellular and Molecular Neuroscience

从分子到网络

细胞和分子神经科学导论（原著第二版）

John H. Byrne, James L. Roberts



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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 text book 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 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 twenty 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.

John H. Byrne
James L. Roberts

第 1 章　神经组织的细胞组成

在脑组织内，几种类型的细胞成分集合在一起发挥正常的功能。其中神经元是主要的信息交通细胞，它通过突触的方式与其他神经元之间形成复杂的环路；神经胶质细胞为神经元提供支持，维持神经元发挥正常的生理功能，同时还具有生成髓鞘、分泌营养因子、清除细胞和分子碎片等功能，另外神经胶质细胞还参与血脑屏障的构成，保证了神经系统发挥正常功能所需的内环境。

神经元

神经元是中枢神经系统内最基本的细胞成分。神经系统的活动依赖于单个神经元和（或）相关的神经元群之间复杂的细胞间相互作用。神经元可以构成脑功能的结构基础——环路。巨型环路可能涉及一个脑区向另一个脑区的投射；微环路则反映同一脑区内局部的细胞间联系。对这些巨型或微环路进行具体的分析，是我们了解生理和病理状态下特定皮层功能的结构基础所必需的步骤。概括地说，神经元可分为 5 种基本的类型：局部联系抑制性神经元、远距离投射抑制性神经元、局部联系兴奋性神经元、远距离投射兴奋性神经元，以及影响神经递质传递的神经调节神经元。在此分类的基础上，可根据神经元的解剖学特性，联系其特定的功能并结合特殊的细胞特性进一步分类。

神经元形态学的基本特征

在形态结构上，典型的神经元可被划分为三个主要部分：①细胞体，又称为核周体，包含细胞核和大量的细胞器；②数目不等的树突结构，从核周体发出，分支形成树突树，在不同类型神经元中其大小和形状也不同；③单根轴突，多从细胞体延伸而出，往往要比树突的分支更长。细胞体和树突是神经元接受信息传入的主要结构，树突分支大大增加了神经元接受信息的面积。根据树突分支的特殊形状，可将神经元分为不同的形态学类型。轴突主要负责传出神经元的信息。轴突从细胞体发起的部位称为轴丘，是神经元产生动作电位的部位。轴突又分为有髓鞘和无髓鞘两种类型。轴突也发出许多分支，既有局部微环路中的反馈性分支，也有向不同脑区甚至是皮层下结构的分支投射；而最长的分支投射可以从皮层直达脊髓的前角。轴突的终末与其他神经元形成突触联系。

突触　突触结构包括突触前成分、突触间隙和突触后成分三部分。突触前成分主要由突触前神经元的轴突终末特化的终扣构成，突触后成分主要由突触后神经元的胞体和树突膜特化而成。突触前成分和突触后成分都含有致密带，突触前成分与突触后成分的区别在于前者含有突触囊泡。当突触前和突触后的致密带厚度相同时，称其为对称性突触（又称为 Gray Ⅰ型突触），其突触前含有多角形或不规则形状的囊泡，多为抑制性突触；当突触后致密带厚于突触前致密带时，则称其为非对称性突触（又称 Gray Ⅱ型突触），其含有清亮的卵圆形囊泡，多为兴奋性突触。在大脑和小脑皮质内，Gray Ⅰ型突触多位于胞体和树突干，而 Gray Ⅱ型突触多位于树突棘。突触前成分除含有突触囊泡外，在活性带上还含有丰富的电压依赖性钙通道，这是突触囊泡融合与递质释放所必需的。而在突触后成分的致密带中，则主要聚集着大量的递质受体蛋白以及没有明显功能的分子，如 PSD-95，其可以作为突触后成分的标记物。而突触间隙也是非常重要的结构，它可以使递质释放局限在狭小的空间内，从而快速达到峰值浓度。

树突棘 树突棘是在某些神经元的树突干上发出的突起，它是突触联系的部位，尤其是兴奋性突触。19 世纪末，Golgi 和 Ehrlich 分别用银浸染和亚甲蓝染色方法在不同神经元的树突干上发现了附着的树突棘。锥体细胞和浦肯野氏细胞都含有大量的树突棘。树突棘可以增加神经元的表面积，若一个锥体细胞含有 20 000 个树突棘，则可以使细胞表面积增加 40%之多。树突棘是一种动态的结构，它可以调控与突触传递及突触效能相关的神经化学活动。在某些实验或临床的神经病理条件下，树突棘会发生病理性改变，树突棘的密度也会发生变化。从形态学结构看，树突棘是从树突干发出的狭长的蛋白质，包含一个颈部以及一个卵圆形的球部。从超微结构看，树突棘中含有较多的细丝，其主要由肌动蛋白和α、β微管蛋白构成，而神经微管和神经微丝只在树突干中存在。树突棘中也极少含有线粒体和游离核糖体，但在树突棘基底部的树突干部位却有大量的多聚核糖体，这提示其具有局部合成蛋白质的功能。

不同类型的典型神经元

（1）局部联系抑制性神经元

在大脑皮层和皮层下结构中含有大量不同的抑制性中间神经元，篮状细胞、串珠样细胞和双束细胞是大脑皮层内三类主要的抑制性中间神经元。它们都含有抑制性神经递质，都与皮层内的锥体细胞形成突触联系，对锥体细胞进行抑制性调控。但三类抑制性中间神经元的树突和轴突的分支分布各不相同，尤其是它们的轴突形态各异，这成为细胞分类和命名的主要依据之一。以上三类神经元与锥体细胞的不同部位形成突触结构，其中篮状细胞与锥体细胞的胞体形成突触；串珠样细胞则与锥体细胞的轴突起始节段形成独特的轴-轴突触，因而也被称为轴-轴突触细胞；双束细胞则主要与锥体细胞的树突干和树突棘形成突触联系。这种突触形成部位上的差异暗示着三类细胞对锥体细胞的调控作用不同。

（2）远距离投射抑制性神经元

中等棘突细胞是特异存在于纹状体和部分基底节中的抑制性神经元。它散乱地分布在尾状核和壳核内。与基底节中其他神经元不同，中等棘突细胞相对较大，且树突在各个方向上都有较多的分支，同时树突棘的密度较高。它可以接受来自大脑皮层、丘脑以及黑质的多巴胺神经元等多个来源的信息，同时传出大量的信息。这些神经元的神经化学特性极不均一，除含有 GABA 外，还可能含有数种神经肽和钙结合蛋白。纹状体退行性病理改变引起的亨廷顿舞蹈症中，在早期会出现大量的中等棘突细胞丢失。浦肯野氏细胞是小脑皮质中具有显著特征的一种神经元。它在小脑皮质的分子层和颗粒层之间排列成行，是其中最大的神经元。其树突高度分支形成树突树进入分子层，形状如酒杯；其顶树突上有大量的树突棘存在，与颗粒层和脑干的传入纤维形成联系，每一个树突的分支决定一个独立的小脑皮层功能区。它的轴突穿行小脑白质，与小脑深层核团及前庭核团形成联系。这些细胞含有抑制性神经递质 GABA 以及钙结合蛋白。小脑共济失调已被证实与浦肯野氏细胞的退行性病变有直接关系。

（3）局部联系兴奋性神经元

棘突星状细胞是皮层内的兴奋性中间神经元，是锥体细胞兴奋性传入的主要来源之一。棘突星状细胞胞体呈小多角形，其树突分支上有大量的树突棘，但棘突星状细胞没有顶树突，且树突分支走行以水平方向为主，局限于胞体所在的细胞层内。其轴突的投射主要在皮层内，且呈辐射状，主要联络皮层的Ⅳ层（丘脑传入层）与Ⅲ、Ⅴ、Ⅵ层（投射层）。其神经递质同为谷氨酸。棘突星状细胞的分布具有区域和层次特异性，可将丘脑的传入依照躯体定位关系高保真地传递到相应的感觉脑区，这些细胞是构成大脑功能性脑区的结构基础。

（4）兴奋性投射神经元

锥体细胞是大脑皮层内最主要的兴奋性神经元，所有的皮层信息传出都是通过锥体细胞

完成的。它是高度极化的细胞，走行方向与大脑皮层的软膜面垂直。其树突从胞体的顶部和基底部发出，树突的分布范围视胞体所在的细胞层而不同，可以局限在皮层的几个细胞层内，也有的贯穿整个皮层厚度，达几个毫米。其轴突向皮层下投射，并发出多支回返式侧突，这是其重要的结构特征之一。其神经递质为谷氨酸。锥体细胞的胞浆中含有脂褐素结构。锥体细胞可根据其形态、分布和联系进行更细的分类。脊髓运动神经元胞体位于脊髓前角，其轴突离开中枢进入外周支配肌肉。根据支配靶点的不同，可将运动神经元分为α运动神经元和γ运动神经元，其中前者支配骨骼肌，后者支配肌梭。α运动神经元是整个中枢神经系统中最大的神经元。其胞体为多角形，其中含有丰富的细胞质成分。其多棘的树突分支主要局限在脊髓前角，其轴突离开中枢穿过前角成为外周神经。脊髓运动神经元在脊髓前角的分布并不是随机的，而是与躯体和四肢的肌肉群之间存在着明确的躯体定位关系。其神经递质为乙酰胆碱。下运动神经元疾病（如肌无力）与脊髓运动神经元的严重受损密切相关。

（5）神经调节神经元

黑质的多巴胺能神经元是主要位于黑质致密部和腹盖区的较大的神经元。其显著特征是细胞质中含有神经黑色素的致密颗粒，因而可以呈色。该细胞中等大小，为纺锤形或梭形，具有几个较大的辐射分支的树突，其轴突从胞体或树突发出，投射至大脑皮层和基底节的广泛区域。其以多巴胺为神经递质，细胞内含有酪氨酸羟化酶。黑质的多巴胺神经元损伤与帕金森综合征的发病有直接关系。

神经胶质细胞

神经胶质细胞的命名，代表着人们对于胶质细胞功能最初的认识，即无活性的连接细胞。随着研究的深入，神经胶质细胞许多新的重要作用被发现。在中枢神经系统内，少突胶质细胞、星形胶质细胞和小胶质细胞是三类主要的神经胶质细胞，而雪旺氏细胞是外周神经系统中的主要神经胶质成分。

少突胶质细胞和雪旺氏细胞

大部分神经功能的实现都依赖于神经元环路之间快速的交通。如何使单根裸露的轴突能更快速地传导动作电位是生物体必须解决的进化课题。在进化过程中，生物界出现了两种解决此问题的方法。无脊椎动物通过使轴突变粗加快了动作电位的传导，最典型的代表就是枪乌贼，其巨大轴突粗如自动铅笔芯。而脊椎动物则进化产生了轴突的髓鞘结构，即轴突外包裹了许多髓鞘节段，各节段之间裸露的轴突部分称为郎飞氏节。由于髓鞘的绝缘特性，动作电位在有髓神经上是跳跃式传导，因而速度大大提高。中枢神经系统中轴突髓鞘主要由少突胶质细胞形成。因为中枢神经系统位于颅腔和椎管内，为减少胶质细胞所占空间，一个少突胶质细胞可以伸出多个突起，包裹多个轴突形成多个节间段；而且其形成髓鞘的蛋白与外周神经髓鞘也不同，其髓鞘厚度比外周髓鞘薄约 30%。外周神经系统轴突髓鞘主要由雪旺氏细胞形成。由于外周神经的走行分布使其相对容易受损，进化的压力促使外周神经的髓鞘具有粗大和可再生的特性。其中一个雪旺氏细胞只包裹一个轴突形成一个节间段。在神经损伤时，雪旺氏细胞还具有分泌生长因子、清除碎片和轴突导向作用。髓鞘是通过蛋白质与蛋白质之间的相互作用，使胶质细胞突起的细胞膜之间压紧并熔合而成的。在哺乳类动物，外周髓鞘主要蛋白质为 P_0 蛋白，而中枢内髓鞘形成蛋白主要是 DM20 和蛋白脂蛋白。如果基因突变影响了髓鞘的形成，动物会表现出行为上的异常。现已有多种与髓鞘功能相关的基因突变动物，如战栗鼠等，其为研究不同髓鞘蛋白的功能提供了线索。

星形胶质细胞

星形胶质细胞遍布于整个中枢神经系统内，在部分脑区占脑容量的30%～50%。其有两种主要的形态类型，即原生质型和纤维型，分别存在于灰质和白质中。从胚胎发育上讲，星形胶质细胞由径向胶质细胞发育而来。在成熟的小脑和视网膜中，某些星形胶质细胞仍保留部分径向细胞的特性，如Bergmann胶质细胞和Müller细胞。星形胶质细胞在神经元以及少突胶质细胞周围形成栅栏，并伸出突起与软脑膜和室管膜形成胶质界膜，分隔脑实质。其突起还覆盖毛细血管，并在有髓纤维的郎飞氏节处形成袖套。星形胶质细胞还包裹突触和树突，并发出突起至神经元胞体。星形胶质细胞之间以缝隙连接的方式形成合胞体。它具有许多细胞和免疫学特性，如星形胞体、毛细血管壁上的终足、胶原纤丝酸性蛋白（GFAP）、S-100、谷氨酸合成酶等，这些都是其明显的标志。星形胶质细胞具有许多重要的功能，除参与构成血脑屏障外，还包括发育早期对神经元的诱向和迁移、合成分泌中枢神经系统的基质蛋白和粘连分子、参与毛细血管生成、分泌众多生长因子和细胞因子、参与中枢神经系统的发育和损伤后修复、对突触传递的神经递质进行快速摄取和灭活。星形胶质细胞可以摄取突触释放的兴奋性递质谷氨酸，并将其转化为谷氨酰胺释放到细胞外；后者再由神经元摄取，重新合成谷氨酸和GABA。另外，它可以包裹金属离子、内源性兴奋物质以及异源性生物，从而发挥解毒作用。星形胶质细胞被激活后可以产生胞内钙波，胞内钙波可以通过第二信使的介导，扩散通过缝隙连接。星形胶质细胞的肿胀和增生是许多中枢神经系统的疾病重要的病理表现之一。

小胶质细胞

传统的观点认为大脑是免疫反应的特免部位，因为有血脑屏障可以阻挡血液中的免疫细胞进入脑内。但现在的研究已经证实，在中枢神经系统内也可以发生免疫反应，尤其是在皮质产生炎症时。小胶质细胞就是免疫系统在中枢神经系统内的常驻代表，它发挥着类似吞噬细胞的功能。大多数小胶质细胞是由骨髓源性单核细胞衍生而来，它们在大脑发育的早期进入脑实质中。它们可以清除衰老死亡的细胞，保留了单核细胞和吞噬细胞的免疫学特性。在中枢神经系统发育早期，小胶质细胞分泌细胞因子和生长因子，参与纤维束以及胶质和血管的生成。它还可以将抗原呈送至T淋巴细胞。关于小胶质细胞在健康成熟的脊椎动物中枢神经系统中的作用，目前了解相对较少。在正常情况下，小胶质细胞胞体呈杆状，其突起向各个方向对称分布，各细胞的突起之间很少发生交叠和联系。在不同的脑区，小胶质细胞的数量和形状会有所差异。小胶质细胞被认为在脑组织的内稳态中发挥重要作用。在病理状态（如脑损伤或神经退行性变）下，小胶质细胞会被激活，并在细胞的形态和抗原表达上有别于正常状态。

大脑的脉管系统

中枢神经系统有十分丰富的血管网络，主要分布在大脑皮层和皮层下的灰质结构中，而白质中少有血管。在大脑皮层，血管的分布呈明显的区域和板层差异，神经元数量越多、突触密度越高的部位毛细血管网的分布越密集。当大脑动脉主干或分支被栓塞时，会引起其支配的相应脑组织缺血、缺氧而迅速坏死。若血管阻塞渐进性发生，则会引起慢性的血管性痴呆，这种情况多见于老年人。

血脑屏障

中枢神经系统内的毛细血管构成一种保护性屏障，限制循环系统的液体和细胞成分进入

脑组织，其功能类似于血视网膜屏障，叫做血脑屏障。其作用在于维持脑内环境的稳定。血脑屏障的构成除毛细血管的内皮细胞外，还包括基膜、周细胞和星形胶质细胞终足等成分。脑内毛细血管内皮细胞与系统循环毛细血管内皮细胞最大的区别在于，前者细胞之间是紧密连接的，从而可以阻止液体进入细胞间隙。由于脑组织有着较大的代谢需求，因而在脑内的毛细血管内皮细胞上存在较多的转运体，如葡萄糖同工转运体 1 和中性氨基酸转运系统，以及转铁蛋白受体等，它们可将营养成分快速转运至脑内，满足神经细胞功能需要。脑内除了最后区和室周结构等特殊部位，都存在血脑屏障。血脑屏障一旦破坏，则其通透性增加，可使液体在脉管周围累积，形成水肿。这是许多神经系统疾病的脑内病理表现之一，如多发性硬化症、获得性免疫缺陷综合征以及阿尔茨海默病等。从治疗的角度讲，有时候也需要增加血脑屏障的通透性，从而使药物能进入脑内发挥作用。所以体外血脑屏障系统的开发，对于研发新的神经治疗药物具有重要的意义。

（第四军医大学　李　震　　陈　军）

目　录

第 1 章　神经组织的细胞组成……1
第 2 章　神经系统亚细胞结构：细胞器及其功能……19
第 3 章　脑能量代谢……49
第 4 章　轴突和树突的电紧张特性……111
第 5 章　膜电位和动作电位……133
第 6 章　离子通道的分子特性……159
第 7 章　可兴奋膜的动力学性质……181
第 8 章　神经递质的释放……217
第 9 章　突触传递的药理学与生物化学：经典神经递质……267
第 10 章　脑内非经典信号……301
第 11 章　神经递质受体……321
第 12 章　胞内信号转导……359
第 13 章　神经元基因表达与蛋白合成的调节……391
第 14 章　胞内信号通路的建模和分析……413
第 15 章　神经系统中以 Connexin 和 Pannexin 为基础的通道：缝隙连接及其他……445
第 16 章　突触后电位和突触整合……469
第 17 章　复杂信息在树突的加工与处理……489
第 18 章　神经网络信息处理……513
第 19 章　学习与记忆：基本机理……539
第 20 章　神经变性病的分子与细胞机理……609

索引……631

CHAPTER

1

Cellular Components of Nervous Tissue

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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 and incompletely understood functions. These include myelination, secretion of trophic factors, maintenance of the extracellular milieu, and scavenging of molecular and cellular debris from it. 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 central nervous system (CNS). All neurological processes are dependent on complex cell–cell interactions between single neurons and/or groups of related neurons. Neurons can be categorized according to their size, shape, neurochemical characteristics, location, and connectivity, which are important determinants of that particular functional role of the neuron 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 (eg., pyramidal neurons in the cerebral cortex), and neuromodulatory neurons that influence neurotransmission, often at large distances. Within these general classes, the structural variation of neurons is systematic, and careful analyses 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 most cases, much farther from the cell body than the dendritic arbor (Fig. 1.1). Dendrites may be spiny (as in pyramidal cells) or nonspiny (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. 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 may receive a very limited pool of afferents, whereas the widely expanded dendritic arborizations of a large pyramidal neuron will receive highly diversified inputs within the different cortical layers in which segments of the dendritic tree are present (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 following text).

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.

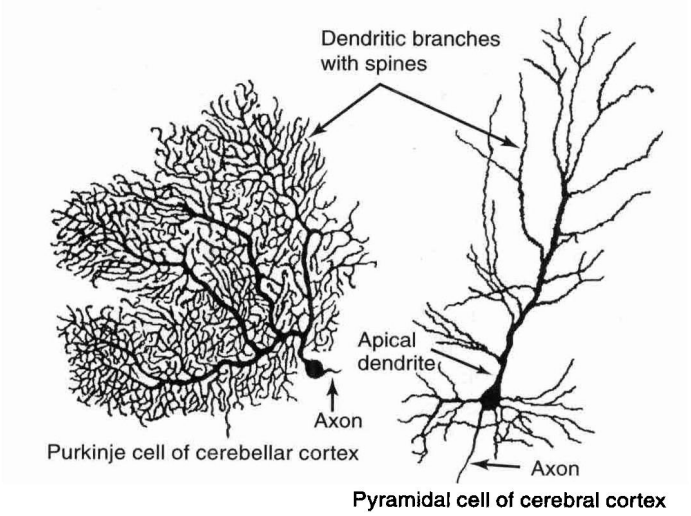

FIGURE 1.1 Typical morphology of projection neurons. (Left) A Purkinje cell of the cerebellar cortex and (right) a pyramidal neuron of the neocortex. These neurons are highly polarized. Each has an extensively branched, spiny apical dendrite, shorter basal dendrites, and a single axon emerging from the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

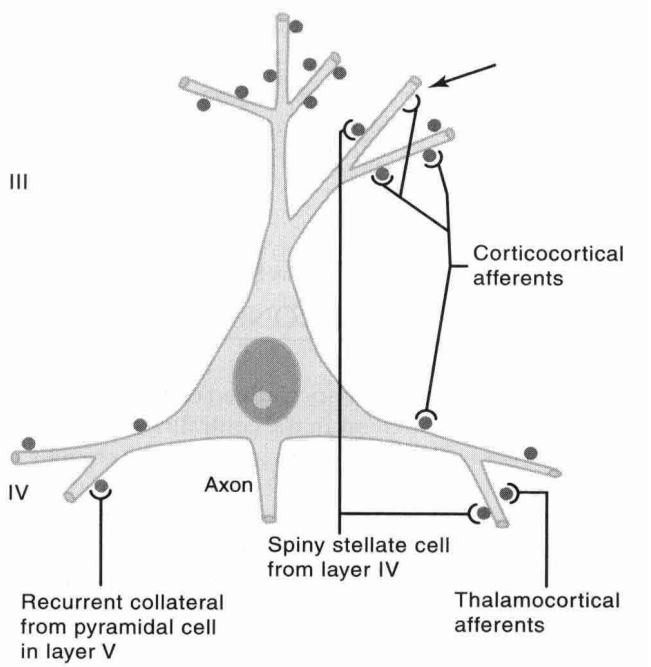

FIGURE 1.2 Schematic representation of four major excitatory inputs to pyramidal neurons. A pyramidal neuron in layer III is shown as an example. Note the preferential distribution of synaptic contacts on spines. Spines are labeled in red. Arrow shows a contact directly on the dendritic shaft.

Whereas dendrites and the cell body can be characterized as domains of the neuron that receive afferents, the axon, at the other pole of the neuron, is responsible for 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. 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 be extremely ramified, 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 symmetric and have variably

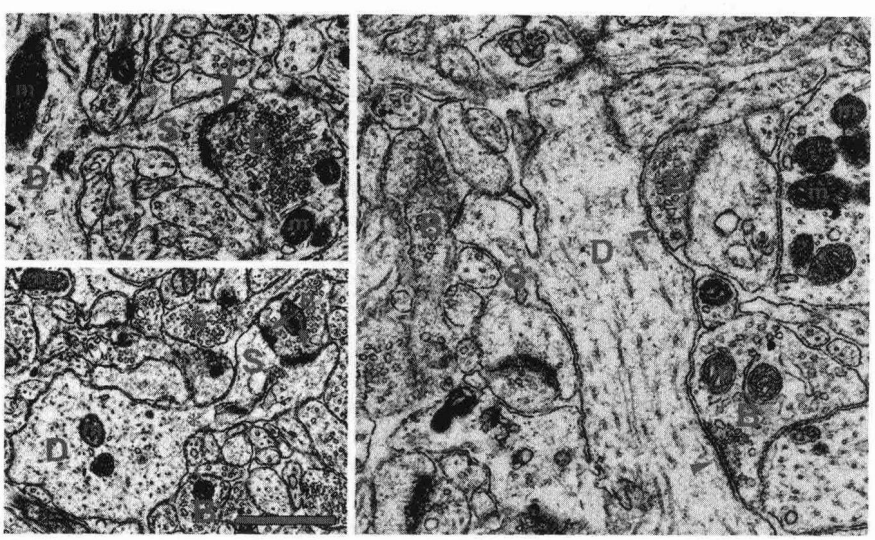

FIGURE 1.3 Ultrastructure of dendritic spines (S) and synapses in the human brain. Note the narrow spine necks (asterisks) emanating from the main dendritic shaft (D) and the spine head containing filamentous material, and the cisterns of the spine apparatus particularly visible in the lower panel spine. The arrows on the left panels point to postsynaptic densities of asymmetric excitatory synapses (arrows). The apposed axonal boutons (B) are characterized by round synaptic vesicles. A perforated synapse is shown on the lower left panel. The panel at right shows two symmetric inhibitory synapses (arrowheads) on a large dendritic shaft (D). In this case the axonal boutons (B) contain some ovoid vesicles compared to the ones in asymmetric synapses. The dendrites and axons contain numerous mitochondria (m). Scale bar = 1 μm. Electron micrographs courtesy of Drs. S.A. Kirov and M. Witcher (Medical College of Georgia), and K.M. Harris (University of Texas – Austin).