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基础神经科学系列 2

Nervous System Development

神经系统发育

Larry Squire, Darwin Berg, Floyd Bloom
Sascha du Lac, Anirvan Ghosh, Nicholas Spitzer

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基础神经科学系列②

Nervous System Development

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总 导 读

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人脑或神经系统是我们已知的宇宙中最复杂的物质结构，神经科学是探索脑的奥秘的科学，是21世纪迅猛发展的生命科学中最为突出的领域之一。过去的十多年中，分子生物学和计算机科学技术的快速发展，极大地推动了神经科学的发展，人类基因组DNA序列的阐明及其对神经科学的推动、脑功能成像技术研究人脑和心理活动的巨大进展便是最突出的代表。对许多神经元活动的基本过程，神经科学家已经可以通过基因操作，在基因及其编码的蛋白分子的结构和功能水平上进行描述和分析，从而精细地研究其复杂的细胞膜上和胞内信号的调控分子机制。脑功能成像技术使得过去只能停留在人脑这个“黑箱”外、对心理现象的脑机制进行各种猜测和假说的时代成为过去，人脑的认知和思维活动变得“看得见”了。神经科学不仅吸引着各类神经生物学家、化学家和物理学家，而且吸引分子生物学家、计算机科学家和心理学家纷纷加入其中，成为真正意义上的多种学科交叉的科学。

从20世纪末到21世纪初，神经科学已经发展到从分子、细胞到系统、整体行为和心理的各个水平上进行研究的阶段，几乎没有一个神经科学家能够独立地主编或纂写一本关于神经科学的全面、深入的教科书。Academic Press 2008年出版的 *Fundamental Neuroscience*（第三版）就是由六位美国加利福尼亚州大学圣迪亚哥分校的著名神经科学家联合主编的教科书，他们中有三位是美国科学院或文理科学院院士，两位曾经担任过神经科学会（Society for Neuroscience）——世界上最大的学术团体之一的主席。在这么强的主编阵容的领导下，有约100位神经科学家参与写作了这本书内相关领域内容，从而使得这本书具有高度的科学性和权威性。

本书是针对刚刚进入神经科学的研究生而写的，这些学生在大学本科阶段，有的主修了生物学，有的主修了心理学、物理学或化学、电子工程学，甚至英国文学。为了使更为广泛的学生能够更好地理解和开阔视野，书内将一些解释性材料置于正文的方框内（包括关键的实验、病历、实验方法和重要的概念等），并介绍一些有关的参考文献和进一步阅读的补充材料，供读者学习深入钻研。此外，本书虽然对与临床医学直接有关的神经科学内容介绍不多，但医科学生可以使用本书所介绍的神经科学基本原理找到临床方面的有关材料。对于希望了解自己研究领域以外知识的学者、活跃在第一线的神经科学家，或希望进入神经科学其他领域的科学家，本书也将为他们提供某些有用的信息，介绍一些挑战性的研究方向。

相对于这本书的第二版，在第三版的 *Fundamental Neuroscience* 中，约有30%的内容做了修改和补充，而且篇幅也减少了30%，将内容庞杂的神经科学的基本原理描述得更加精练和突出，使读者有一个条理清晰的知识结构。新增加的内容反映了近来神经科学发展较快的领域，例如树突的发育、化学感觉、小脑、眼动、昼夜定时、睡眠和梦，以及意识等。

六位主编将本书分为七个部分：

（1）**神经科学总论**。除了介绍神经科学发展的历史、神经系统的名词、解剖结构和功能组织的特点和原理外，还着重介绍了当前神经科学研究中的责任问题、科学研究中的不端行为（伪造、歪曲和剽窃）的定义和巨大危害性。对于即将进入神经科学领域的年轻学生，规范了科学研究中的行为准则，具有深远的教育意义。这对于浮躁之风盛行的我国科技界，更具有重大的现实意义。

（2）**细胞和分子神经科学**。这一部分在细胞和分子水平上详细地阐述了神经元胞体、轴突和树突结构和功能特性，动作电位的产生，细胞内的信号转导，突触和化学递质释放、递质和受体等，此外，特别详细地介绍了树突在复杂的信息处理过程中的作用，以及脑的能量代谢（包括神经元与星型胶质细胞）在代谢中的作用等新内容，令人耳目一新。

（3）**神经系统发育**。这是神经科学中发展最快的前沿领域之一，内容很丰富。极其复杂的神经系统从胚胎发生开始，按照基因调控所决定的时间-空间模式发育，经历了胚胎发育各个阶段的细胞分裂、分化、迁移，通过神经元轴突顶端的生长锥对靶细胞的选择实现拓扑投射关系的形成以及突触的形成。但遗传因素并不能决定一切，在动物出生后的关键期内，环境因素对其神经系统的发育产生某些决定性的影响，反映在“用进废退”的突触的精简过程中，而所有这些过程无不与细胞内外的化学信息物质有密切关系。本部分的内容极为丰富，为读者提出了许多当前极具挑战性的科学问题。

（4）**感觉系统**。动物和人类依靠感觉系统获取外界信息，躲避敌害，获取食物。而人类则具有特别高度发达的感觉系统，从而得以认识世界并能动地改造世界。本部分内容介绍化学感觉、躯体感觉、听觉和视觉系统的感受器、感觉通路和中枢机制。各个不同的感觉系统通过不同的感受器将外界的不同信息独立地转化为神经信号，传入中枢神经系统进行处理。感受器对中枢的拓扑投射决定了感觉系统的并行的解剖通路和特殊生理功能，感觉神经信号的时间编码在空间上受到侧抑制的作用，进一步提高了敏感性。感觉皮层内部及其与上下各结构间存在着几乎一样的投射关系，各种感觉皮层均有相同的六层细胞结构和功能柱的组构，通过复杂的信息处理产生了知觉。这一部分内容一定也会引起从事研究计算机科学和技术、机器人和信息科学的学者们的兴趣。

（5）**运动系统**。本部分内容包括脊髓和周围神经系统、基底神经节、小脑和运动皮层所组成的整个传统的运动系统复杂的结构和功能。本部分还特别介绍了眼动部分，这正是其他神经科学教科书中容易忽视的内容。眼球的运动由三对颅神经支配，起着注视和移动注视的作用，以保持视网膜像稳定可视和眼睛持续跟踪重要视觉目标。眼动不仅与运动控制有关，而且与视觉系统、前庭器官、神经可塑性和注意、感知等高级机制有关，涉及神经系统的所有方面，所以眼动提供了一个研究整个神经系统控制机制的窗口。相信运动系统部分将对从事自动化、机器人和工程学工作的学者有所启发。

（6）**调节系统**。本部分将神经系统对整体性活动的各种神经调节功能做了分门别类的介绍，包括下丘脑的总体调节作用；自主神经系统对内脏器官的控制；对心血管系统和呼吸系统的神经控制；摄食和代谢、进水和体液调节；昼夜定时和睡眠、做梦；神经内分泌系统；动机和成瘾等。本部分内容相对比较丰富，与生理科学的交叉较多，占的篇幅也较大，作为神经科学的学生或学者是不能不了解清楚的。

（7）**行为和认知神经科学**。这部分的内容是近来神经科学发展比较快的领域，涉及的内容很广泛：认知的发育和衰老；对物体的视觉感知；空间的识别；注意；学习和记忆的基础和脑机制；语言和交流；前额叶皮层和脑的执行功能；意识方面的研究成果。由于无损伤的脑功能成像技术（例如功能磁共振成像、多导脑电图和脑磁图）、穿颅磁刺激技术在人类认知科学研究中的应用，使得过去无法用实验探索的人脑的高级功能和心理学现象的神经机制成为可能，而清醒猴、鼠的慢性埋藏微电极阵列记录的行为实验技术广泛应用，将行为学研究和脑内部神经机制的研究结合起来，大大地推进了这一领域的发展，新的发现与日俱增。

由近百名神经科学家集体编著的 *Fundamental Neuroscience*（第 3 版），内容极为丰富，覆盖面很大，但在六位主编的精心组织下，编排得非常有利于读者的阅读：七大部分的内容被分为若干专题的小节，节内又用鲜明的小标题画龙点睛地指出叙述内容的要点。在许多地方还有神经科学历史上经典实验的介绍，在某个专题开始时经常附有一个简要的总论，结束时往往有一个简短结论或小结。每一专题内容均给出文献和阅读的材料，为读者深入研究提供了丰富的知识来源。

我相信科学出版社购得 *Fundamental Neuroscience*（第 3 版）在中国的出版权，并在我国出版此书一举，将是对我国神经科学的教育和科研事业发展的一个重要贡献。

导　读

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对神经发育的研究，从传统的形态学描述，到细胞、分子机理的揭示，经过一百多年，是一个交叉了多个学科、应用了多个技术、充满活力的领域。

发育神经生物学研究两大类问题。第一类有关神经系统细胞的生和死。神经发育始于动物胚胎早期，新生期仍然活跃，在成年动物仍有部分区域有新的神经细胞形成。神经系统起源于外胚层。神经胚层有区域性（前后、腹背、节段、左右）差别。神经干细胞可以产生自己，并产生前体细胞。前体细胞迁移到起功能的位置，根据其来源、局部环境分化成多种神经细胞和神经胶质细胞。最初产生的细胞数量多于最后的需要，一些细胞有选择性地生存下来，其他细胞死亡。分化后的神经细胞不能分裂，需要有机制长期维持其生存。

神经发育的第二大类问题是神经细胞之间（或者神经细胞和靶细胞之间）联系的建立和修饰。神经细胞发出纤维，投射到其他细胞建立神经通路形成信息联络网。神经细胞间连接不仅在发育过程中被控制，而且，和多数其他系统不同，在成年动物中还常调节神经细胞间的连接，调节和修饰联接是神经可塑性（如学习、记忆）的关键。

神经系统的发育和其他系统的发育有相同原理，也有神经系统特有的机理。神经细胞和神经胶质细胞的命运确定、型式发生、分裂、分化和其他系统同类过程在原理上无区别。迄今也未发现神经细胞的凋亡机理和其他细胞有本质上的差别。分化后神经细胞的长期生存是一个特殊现象，尚不清楚在原理上的特别之处。神经细胞建立和修饰联系是神经系统特殊的过程，其中有神经细胞特有的机理。但是，在这个特殊的过程中，并非所有机理都是神经细胞特有的。比如神经纤维导向，原以为这个依赖神经细胞特殊结构（生长锥）进行的特别步骤，使用的是神经细胞特有的原理；但进一步研究后发现，神经导向的机理和白细胞趋化、血管内皮细胞定向生长都共享一些原理。

神经发育是正常神经系统功能的基础。发育异常可以导致多种疾病。脑的形态异常和先天性智力障碍，显而易见是神经发育的问题。还有一些疾病，如一部分癫痫，也和发育有关。神经细胞死亡的正常调节和异常发生，不仅与发育有关，而且与神经退行性病变的发生和治疗相关。近年提出精神分裂症和发育有关。外伤或病变造成神经纤维损失后，如何修复，也需要了解神经纤维生长和连接的机理。治疗帕金森病的途径之一是细胞移植。如何选择细胞、是否和如何定向分化干细胞，都是神经发育的问题。所以，理解神经发育，不仅满足科学家的好奇心，也有助于人类预防、诊断和治疗疾病。

发育神经生物学与形态学有密切的关联。传统的解剖、组织学到现代成像技术都被用于研究神经发育。19 世纪，意大利科学家高尔基（Camillo Golgi）发明了观察神

经系统的有效染色方法。现代神经科学之父、西班牙科学家卡哈尔（Santiago Ramón y Cajal）等通过观察不同时期的胚胎切片，描绘了神经发育的基本步骤，留下精美且准确的图片。卡哈尔不满足于现象，凭他的想象力，依据于固定的标本得到的资料，提出了动态的神经系统功能和发育的概念。在功能上，他提出的最重要概念是神经元法则，认为神经细胞是神经信息传递的基本单元。在发育上，卡哈尔发现了轴突末端的生长锥，提出了神经纤维导向的概念。许多研究者在更精细水平发现新的神经系统的功能和形态，不断提出发育神经生物学的问题。神经元具有树突和轴突的极性，就会引出极性形成的发育问题。神经传导需要绝缘，自然引出髓鞘如何识别并有序地包埋神经纤维的发育问题。形态学发现分子在神经细胞局部分布，引起定位机理的研究。

发育神经生物学与发育生物学紧密相关。至少从亚里士多德开始，就有文献记载人类提出发育的可能机理。现代发育生物学起源于 19 世纪末，德国胚胎学家 Wilhelm Roux（1888）和 Hans Driesch（1892）等用两栖类进行的研究，开启了实验胚胎学研究。20 世纪初，德国胚胎学家 Hans Spemann 用两栖类动物做了一系列移植实验，1924 年，他和学生 Hilde Mangold 发现了中胚层诱导外胚层产生神经系统，提出神经诱导的概念。现在知道，胚胎发育中，诱导在多个系统决定细胞命运，诱导可以在一群细胞和另外一群细胞间发生，也可以在两个细胞间发生。诱导是发育生物学的中心概念之一。

发育神经生物学与遗传学密切相关。摩尔根（Thomas H. Morgan）对遗传学的兴趣和他对发育的兴趣有关。19 世纪末，他还在研究两栖类的发育。20 世纪早期，他和他的学生，特别是 Calvin Bridges、Alfred Sturtevant、Hermann Muller 用果蝇做的研究，奠定了现代遗传学的基础，并使果蝇成为一个强有力的模式动物，对发育生物学和发育神经生物学都有很大的推动。加州理工学院的路易斯（Edward Lewis）对双胸复合体的研究，最终导致同源异形基因（homeotic gene）的发现，有助于理解细胞命运与节段相关的原理。德国的纽丝兰-沃哈德（Christiana Nüsslein-Volhard）和美国的维西豪斯（Eric Wieschaus）等开创的用饱和突变研究果蝇型式发生的方法，既揭示了发育的原理，也找到了很多一般发育和神经发育的基因。不仅他们的原理在动物界保守，许多基因也在高等动物起作用。20 世纪 60 年代，英国剑桥分子生物学实验室的 Sydney Brenner 开创通过遗传学用秀丽线虫研究神经系统的方法，对神经发育有很大的促进。神经导向的分子，最初是用线虫遗传突变所发现。John White 的工作使秀丽线虫（Caenorhabditis elegans）成为惟一知道全部神经连接的动物。鼠的遗传学，特别是因为转基因技术和基因剔除技术，推动了神经发育的研究。遗传学分析人的疾病，如大脑皮层的发育障碍的疾病，帮助揭示了神经发育的重要分子。

发育神经生物学与细胞生物学有双向作用。不仅细胞生物学概念和技术常应用于发育神经生物学，而且有一些基本细胞生物学过程首先在研究神经发育的过程中发现。胚胎诱导现象是最早发现的细胞-细胞相互作用之一。程序性细胞死亡最早在神经发育过程中发现。第一个生长因子也是在神经发育中发现。为了研究神经发育，Ross G. Harrison 在体外培养神经细胞，从而发明了细胞培养的方法，成为细胞生物学的一个基本方法。细胞生物学发现肌动蛋白多聚化及其调节的机理，有许多可以运用到神经

细胞的运动和导向过程，甚至有部分可以应用到神经可塑性：突触后组分（树土棘）中肌动蛋白多聚化的调节在突触形成和改编中起作用。

发育神经生物学与生物化学和分子生物学相关。神经生长因子的最终确定依赖于生化纯化。理解神经发育起重要作用分子的机理，依赖于信号转导的生化和分子生物知识。分子生物学进步带来的原位杂交、免疫学带来的抗体技术推动神经发育的形态学研究。分子生物学发展带来的基因剔除、转基因等帮助证明了一些神经发育关键分子的作用。

发育神经生物学与进化生物学相关，虽然这是神经发育研究薄弱的环节。进化上出现越来越复杂的神经系统，需要靠选择神经发育相关的过程来实现。人脑和其他动物脑的差别，首先就是发育的差别。这些差别是什么及它们是如何发生的，仍然是有趣而没有得到解决的问题。

神经发育并不只是早期发育的问题，也不仅是形态发生。出生后的发育、行为的发育，有形态变化，也有功能变化。目前对出生后神经发育的了解要远少于胚胎期发育，对行为发育的了解要远少于形态发育，对环境对神经发育的影响的了解要少于基因对神经发育的影响。所以，发育神经生物学不是一个平衡发展的学科，也不是一个走进终结期的学科，还有重要的问题有待深刻地研究。

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VII
BEHAVIORAL and COGNITIVE NEUROSCIENCE

Preface to the Third Edition

In this third edition of *Fundamental Neuroscience*, we have tried to improve on the second edition with a volume that effectively introduces students to the full range of contemporary neuroscience. Neuroscience is a large field founded on the premise that all of behavior and all of mental life have their origin in the structure and function of the nervous system. Today, the need for a single-volume introduction to neuroscience is greater than ever. Towards the end of the 20th century, the study of the brain moved from a peripheral position within both the biological and psychological sciences to become an interdisciplinary field that is now central within each discipline. The maturation of neuroscience has meant that individuals from diverse backgrounds—including molecular biologists, computer scientists, and psychologists—are interested in learning about the structure and function of the brain and about how the brain works. In addition, new techniques and tools have become available to study the brain in increasing detail. In the last 15 years new genetic methods have been introduced to delete or over-express single genes with spatial and temporal specificity. Neuroimaging techniques such as functional magnetic resonance imaging (fMRI) have been developed that allow study of the living human brain while it is engaged in cognition.

This third edition attempts to capture the promise and excitement of this fast-moving discipline. All the chapters have been rewritten to make them more concise. As a result the new edition is about 30% shorter than previous editions but still covers the same comprehensive range of topics. The volume begins with an opening chapter that provides an overview of the discipline. A second chapter presents fundamental information about the architecture and anatomy of nervous systems. The remainder of the volume (Sections II–VII) presents the major topics of neuroscience. The second section (Cellular and Molecular Neuroscience) considers the cellular and subcellular organization of neurons, the physiology of nerve cells, and how signaling occurs between neurons. The third section (Nervous System Development) includes discussion of neural induction, cell fate, migration, process outgrowth, development of dendrites, synapse formation, programmed cell death, synapse elimination, and early experience including critical periods. The fourth and fifth sections (Sensory Systems and Motor Systems) describe the neural organization of each sensory modality and the organization of the brain pathways and systems important for locomotion, voluntary action, and eye movements. The sixth section (Regulatory Systems) describes the variety of hypothalamic and extra-hypothalamic systems that support motivation, reward, and internal regulation, including cardiovascular function, respiration, food and water intake, neuroendocrine function, circadian rhythms, and sleep and dreaming. The final section (Behavioral and Cognitive Neuroscience) describes the neural foundations of the so-called higher mental functions including perception, attention, memory, language, spatial cognition, and executive function. Additional chapters cover human brain evolution, cognitive development and aging, and consciousness. The volume will be accompanied by an easily accessible companion website, which will present all the figures and increase the flexibility with which the material can be used.

The authors listed at the ends of the chapters and boxes are working scientists, experts in the topics they cover. The Editors edited the chapters to achieve consistency of style and content. At Academic Press/Elsevier Science, the project was coordinated

by Hilary Rowe and Nikki Levy (Publishing Editors), and we are grateful to them for their leadership and advice throughout the project. In addition, Meg Day (Developmental Editor) very capably coordinated the production of the book with the help of Sarah Hajduk (Publishing Services Manager) and Christie Jozwiak (Project Manager).

The Editors of *Fundamental Neuroscience* hope that users of this book, and especially the students who will become the next generation of neuroscientists, find the subject matter of neuroscience as interesting and exciting as we do.

The Editors

About The Editors

Larry R. Squire is Distinguished Professor of Psychiatry, Neurosciences, and Psychology at the University of California School of Medicine, San Diego, and Research Career Scientist at the Veterans Affairs Medical Center, San Diego. He investigates the organization and neurological foundations of memory. He is a former President of the Society for Neuroscience and is a member of the National Academy of Sciences and the Institute of Medicine.

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SECTION III

NERVOUS SYSTEM DEVELOPMENT

CHAPTER

14

Neural Induction and Pattern Formation

This chapter covers some of the key events that take place in the early stages of development of the vertebrate nervous system, a period during which structures such as the neural tube, placodes, and neural crest are formed, setting in place the foundations on which a functioning nervous system is subsequently built. The first part of the chapter describes how these embryonic structures first are specified by inductive tissue interactions and how they form by the process of morphogenesis. The second part of the chapter describes the extensive early developmental events required for regionalizing the nervous system along its different axes. Regionalization requires the complex processes of neural patterning that endow neural precursor cells with the ability to give rise to correct types of neuron in appropriate locations in the adult nervous system. These processes are gradual, continuous, and begin when neural tissue first forms. We describe some of the processes underlying neural patterning, beginning with how polarity along each of the neuraxes is first established, and progressing to more fine levels of regional organization.

NEURAL INDUCTION

Embryonic Origins of the Nervous System

The progenitor cells that form the vertebrate nervous system can be traced back in development to an epithelial cell layer, called the ectoderm, that covers the outside of the embryo during gastrulation (Fig. 14.1). Ectodermal cells give rise to different tissue derivatives depending on axial position. The dorsal-most ectoderm thickens to form the *neural plate*, a structure in the shape of a key-hole with the broad end located anteriorly. During a complex morphogenetic process called *neurulation*, cells in the neural plate give rise to the neural tube and, subsequently, the central nervous system (CNS). Ectodermal cells lying more ventrally at the edges of the neural plate, the neural folds, come to lie at the dorsal surface of the neural tube during neurulation, form the *neural crest* and emigrate, subsequently giving rise to most of the peripheral nervous system. The ectodermal cells lying even more ventral around the edge of the cranial neural plate constitute a domain where various sensory structures such as the ear, nose, and cranial sensory ganglia will arise from isolated ectodermal areas called placodes. Finally, ectodermal cells on the extreme ventral side of the embryo give rise to the skin or epidermis. The first step in forming the nervous system, therefore, is to establish these different regions of ectoderm along the dorsoventral (DV) axis of the embryo soon after gastrulation is complete. The key mechanism that establishes these different subregions of ectoderm involves inductive interactions that were discovered in the early part of the last century. More recently, the molecules that underlie embryonic induction have been defined and their action understood.

Neural Induction and the Organizer

In the 1930's, Mangold and Spemann discovered neural induction during experiments in which they transplanted small pieces of tissues from one amphibian embryo to another at pregastrulae stages. The key observation was made when they transplanted a small piece of tissue from a region called the dorsal blastopore lip (DBL), and the host embryo responded to the grafted tissue by forming a complete secondary dorsal axis (Fig. 14.2). Importantly, most of the tissues

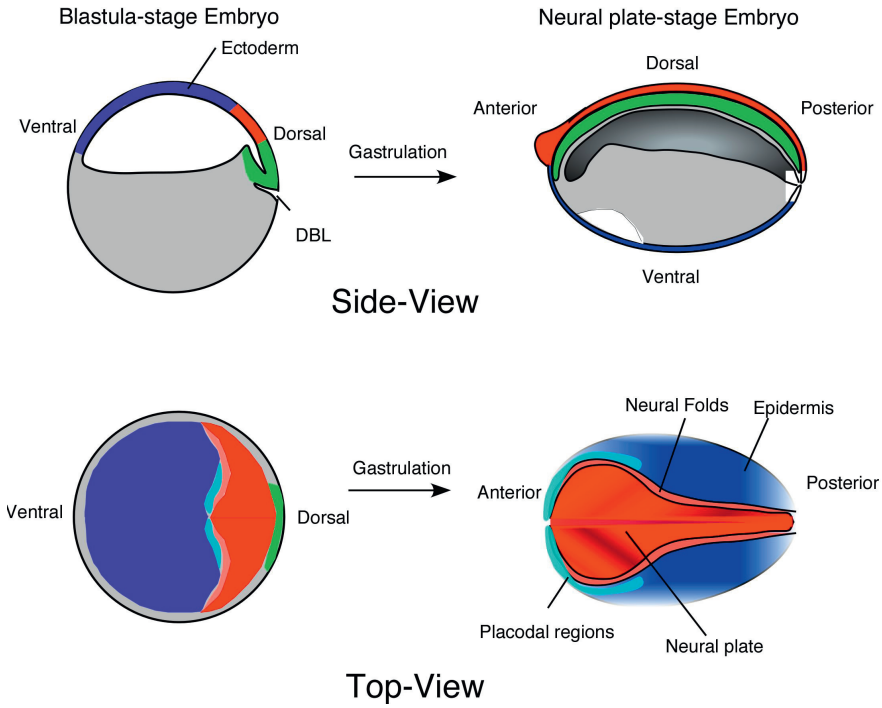

FIGURE 14.1 Ectoderm is subdivided into different fates during gastrulation. Shown is a cross-sectional side view, and top view of an amphibian embryo before (blastula-stage) and after gastrulation (neural plate-stage). During gastrulation, the grey and green (dorsal mesoderm) regions of the blastula involute inward, and the ectoderm (blue/red) at the top spreads over the outside of the embryo, and extends along anterior-posterior axis. As this process occurs, signals emanating from the dorsal and ventral sides of the embryo specify different fates, so that dorsal ectoderm (red) becomes neural tissue while ventral ectoderm (blue) becomes epidermis.

in the secondary dorsal axes were not derived from the transplanted tissue but rather from the tissue in the host embryo. In particular, the secondary dorsal axis contained a complete nervous system that was derived entirely from the ventral ectoderm of the host embryo, a tissue that would have differentiated into skin in the absence of a graft. The implication of this observation was that the transplanted tissue can act as a source of inducing signals that can cause ventral ectoderm to form neural tissue, and that this inductive interaction normally occurs on the dorsal side of the embryo. Tissue in the DBL was later termed the organizer because of its ability, when transplanted, to reprogram the ventral side of the embryo to form dorsal tissues, not only in the ectoderm but also in the internal mesodermal tissues. Following Mangold and Spemann's lead, it was subsequently found all vertebrate embryos appear to contain a region, called *Spemann's organizer*, which can induce ectoderm to form neural tissue.

Organizer transplantation experiments also gave the first indication that signals produced by Spemann's organizer were responsible for inducing different regions of the CNS. In these experiments, smaller regions of the DBL were used, and taken from embryos at different stages. The DBL of **younger** embryos contains the first involuting tissue and, when transplanted, induces head structures that contained neural tissue from the anterior portions of the neuraxis. Conversely, the DBL from **older** embryos involutes later and, when transplanted, induces tail structures that contained neural tissue from just the posterior portions of the neuraxis. The organizer, therefore, can be subdivided into two parts, a head and trunk/tail organizer, which specify different regions of the CNS along the AP axis. The role of the organizer tissue in the regionalization of the CNS is discussed further in a later section.

The Molecular Nature of Neural Inducers

The molecular nature of the inducers produced by organizer tissue remained elusive until the 1990's, when key biochemical pathways that mediate cell-cell signaling in animal development were identified using the tools of molecular genetics. One such pathway is a subfamily of TGFB-like factors, called the bone morphogenetic proteins (BMPs), which has proven to be remarkably conserved in action across the animal kingdom, from flies to humans (Bier, 1997). The core components of this pathway are the BMP

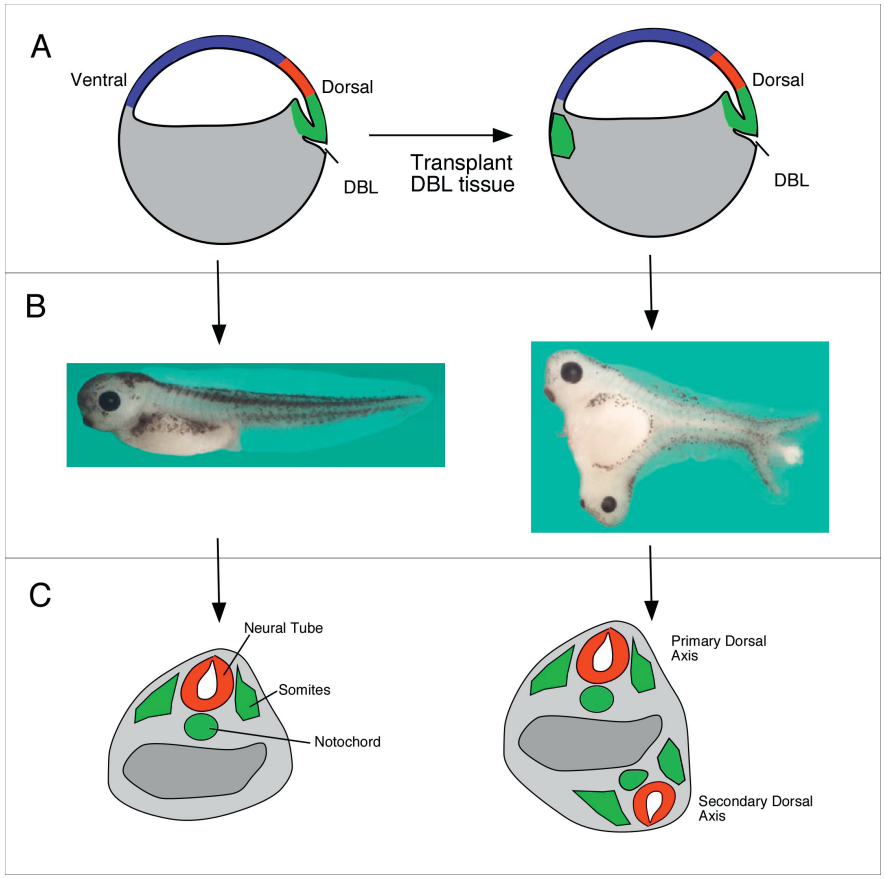

FIGURE 14.2 Organizer transplant experiment of Mangold and Spemann. (A) Tissue around the DBL was removed from one embryo and placed into the ventral side of another. (B) The transplanted DBL, if large enough, will cause a complete second dorsal axis to form on the host embryo, resulting in twinning. (C) Cross-section through the tadpoles shows that the second dorsal axis contains a complete nervous system. Importantly, by using tracers, one can show that the nervous system in this new dorsal axis is not derived from the transplanted tissue, but rather from host tissue, fated to give rise to ventral tissues in the absence of a graft.

ligands, secreted extracellular proteins that bind and activate a small family of heterodimeric cell surface receptors, which in turn transduce a signal by intracellular phosphorylation events that ultimately lead to changes in the activities of transcription factors, the SMAD proteins (Fig. 14.3). Importantly, the core activity of this signaling pathway is subjected to complex layers of regulation, both positive and negative (Fig. 14.3). This complex regulation is required to induce neural tissue by creating a gradient of BMP signaling activity across the DV axis of the ectoderm, although for a purpose not envisioned by the early embryologists (Weinstein and Hemmati-Brivanlou, 1999).

The Default Model

The current view of neural induction, the default model, stems from experiments using the amphibian *Xenopus laevis*, mainly because of an assay where the ectoderm can be explanted into culture before gastrulation into a simple salt solution. Ectoderm isolated before gastrulation differentiates into ventral epidermal tissue in culture. However, if BMP signaling is inhibited experimentally in these ectodermal explants, epidermal differentiation is suppressed, and neural tissue forms instead, presumably as a default pathway. The converse result can also be obtained using the fact that when isolated ectodermal cells are dissociated into single cells, they form nerve cells. However, if BMP4 is added to these cells, they revert back to epidermis. These early experiments were instrumental in showing that BMPs are potent epidermalizing agents and that blocking BMP signaling was sufficient to induce the ectoderm to form neural tissue as a default pathway. The ventral ectoderm of *Xenopus* and other vertebrate embryos was subsequently shown to express several BMPs ligands, consistent with their epidermalizing effects (Fig. 14.3).