



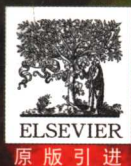
· 导读版 ·

Development of the Nervous System

神经系统发育

(第二版)

Dan H. Sanes, Thomas A. Reh, William A. Harris



科学出版社
www.sciencep.com

Development of the Nervous System

Second Edition

神经系统发育

(第二版)

Dan H. Sanes

Thomas A. Reh

William A. Harris

科学出版社

北 京

图字:01-2006-7325 号

This is an annotated version

Development of the Nervous System

Dan H. Sanes, Thomas A. Reh, William A. Harris

Copyright © 2006, Elsevier Inc.

ISBN 13: 978-0-12-618621-5

ISBN 10: 0-12-618621-9

ISBN 13: 978-0-12-369447-8(CD-ROM)

ISBN 10: 0-12-369447-7(CD-ROM)

All rights reserved.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system, without permission in writing from the publisher.

AUTHORIZED EDITION FOR SALE IN P. R. CHINA ONLY

本版本只限于在中华人民共和国境内销售

图书在版编目(CIP)数据

神经系统发育:英文/(美)萨兹(Sanes, D. H.)等编著. —影印本. —北京:科学出版社,2007

ISBN 978-7-03-018282-1

I. 神… II. 萨… III. 神经系统-发育-英文 IV. R322.8

中国版本图书馆 CIP 数据核字(2006)第 152449 号

责任编辑:田慎鹏/责任印制:钱玉芬/封面设计:耕者设计工作室

科学出版社 出版

北京东黄城根北街 16 号

邮政编码:100717

<http://www.sciencep.com>

北京佳信达艺术印刷有限公司 印刷

科学出版社发行 各地新华书店经销

*

2007 年 1 月第 一 版 开本:889×1194 1/16

2007 年 1 月第一次印刷 印张:24 3/4

印数:1—2 500 字数:682 000

定价:68.00 元 (附光盘)

如有印装质量问题,我社负责调换

第一版序

众所周知人脑是我们已知世界中最为复杂的一个物体，数以十亿计的细胞和细胞间数以万亿计的各种联系是其中最为奥妙的部分。探寻神经系统中细胞产生感觉、行为以及高级精神活动的方式已经成为科学界中成果最为丰硕的一个领域。但是，神经科学家们已经意识到他们研究的是一个不断发生着变化的目标：生长和改变与脑的功能是一个统一的整体，并且只有在此统一的基础上我们才能研究其它任何与之相关的东西。行为胚胎学家 George Coghill 指出，“人体实际上就是一部机器，但是这部机器在其有限的生命、感知和成长中在不断自我创造和自我运行”。因此，为了认识脑，我们需要了解这部机器是怎样起源以及在其一生的时间中它是怎样变化的。

脑的构成是一系列发育阶段的整合体，由最初少量胚胎细胞成为神经前体细胞开始，随着神经细胞之间联系的形成以及它们电活动特征的显现，到脑开始处理信息并且介导行为功能。虽然一些潜在的环路在胚胎发育期就已经构建在神经系统中，但脑与这个世界的联系却是不断更新的，并逐步改变着脑的功能构筑。这些变化发生的机制似乎是一个渐进的过程，它在发育过程中对脑的结构进行塑造。因此，本书涵盖了这些发育阶段的每一步骤，所以涉及的面相对广泛。

理解神经系统的发育对广大生物学家来说有着重要意义，对发育的研究引领我们看到许多生物体在进化中的联系。上世纪关于种系发生和个体发生的法则已经被目前更深层次的理解所代替，即进化发生的方式会受到发育中变化的影响。当然，脑也毫无例外地遵循这样的原则。因此，我们认为，理解发育的进程怎样随时间而改变将有助于深入理解令我们更加人性化的进化过程。

本书的目的就是为高年级学生或那些有生物学背景的研究工作者提供一个神经发育过程的纲要，这与广泛的文献综述在目的是完全不同的。在最近一次的 MEDLINE 搜索中发现（以神经/神经元/神经的和发育/胚胎学/成熟为检索词），从 1966 年到 1999 年，在神经发育领域发表的论文已达到 56 840 篇，而我们只阅读了这些文章和 1966 年以前的数千篇文献中的一小部分。为了解决这个实际问题，我们参考了权威的书籍、最新的文献综述和会议论文，并对我们在本书中选用的实验都进行了咨询。即便如此，疏漏也在所难免。因此，有兴趣的学生可以通过查阅文献和综述对某些部分作更加详细的了解。另一个需要考虑的就是，我们是在分子生物学的变革开始后来编写这本高年级生物学教材的，所以涉及的主题大部分都包括了分子的特性。除此以外，关于某一族分子最有启发性的实验在非神经组织中常常都已经进行过了，即使我们仅选择一些在神经系统中作用较明确的基因和蛋白质，也可能使大多数章节看上去就像一长串单词的堆砌。因此，在给学生最新信息和努力抓住他们兴趣的两者之间，我们找到一个平衡点来写这本书，把最新的综述文章作为我们写书时的附录供学生参考，而避免罗列繁多的分子家族。

本书在写作过程中得到了许多科学家的大力支持，他们是（按照字母顺序）：Chiye Aoki, Michael Bate, Olivia Bermingham-McDonogh, John Bixby, Sarah Bottjer, Martin Chalfie, Hollis Cline, Martha Constantine-Paton, Ralph Greenspan, Voker Hartenstein, Mary Kintner, Sue McConnell, Ilona Miko, Ronald Oppenheim, Thomas Parks, David Raible, Henk Roelink, Edwin Rubel, John Rubenstein, David Ryugo, Nancy Sculerati, Carla Shatz, and Tim Tully。

（蔡文琴 译）

第二版序

众所周知人脑是我们已知世界中最为复杂的一个物体，数以十亿计的细胞和细胞间数以万亿计的各种联系是其中最为奥妙的部分。尽管我们对于脑的认识还远远不够，但是研究组成神经系统的神经元和胶质细胞产生感觉、行为和高级精神活动的方式已经成为科学研究中成果最丰硕的领域。然而，越来越多的神经科学家意识到他们研究的是一个不断发生变化的目标，它的改变与脑的功能是一个整体，构成了学习、感知和行为的基础。因此，为了认识脑的功能，我们必须理解这些神经环路是如何发生的，以及它们在成熟过程中以怎样的方式被调节。Santiago Ramón y Cajal 是现代神经科学的奠基人之一，他之所以可以在研究神经系统细胞构成方面获得杰出的成就，在很大程度上是因为他的研究目标是胚胎脑，换句话说，他选择的研究对象是“年轻的树，正处于成长阶段，而不是已经完全长成而不再变化的森林”。

脑的构成是一系列发育阶段的整合体，由最初少量胚胎细胞成为神经前体细胞开始，到接近行为出现为止，这就是本书所涵盖的内容。脑与世界的联系总是在不断地更新，同时这些更新也改变着脑内突触的联系。这种变化发生的机制似乎是一个渐进的过程，它在发育过程中对脑的结构进行塑造。

对发育的研究使我们可以洞察生物体之间在进化中的关系。上世纪关于种系发生和个体发生的法则已经被目前更深层次的理解所代替，即进化发生的方式会受到发育中变化的影响。当然，脑也毫无例外地遵循这样的原则。因此，我们认为，理解发育的进程怎样随时间而改变将有助于深入理解令我们更加人性化的进化过程。

本书的目的就是为高年级学生和有一些生物学背景的研究者提供一个关于神经发育过程的纲要，这与广泛的文献综述在目的上是完全不同的。在第一版中，我们已经提到本领域在 1966 年到 1999 年期间约有 54 000 篇论文发表。而在已经过去的四年中又有 25 000 篇论文发表（以神经/神经元/神经的和发育/胚胎学/成熟以及 2000~2004 为检索词）。因为我们不可能把所有研究中的精彩部分完全囊括，所以在给学生最新信息和努力抓住他们兴趣的两者之间，我们找到一个平衡点来写这本书，把最新的综述文章作为我们写书时的附录供学生参考，而避免罗列繁多的分子家族。有兴趣的学生可以通过查阅文献和综述对某些部分作更加详细的了解。

本书在讨论和编辑过程中得到了以下这些人员的帮助，他们是 Chiye Aoki, Michael Bate, Carla Shatz, Ford Ebner, Edward Gruberg, Christine Holt, Lynne Kiorpes, Vibhakar Kotak, Tony Movshon, Ron Oppenheim, Sarah Pallas, Sheryl Scott, Tim Tully, and Lance Zirpel。

最后还要感谢本书的编辑 Johannes Menzel，衷心感谢他的帮助、建议和鼎力支持。

Dan H. Sanes
Thomas A. Reh
William A. Harris
2005 年 7 月

（蔡文琴 译）

Preface to the First Edition

The human brain is said to be the most complex object in our known universe, and the billions of cells and trillions of connections are truly wonders of enormous proportions. The study of the way that the cellular elements of the nervous system work to produce sensations, behaviours, and higher order mental processes has become a most productive area of science. However, neuroscientists have come to realize that they are studying a moving target: growth and change are integral to brain function and form the very basis by which we can learn anything about it. As the behavioral embryologist George Coghill pointed out, "Man is, indeed, a mechanism, but he is a mechanism which, within his limitations of life, sensitivity and growth, is creating and operating himself." To understand the brain, then, we need to understand how this mechanism arises and the ways in which it can change throughout a lifetime.

The construction of the brain is an integrated series of developmental steps, beginning with the decision of a few early embryonic cells to become neural progenitors. As connections form between nerve cells and their electrical properties emerge, the brain begins to process information and mediate behaviors. Some of the underlying circuitry is built into the nervous system during embryogenesis. However, interactions with the world continuously update and adapt the brain's functional architecture. The mechanisms by which these changes occur appear to be a continuation of the processes that sculpt the brain during development. Since the text covers each of these developmental steps, it is relatively broad in scope.

An understanding of the development of the nervous system has importance for biologists in a larger context. Studies of development have led to insights into the evolutionary relationships among organisms. The dogma of phylogeny and ontogeny of

the last century has been superseded by a deeper understanding of the ways in which evolutionary change can be effected through changes in development. The brain is no exception to these rules. We should expect that insight into the evolution of that which makes us most human will be gained from an appreciation of how developmental processes are modified over time.

The goal of this text is to provide a contemporary overview of neural development for undergraduate students or those who have some background in the field of biology. This intent is not compatible with a comprehensive review of the literature. A recent MEDLINE search of publications in the field of neural development [(neural or neuron or nervous) and (development or embryology or maturation)] yielded 56,840 papers published between 1966 and 1999. We admit, up front, to having read only a fraction of these papers or of the thousands that were published before 1966. As a practical matter, we made use of authoritative books, contemporary review articles, hallway conversations, and e-mail consultations to select the experiments that are covered in our text. Even so, we expect that important contributions have been missed inadvertently. Therefore, advanced students will find themselves quickly turning to specialized texts and reviews. Another compromise that comes from writing an undergraduate biology book well after the onset of the revolution in molecular biology is that all subjects now have a rather broad cast of molecular characters. In addition, the most instructive experiments on a particular class of molecules have often been performed on nonneural tissue. Even if we chose to cover only the genes and proteins whose roles have been best characterized in the nervous system, most chapters would run the risk of sounding like a (long) list of acronyms. Therefore,

we charted a compromise between the need to update students and our strong inclination to hold their attention. The book does not contain exhaustive lists of molecular families, and the most current articles must serve as an appendix to our text.

Among the many scientists who helped us through discussions, unpublished findings, or editorial comment are (in alphabetical order) Chiye Aoki,

Michael Bate, Olivia Bermingham-McDonogh, John Bixby, Sarah Bottjer, Martin Chalfie, Hollis Cline, Martha Constantine-Paton, Ralph Greenspan, Voker Hartenstein, Mary Beth Hatten, Christine Holt, Darcy Kelley, Chris Kintner, Sue McConnell, Ilona Miko, Ronald Oppenheim, Thomas Parks, David Raible, Henk Roelink, Edwin Rubel, John Rubenstein, David Ryugo, Nancy Sculerati, Carla Shatz, and Tim Tully.

Preface to the Second Edition

The human brain—perhaps the most complex object in our universe—is composed of billions of cells and trillions of connections. It is truly a wonder of enormous proportions. Although we are far from a thorough understanding of our brains, study of the way that the cellular constituents of the nervous system, the neurons and glia, work to produce sensations, behaviors, and higher order mental processes has been a most productive area of science. However, more and more, neuroscientists are realizing that we are studying a moving target—growth and that changes are integral to brain function, forming the very basis for learning, perception, and performance. To comprehend brain function, then, we must understand how the circuits arise and the ways in which they are modified during maturation. Santiago Ramón y Cajal, one of the founders of modern neuroscience, was able to make his remarkable progress in studies of the cellular makeup of the nervous system in large part because of his work with the embryonic brain, choosing to study “the young wood, in the nursery stage . . . rather than the . . . impenetrable . . . full grown forest.”

The construction of the brain is an integrated series of developmental steps, starting with the decision of a few early embryonic cells to become neural progenitors and nearing completion with the emergence of behavior, which is the scope of this book. Interactions with the world continuously update and adapt synaptic connections within the brain, and the mechanisms by which these changes occur are fundamentally a continuation of the same processes that sculpted the emerging brain during embryogenesis.

Studies of development have also led to insights about the evolutionary relationships among organisms. The dogma of phylogeny and ontogeny of the last century has been superseded by our current deeper understanding of the ways in which evolutionary change can be effected through changes

in development. The brain is no exception to these rules, and we can expect that much insight into the evolution of that which makes us most human will be gained from an appreciation of how developmental processes are modified over time.

The goal of this text is to provide a contemporary overview of neural development both for undergraduate students and for those who have some background in the field of biology. This intent is not compatible with a comprehensive review of the literature. In the first edition, we noted that there were about 54,000 papers published in this field between 1966 and 1999. Another 25,000 have appeared during the past 4 years (using the search string “neural or neuron or nervous” and “development or embryology or maturation” and 2000:2004). We charted a compromise between the need to update students and our strong inclination to hold their attention. The book does not contain exhaustive lists of molecular families, and the most current review articles must serve as an appendix to our text. Since the text does not encompass many exciting areas of research, students will find themselves quickly turning to specialized texts and reviews.

Among those who helped us through discussion and editorial comment are: Chiye Aoki, Michael Bate, Carla Shatz, Ford Ebner, Edward Gruberg, Christine Holt, Lynne Kiorpes, Vibhakar Kotak, Tony Movshon, Ron Oppenheim, Sarah Pallas, Sheryl Scott, Tim Tully, and Lance Zirpel.

Finally, we acknowledge our editor, Johannes Menzel, with particular gratitude, for his help, advice, and perseverance.

Dan H. Sanes
Thomas A. Reh
William A. Harris
July 2005

目 录

第一版序	xi
第二版序	xiii
1. 神经系统简介	1
神经元的发育和进化	1
多细胞动物早期胚胎学	1
神经组织的衍化	3
神经组织发生时与相邻组织的相互作用	9
神经诱导物的分子特征	13
神经诱导的保守性	16
调控成神经细胞分离时外胚层细胞间的相互作用	20
脊椎动物中的 Notch、Delta 和 Achaete Scute 基因	25
颈板活化的联合诱导作用	27
小结	28
2. 极化与分裂	29
神经系统的区域特征	29
前后轴与 HOX 基因	30
HOX 基因在神经系统的功能	33
信号传递分子引导形成脊椎动物身体的前后轴：头和尾	36
发育中脑的构建中心	39
端脑发育、前脑前部基因组 (prosomeres) 与 PAX 基因	42
神经管的背腹极化	46
背侧神经管与神经嵴	50
大脑皮层的构成	52
小结	55
3. 发生与迁移	57
细胞周期基因控制发育中神经元产生的数量	62
祖细胞间相互作用调节细胞数量	63
神经元和神经胶质细胞的发生	69
大脑皮质的组织发生	71
室管膜下区：神经发生的第二个区域	75
小脑皮质的神经发生	76
神经元迁移的分子机制	78
胚胎后期与成年的神经发生	82
小结	85

4. 定向与分化	87
固定细胞系中的转录次序	88
定向作用的时空调整	91
不对称细胞分裂及分裂后细胞的不同命运	93
细胞间相互作用产生复杂化	94
通过细胞间及细胞与局部环境的相互作用实现特化和分化	97
感应性与组织发生	100
内外因素的相互作用对组织发生的影响	102
细胞类型的空间及层次分布	106
小结	109
5. 轴突生长与导向	111
生长锥	114
动态的细胞骨架	116
生长锥怎样持续生长?	121
什么给生长锥提供导向信号?	123
细胞黏附及其标记的通路	124
排斥性导向信号	127
趋化性、梯度性及局部信号	130
视觉通路	133
中线	134
吸引与排斥: 脱敏作用及适应性	134
信号转导	137
小结	138
6. 靶标选择	145
脱离纤维束	145
靶位点的识别及进入	147
末梢在靶位点中减速前进并形成分支	148
边界效应阻止不当的靶点定位	149
局部解剖学定位图	152
Ephrin 及其化学专一性	153
走行线路的易变性及其精确的调整	158
突触终末在三维空间即特异板层中的定位	162
细胞和突触的靶点定位	164
发现靶点	166
小结	170
7. 自然发生的神经元死亡	173
神经元死亡时呈现怎样的状态?	173
前体细胞的早期消亡	174
多少分化后的神经元会死亡?	174

神经元依赖于突触靶点的存活	176
NGF (神经生长因子): 靶源性促存活因子	180
神经营养素家族	182
神经营养素受体 TRK (酪氨酸受体激酶家族) 家族	184
神经营养素信号怎样到达胞浆?	186
P75 神经营养素受体	186
促神经元存活因子开辟新天地	188
细胞存活的内分泌调节	190
细胞死亡需要特殊蛋白质合成	192
细胞内信号传递	193
死亡因子: 胱天蛋白酶	196
BCL-2 蛋白: 凋亡的调节者	200
靶点的突触传递	201
细胞存活的中枢调节	202
小结	206
8. 突触形成及功能	207
新形成的突触是怎样的?	211
突触功能的首要标志	215
形成突触的决定因素	218
黏性突触	220
生长锥转变为突触前终末	221
神经肌肉接头处受体成簇化分布意味着突触后成分的分化	222
突触前终末诱导突触后受体聚集	224
Agrin: 一种跨突触的成簇化信号分子	226
Agrin 的突触后反应	227
中枢神经系统中的受体成簇化信号分子	229
中枢神经系统中膜内蛋白与受体聚集	230
新受体的表达及嵌入	233
神经元的活化调节受体的表达	235
Neuregulin: 突触后转录的一个调控分子	236
信号传递的成熟及受体亚型的转变	238
神经递质重摄取过程的成熟	241
短期可塑性	242
突触抑制的表现	243
突触抑制在发育中是否就是抑制性的?	243
小结	244
9. 突触连接的精细度	247
突触连接的早期形式	247
清除功能性突触	249
轴突分支的细化或清除	250

部分终末扩展或保持稳定状态	255
神经活动调节突触连接	255
感觉信息编码特征反映突触的重排	262
神经活动有助于感觉定位的调校	265
自发活动以及传入信息分析	267
可塑性的多种形式存在时间限制	271
突触跨越微小空间距离的相互作用	271
异突触抑制	272
清除突触后受体	274
细胞内钙的参与	276
NMDA 受体及钙信号传递	276
第二信使系统的作用	278
Metabotropic 受体	279
信息采集调控突触连接	280
沉默性突触	282
内环境稳态：改变越多，越保持原状	283
抑制性突触连接的可塑性	284
突触对神经元形态的影响	285
小结	287
 10. 行为的发生	 289
行为的个体发生	289
遗传及环境机制	290
环境对行为发生的决定作用	291
动物的第一次运动	291
自发运动的机制	293
胚胎的运动：不协调的还是整体性的？	294
主动性在协调性行为发生中的作用	296
阶段特异性行为	297
对世界感知的开始	299
对婴儿的提问	300
锐利的视觉	301
精确的听觉	302
与性有关的特殊行为	305
遗传的性别	306
性激素信号分子	306
性激素调控脑的性别	307
遗传调控脑的性别	308
在脑中歌唱	309
从生殖腺到脑	310
学习与记忆	311
妈妈在哪里？	312

恐惧与厌恶	314
脑与脑之间的信息获得	317
语言	319
小结	321
参考文献	323
索引	361

Contents

Preface for the First Edition	xi
Preface for the Second Edition	xiii

1. Neural Induction 1

Development and Evolution of Neurons	1
Early Embryology of Metazoans	1
Derivation of Neural Tissue	3
Interactions with Neighboring Tissues in Making Neural Tissue	9
The Molecular Nature of the Neural Inducer	13
Conservation of Neural Induction	16
Interactions Among the Ectodermal Cells in Controlling Neuroblast Segregation	20
Notch, Delta, and Achaete Scute Genes in Vertebrates	25
Linking Induction to Proneural Activity	27
Summary	28

2. Polarity and Segmentation 29

Regional Identity of the Nervous System	29
The Anterior-Posterior Axis and HOX Genes	30
HOX Gene Function in the Nervous System	33
Signaling Molecules that Pattern the Anterior-Posterior Axis in Vertebrates: Heads or Tails	36
Organizing Centers in the Developing Brain	39
Forebrain Development, Prosomeres, and PAX Genes	42
Dorsal-Ventral Polarity in the Neural Tube	46
Dorsal Neural Tube and Neural Crest	50
Patterning the Cerebral Cortex	52
Summary	55

3. Genesis and Migration 57

Cell-Cycle Genes Control the Number of Neurons Generated during Development	62
---	----

Cell Interactions Control the Number of Cells Made by Progenitors	63
The Generation of Neurons and GLIA	69
Cerebral Cortex Histogenesis	71
The Subventricular Zone: A Secondary Zone of Neurogenesis	75
Cerebellar Cortex Histogenesis	76
Molecular Mechanisms of Neuronal Migration	78
Postembryonic and Adult Neurogenesis	82
Summary	85

4. Determination and Differentiation 87

Transcriptional Hierarchies in Invariant Lineages	88
Spatial and Temporal Coordinates of Determination	91
Asymmetric Cell Divisions and Asymmetric Fate	93
Generating Complexity through Cellular Interactions	94
Specification and Differentiation through Cellular Interactions and Interactions with the Local Environment	97
Competence and Histogenesis	100
The Interplay of Intrinsic and Extrinsic Influences in Histogenesis	102
Interpreting Gradients and the Spatial Organization of Cell Types	106
Summary	109

5. Axon Growth and Guidance 111

The Growth Cone	114
The Dynamic Cytoskeleton	116
What Do Growth Cones Grow On?	121
What Provides Directional Information to Growth Cones?	123
Cell Adhesion and Labeled Pathways	124
Repulsive Guidance	127

Chemotaxis, Gradients, and Local Information	130
The Optic Pathway	133
The Midline	134
Attraction and Repulsion: Desensitization and Adaptation	134
Signal Transduction	137
Summary	138

6. Target Selection 145

Defasciculation	145
Target Recognition and Entry	147
Slowing Down and Branching	148
Border Patrol and Prevention of Inappropriate Targeting	149
Topographic Mapping	152
Chemospecificity and Ephrins	153
Shifting and Fine Tuning of Connections	158
The Third Dimension, Lamina-Specific Termination	162
Cellular and Synaptic Targeting	164
Sniffing Out Targets	166
Summary	170

7. Naturally Occurring Neuron Death 173

What does Neuron Death Look Like?	173
Early Elimination of Progenitor Cells	174
How Many Differentiated Neurons Die?	174
Survival Depends on the Synaptic Target	176
NGF: A Target-Derived Survival Factor	180
The Neurotrophin Family	182
The TRK Family of Neurotrophin Receptors	184
How does the Neurotrophin Signal Reach the Soma?	186
The P75 Neurotrophin Receptor	186
The Expanding World of Survival Factors	188
Endocrine Control of Cell Survival	190
Cell Death Requires Protein Synthesis	192
Intracellular Signaling	193
Caspases: Agents of Death	196
BCL-2 Proteins: Regulators of Apoptosis	200
Synaptic Transmission at the Target	201
Afferent Regulation of Cell Survival	202
Summary	206

8. Synapse Formation and Function 207

What Do Newly Formed Synapses Look Like?	211
The First Signs of Synapse Function	215
The Decision to Form a Synapse	218
The Sticky Synapse	220

Converting Growth Cones to Presynaptic Terminals	221
Receptor Clustering Signifies Postsynaptic Differentiation at NMJ	222
Presynaptic Terminals Induce Receptor Aggregation	224
Agrin, a Transsynaptic Clustering Signal	226
Postsynaptic Response to Agrin	227
Receptor Clustering Signals in the CNS	229
Internal Membrane Proteins and Receptor Aggregation in the CNS	230
The Expression and Insertion of New Receptors	233
Neuronal Activity Regulates Receptor Expression	235
Neuregulin, a Regulator of Postsynaptic Transcription	236
Maturation of Transmission and Receptor Isoform Transitions	238
Maturation of Transmitter Reuptake	241
Short-Term Plasticity	242
Appearance of Synaptic Inhibition	243
Is Inhibition Really Inhibitory during Development?	243
Summary	244

9. Refinement of Synaptic Connections 247

The Early Pattern of Connections	247
Functional Synapses are Eliminated	249
Axonal Arbors are Refined or Eliminated	250
Some Terminals Expand or Remain Stable	255
Neural Activity Regulates Synaptic Connections	255
Sensory Coding Properties Reflect Synapse Rearrangement	262
Activity Contributes to the Alignment of Sensory Maps	265
Spontaneous Activity and Afferent Segregation	267
Many Forms of Plasticity have a Time Limit	271
Synapses Interact Over a Short Distance	271
Heterosynaptic Depression	272
Postsynaptic Receptors are Eliminated	274
Involvement of Intracellular Calcium	276
NMDA Receptors and Calcium Signaling	276
The Role of Second Messenger Systems	278
Metabotropic Receptors	279
Gain Control	280
Silent Synapses	282
Homeostasis: The More Things Change, the More They Stay the Same	283
Plasticity of Inhibitory Connections	284
Synaptic Influence on Neuron Morphology	285
Summary	287

10. Behavioral Development 289

Behavioral Ontogeny	289
Genetic and Environmental Mechanisms	290

Environmental Determinants of Behavioral
 Development 291
 The First Movements 291
 The Mechanism of Spontaneous Movements 293
 Embryonic Movements: Uncoordinated or Integrated? 294
 The Role of Activity in the Emergence of Coordinated
 Behavior 296
 Stage-Specific Behaviors 297
 Beginning to Make Sense of the World 299
 Asking Babies Questions 300
 Sharp Eyesight 301
 Acute Hearing 302
 Sex-Specific Behavior 305
 Genetic Sex 306

Hormonal Signals 306
 Hormonal Control of Brain Gender 307
 Genetic Control of Brain Gender 308
 Singing in the Brain 309
 From Gonads to Brain? 310
 Learning to Remember 311
 Where's Mamma? 312
 Fear and Loathing 314
 Getting Information from One Brain to Another 317
 Language 319
 Summary 321

References 323
Index 361

Neural Induction

DEVELOPMENT AND EVOLUTION OF NEURONS

Almost as early as multicellular animals evolved, neurons have been part of their tissues. Metazoan nervous systems range in complexity from the simple nerve net of the jellyfish to the billions of specifically interconnected neuron assemblies of the human brain. Nevertheless, the neurons and nervous systems of all multicellular animals share many common features. Voltage-gated ion channels are responsible for action potentials in the neurons of hydras, as they are in people. Synaptic transmission between neurons in nerve nets is basically the same as that in the cerebral cortex in humans (Figure 1.1). This book describes the mechanisms responsible for the generation of these nervous systems, highlighting examples from a variety of organisms. Despite the great diversity in the nervous systems of various organisms, underlying principles of neural development have been maintained throughout evolution.

It is appropriate to begin a book concerned with the development of the nervous system with an evolutionary perspective. The subjects of embryology and evolution have long shared an interrelated intellectual history. One of the major currents of late-nineteenth-century biology was that a description of the stages of development would provide the key to the path of evolution of life. The phrase "ontogeny recapitulates phylogeny" was important at the start of experimental embryology (Gould, 1970). Although the careful study of embryos showed that they did not resemble the adult forms of their ancestors, it is clear that new forms are built upon the structures of biological predecessors. One aim of this book is to show how an understanding of the development of the nervous

system will give us insight into its evolution. It is also wise to remember, as Dobzhansky pointed out, that "nothing in biology makes sense except in the light of evolution."

EARLY EMBRYOLOGY OF METAZOANS

The development of multicellular organisms varies substantially across phyla; nevertheless, there are some common features. The cells of all metazoans are organized as layers. These layers give rise to the various organs and tissues, including the nervous system. These layers are generated from the egg cell through a series of cell divisions and their subsequent rearrangements (Figure 1.2). The egg cells of animals are typically polarized, with an "animal pole" and a "vegetal pole." This polarity is often visible in the egg cell, since the vegetal pole contains the yolk, the stored nutrient material necessary for sustaining the embryo as it develops. Once fertilized by the sperm, the egg cell undergoes a series of rapid cell divisions, known as cleavages. There are many variations of cleavage patterns in embryos, but the end result is that a large collection of cells, the blastula, is generated over a relatively short period of time. In many organisms the cells of the blastula are arranged as a hollow ball, with an inner cavity known as a blastocoel. Those cells at the vegetal pole will ultimately develop as the gut, whereas those at the animal pole will give rise to the epidermis and the nervous system. Cells in between the animal and vegetal poles will generate mesodermal derivatives, including muscles and internal skeletal elements. The rearrangement of this collection of cells into the primary (or germ) layers is called