31

Evolution of the Brain in Vertebrates

INTRODUCTION

The origin of vertebrates from ancestral chordates is one of science's persistent mysteries. The earliest vertebrates were a group of soft-bodied deuterostomes, and therefore no fossil record of them exists. Deuterostomes include three major groups, as shown in Figure 31-1—**echinoderms, hemichordates,** and **chordates.** The phylum Chordata comprises the **vertebrates** and the invertebrate chordates—**cephalochordates** (*Amphioxus,* now called *Branchiostoma*) and **urochordates** (tunicates or ascidians). Chordates and hemichordates (pterobranchs and acorn worms), diverged from each other more than 500 million years ago. Fossils of early invertebrate chordates are very scanty and have not yet provided definitive clues as to the origin of the vertebrates.

A model of the earliest vertebrates can be reconstructed from the recognized plesiomorphic features for living vertebrate groups. The earliest vertebrates would thus have been small animals of a fish-like shape with a series of gill slits in the pharynx and segmental body musculature. They would have moved through the water as the result of alternating waves of muscle contractions. These animals had a notochord, derived from the roof of the archenteron (the primitive gut), which is formed during gastrulation, and a dorsal hollow nerve cord. The nerve cord was expanded at its rostral end. Sensory receptive structures for senses including terminal and/or olfactory, visual (retinal photoreceptive), pineal-parapineal photoreceptive, taste, ocataval, and lateral line were present in the early vertebrates, but not all were evolved simultaneously. Finally, whereas in invertebrates, elaboration of the nervous system is generally accomplished by increasing the degree of complexity of individual neurons, elaboration of the nervous system in the earliest vertebrates was characterized by an increase in the number of neurons. Among the living adult invertebrate chordates and the hemichordates, the cephalochordate *Branchiostoma* most closely resembles this model.

One of the groups of deuterostome relatives of *Branchiostoma,* the echinoderms, comprise starfishes, brittle stars, sea urchins and sand dollars, sea lilies and feather stars, and sea cucumbers. In all echinoderms, the nervous system is locally organized. No central component, such as a brain or collection of central ganglia, is present.

In the worm-like hemichordates, no notochord or dorsal hollow nerve cord have been identified. A nerve net is present in the epidermis and contains sensory neurons, interneurons, and some motor neurons. The nerve net is thickened to form a dorsal, solid nerve cord in the proboscis and both dorsal and ventral nerve cords in the trunk. A **neurocord,** which does have a central lumen, is formed by invaginated nervous tissue in the intermediately located collar and connects the dorsal nerve cords of the proboscis and the trunk. The neurocord contains motor neurons and interneurons and may be homologous to the dorsal hollow nerve cord of other chordates. In the neurocord and dorsal nerve cord of the trunk is a collection of giant nerve cells, which are thought to play a role in rapid motor responses.

Among the urochordates, tunicate larvae have the best developed nervous systems. A **cerebral vesicle** is present in the rostral part of the body. It contains a structure called the **statocyst,** which is sensitive to gravity and a very simple eye called an **ocellus.** The cerebral vesicle is continuous with a neural tube that extends through the tail of the larva and lies dorsal to the notochord. The statocyst and ocellus are used to

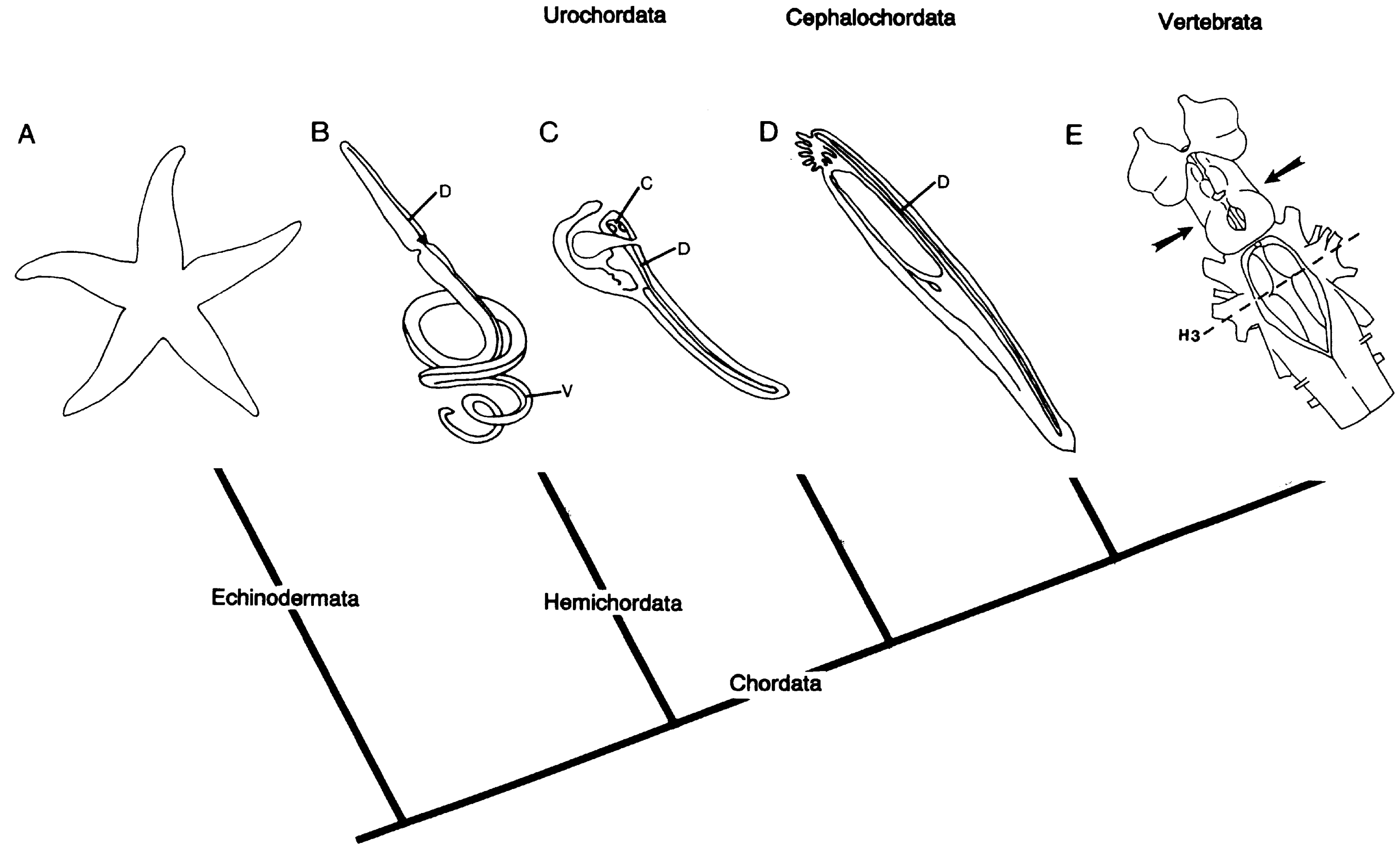

FIGURE 31-1. Dendrogram modeling central nervous system evolution in Deuterostoma. A whole starfish (echinoderm), whole acorn worm (hemichordate), sagittally sectioned tunicate larva (urochordate), sagittally sectioned *Branchiostoma* (cephalochordate), and the brain of a vertebrate (*Ichthyomyzon unicuspis*) are shown. In the latter, the rostral expression boundary of the homeobox gene *Hox-3* is indicated by the dashed line, and the rostral extent of the midbrain is indicated by the paired arrows. Abbreviations: C, cerebral vesicle; D, dorsal nerve cord; v, ventral nerve cord.

guide the larva toward gravity and away from light in order to locate a suitable place for it to attach and begin metamorphosis to the adult form.

In adults of the cephalochordate *Branchiostoma,* a **dorsal hollow nerve cord** is present dorsal to the notochord and can be divided into a dorsolateral sensory zone and a ventral motor zone. Ocelli, which are each formed by only one ganglion cell and one pigmented cell, are distributed along the dorsal nerve cord. At the rostral end of the dorsal nerve cord is a cerebral vesicle. The dorsal roof of the posterior part of the cerebral vesicle contains cells with cilia that produce stacks of lamellae and may be photoreceptive; this set of cells is known as the **lamellar body.** At the junction between the posterior and anterior parts of the cerebral vesicle is a cluster of **infundibular cells** in the ventral part of the vesicle. A cluster of pigment-containing cells and associated flask-shaped and nerve-like cells, called the **frontal eye,** lies at the rostral end of the cerebral vesicle. A pair of **rostral nerves** arises from within the cerebral vesicle, and a segmented series of **dorsal and ventral spinal nerves** arises from the dorsal nerve cord. We will consider these and additional anatomical features of the central nervous system of developing larva of *Branchiostoma* in greater detail below.

Two basic features characterize the organization of the nervous system of chordates. The first of these features involves the regional control of cell proliferation in the radial dimension. In some nonchordate invertebrates, the nervous system is diffusely distributed over the body as a series of ganglia or an interconnected nerve net, whereas in most chordates (or their larval forms), differential regional expansion of a specific radial sector of the nervous system occurs. As a result of induction by the roof of the archenteron, the dorsal part of the nerve net in invertebrate chordates thickens to form the dorsal nerve cord or tube, as does the neural plate in vertebrates. This differential regional expansion reflects a localized and spatially limited increase in the amount of proliferation of nervous tissue.

The second of these features involves the regional control of cell proliferation in the rostrocaudal dimension. The chordate nervous system is characterized by a rostral expansion of the dorsal nervous system, that is, the brain, and this key feature is initially influenced during gastrulation by a caudorostral sequence of induction, brought about by the progressively rostral migration of the roof of the archenteron from its opening, the blastopore. Founder cell populations of neurons are established in the neural plate tissue lying dorsal to the archenteron roof that will each give rise to a specific part of the nervous system.

As discussed in Chapter 9, the process of further regional specification and development has recently been found to be controlled by homeobox genes in chordates, as in a number of nonchordate invertebrates. The segmental, or neuromeric, organization of the brain is a manifestation of the homeobox gene specification of regional development. As in the case of the radially localized formation of a dorsal nerve cord or tube, the rostrocaudal parts of the chordate nervous system reflect localized and spatially limited increases (or decreases) in the amount of proliferation of nervous tissue.

A corollary of the feature of longitudinal differentiation of the central nervous system is the occurrence of changes that affected methods of propulsion that characterized early chordates. Whereas some nonchordate invertebrates use cilia to move their bodies through the water, locomotion in chordate invertebrates (or their larvae) is the result of muscular contractions regulated by longitudinally organized nerve fibers. In *Branchiostoma,* motor responses to stimuli are subject to control by the brain due to the rostrocaudally organized, functional differentiation of the nervous system. Longitudinal transmission of information within the nervous system and the presence of rostrocaudally localized areas of integration and control are keystones of the chordate nervous system.

ANCESTRAL CHORDATES

Several attempts have been made to reconstruct a morphotype of the brain in the earliest vertebrates, but these efforts have been hampered by a relative paucity of information on the central nervous system of the closest outgroup to vertebrates, the cephalochordate *Branchiostoma.* The marked differences that exist between the brains of hagfishes and lampreys have left important questions unanswered as to the plesiomorphic vertebrate condition for a number of traits. Recent findings on developing gastrula and larvae of *Branchiostoma* have dramatically increased our understanding of this cephalochordate, however, and allow for new insights into how the brain of vertebrates evolved.

The adult form of *Branchiostoma* was previously used as an approximate model of the earliest vertebrates. This model implied that the central nervous system in early vertebrates consisted of a spinal cord with a slightly expanded rostral end, presumed to be a forerunner of the hindbrain. This model also implied that the vertebrate midbrain and forebrain arose evolutionarily as further rostral condensations of an epidermal nerve net.

E. Gilland and R. Baker recently proposed that the earliest vertebrates may have resembled the primary gastrula of *Branchiostoma,* as discussed in Chapter 9 (see Fig. 9-7), rather than the adult. They postulated that the entire primary gastrula of an ancestral chordate, resembling that of extant *Branchiostoma* [Fig. 31-2(A)] is homologous to the head of vertebrates. This possibility derives from the findings of P. Holland *et al.* on the location of the rostral expression border of the homeobox gene *AmphiHox* 3 [H3, Fig. 31-2(A)] in the developing *Branchiostoma* gastrula, which appears to be a homologue of the *Hox* paralog group 3 (H3) in vertebrates. Gilland and Baker hypothesized that the first five somites (segmented mesoderm) of *Branchiostoma* are homologous with the somitomeric region of jawed vertebrates (see Fig. 9-9) and that the head of vertebrates is thus homologous with the entire primary gastrula of the ancestral chordate stock. Developing ancestral vertebrates resembling such a gastrula would therefore have had a central nervous system that contained a midbrain, hindbrain, and spinal cord, but the prosencephalon, the paired sense organs, and the anterior part of the head would have been newly aquired with the evolution of the first vertebrates.

A more recent study by T. Lacalli, N. Holland, and J. West provides a detailed anatomical analysis of the larvae of *Branchiostoma* [Fig. 31–2(B and C)] on which out-group comparisons with vertebrates can be based and which allows further insights of fundamental importance for our understanding of central nervous system evolution. In the larvae, four somites are present rostral to the rostral expression border of *Hox*-3 (H3) [(Fig. 31-2(B)]. The central nervous system lies medial to the somites, and several of its landmarks are projected onto the section in Figure 31-2(B) for reference. The part of the central nervous system that lies medial to most of the first somite is shown in Figure 31-2(C), expanded in scale as indicated by the thicker dashed lines.

The rostral end of the nerve cord contains an expanded portion formed by ciliated cells, the cerebral vesicle, most of which is shown in Figure 31-2(C), indicated by the shading. The cerebral vesicle contains a **central canal** that opens to the surface through a **neuropore;** it also contains an **anterior pigment spot** at its rostral end. The anterior pigment spot is formed by the pigment in the caudal ends of several pigment cells; these pigment cells and associated, putative receptor and nerve cells constitute the frontal eye. A pair of rostral nerves join the cerebral vesicle on its ventral aspect. The central canal narrows, as indicated by the arrow in the figure, and at the same rostrocaudal level, a cluster of cells that form the infundibulum are present in the ventral part of the cerebral vesicle. These cells secrete a noncellular strand called **Reissner's fiber,** which extends down the central canal. The narrowing of the central canal and the position of the infundibulum divide the cerebral vesicle into anterior and posterior portions. The posterior portion of the vesicle contains a large structure, the lamellar body, composed of the membranous lamellae in parallel stacks formed by cilia of the cells in this region.

Lacalli *et al.* discussed the putative homology of these features with structures in vertebrates. Due to multiple structural and histochemical similarities, the unpaired frontal eye of *Branchiostoma* appears to be homologous to the retinas of the paired eyes of vertebrates. The infundibular cells appear to be homologous to the infundibulum of vertebrates; infundibular cells in embryonic fish occupy the same position and also secrete a Reissner's fiber. The lamellar body appears to be the homologue of the vertebrate pineal–parapineal complex, due to positional and ultrastructural similarities. The rostral nerves may be homologues of the terminal and/or olfactory nerves, but additional study of them needs to be done.

This analysis reveals that the cerebral vesicle contains structures that appear to be homologues of the vertebrate paired retinas, infundibulum, and pineal–parapineal complex, all of which lie within or are derived from the diencephalon. The rostral nerves may be homologues of rostral (olfactory and/or terminal) telencephalic nerves of vertebrates. Thus, the cerebral

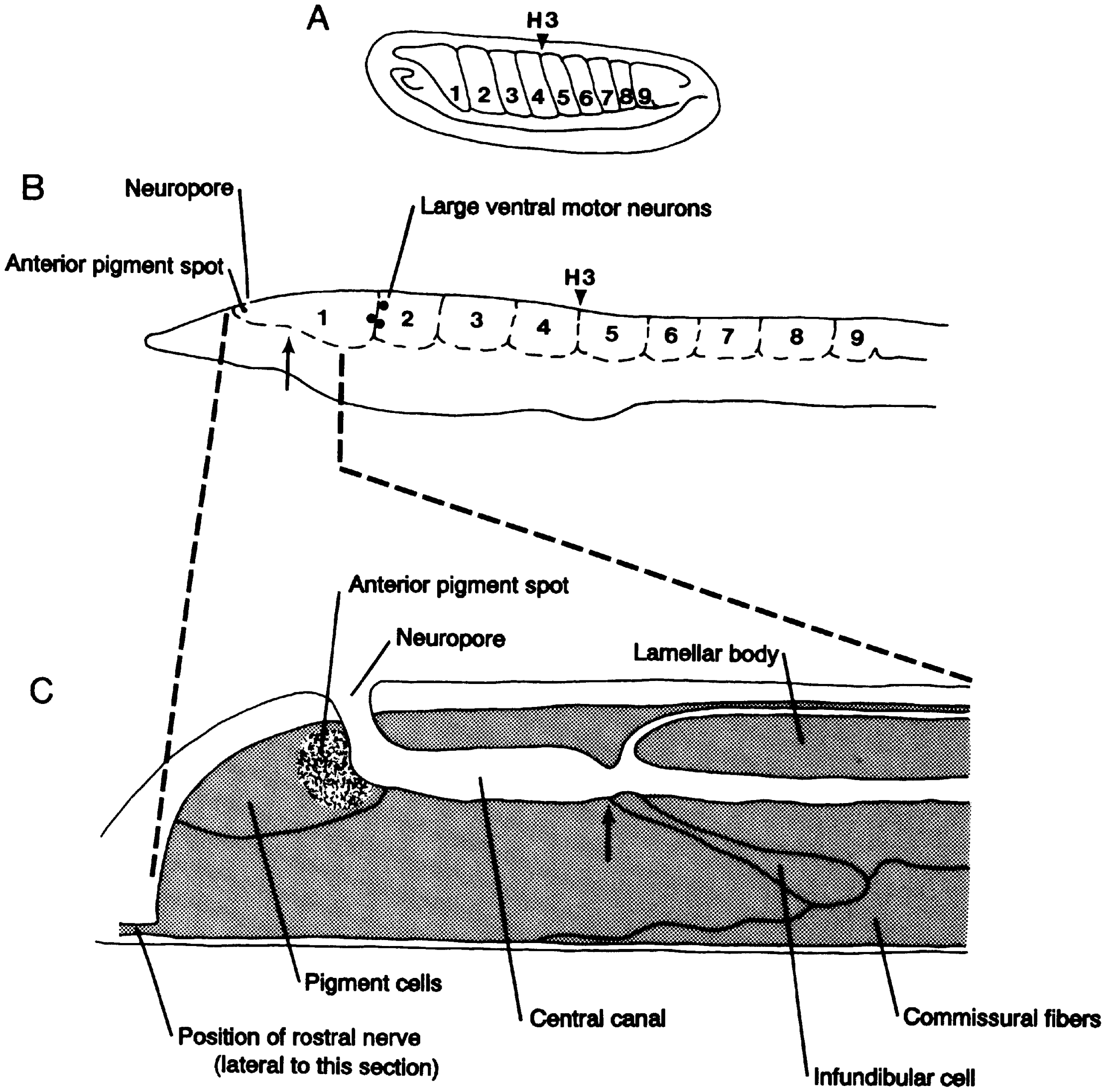

FIGURE 31-2. Drawings of semischematic parasagittal sections through an early developmental stage of *Branchiostoma* (A, also shown in Fig. 9-7) and a larva of *Branchiostoma* (B and C). Rostral is toward the left. Somites are numbered 1–9 in A and B, and the rostral expression limit of *Hox-3* is indicated by H3 in A and B. In C, an enlargement of the part of the nervous system medial to somite 1 is shown, with the cerebral vesicle indicated by shading. A adapted from Gilland and Baker (1993) and used with permission of S. Karger AG. Data for B and C from Lacalli et al. (1994).

vesicle appears to be homologous to the diencephalon, and possibly also the telencephalon, of vertebrates.

Immediately caudal to the cerebral vesicle are several large ventral motor neurons [Fig. 31-2(B)]. Lacalli *et al.* postulated that these may be homologous to the anterior-most of the ventral motor neurons in vertebrates, that is, the oculomotor neurons that innervate the muscles of the eye. If this comparison is correct, the region in which these ventral motor neurons lie in *Branchiostoma* would be the homologue of the vertebrate midbrain.

If we now reconsider the somites in *Branchiostoma* and their possible correspondence to somitomeres and somites in vertebrates, a new model of brain and head evolution emerges, as shown in Figure 31-3 and summarized in Table 31-1. We present this model with the strong caution that it is highly speculative and should be taken only as one of a number of possible solutions to the problem. Data yet to be obtained are needed to clarify the many complex anatomical relationships involved here. For this new model, Figure 31-3 , which can be compared with Figure 9-9, shows the developing neural tube and rhombomeres (A), the somitomeres and somites (B), and the head segments (C) in a developing vertebrate, in comparison with the somites in a *Branchiostoma* larva (D). Table 31-1, which can be compared with Table 9-2, shows the hypothesized relationships of somites in *Branchiostoma* with somitic organization, head segmentation, and cranial nerve organization in vertebrates.

The cerebral vesicle in *Branchiostoma* is aligned with the first somite and appears to be the homologue of the vertebrate diencephalon (and perhaps telencephalon). No somitomere is present in vertebrates that would correspond to the first somite in *Branchiostoma;* whether a corresponding somitic entity was present in the common ancestral stock of cephalochordates and vertebrates is unknown. If the anterior-most ventral motor neurons in *Branchiostoma* [indicated by the large dots in Fig. 31-3(D)] are homologues of vertebrate oculomotor neurons,

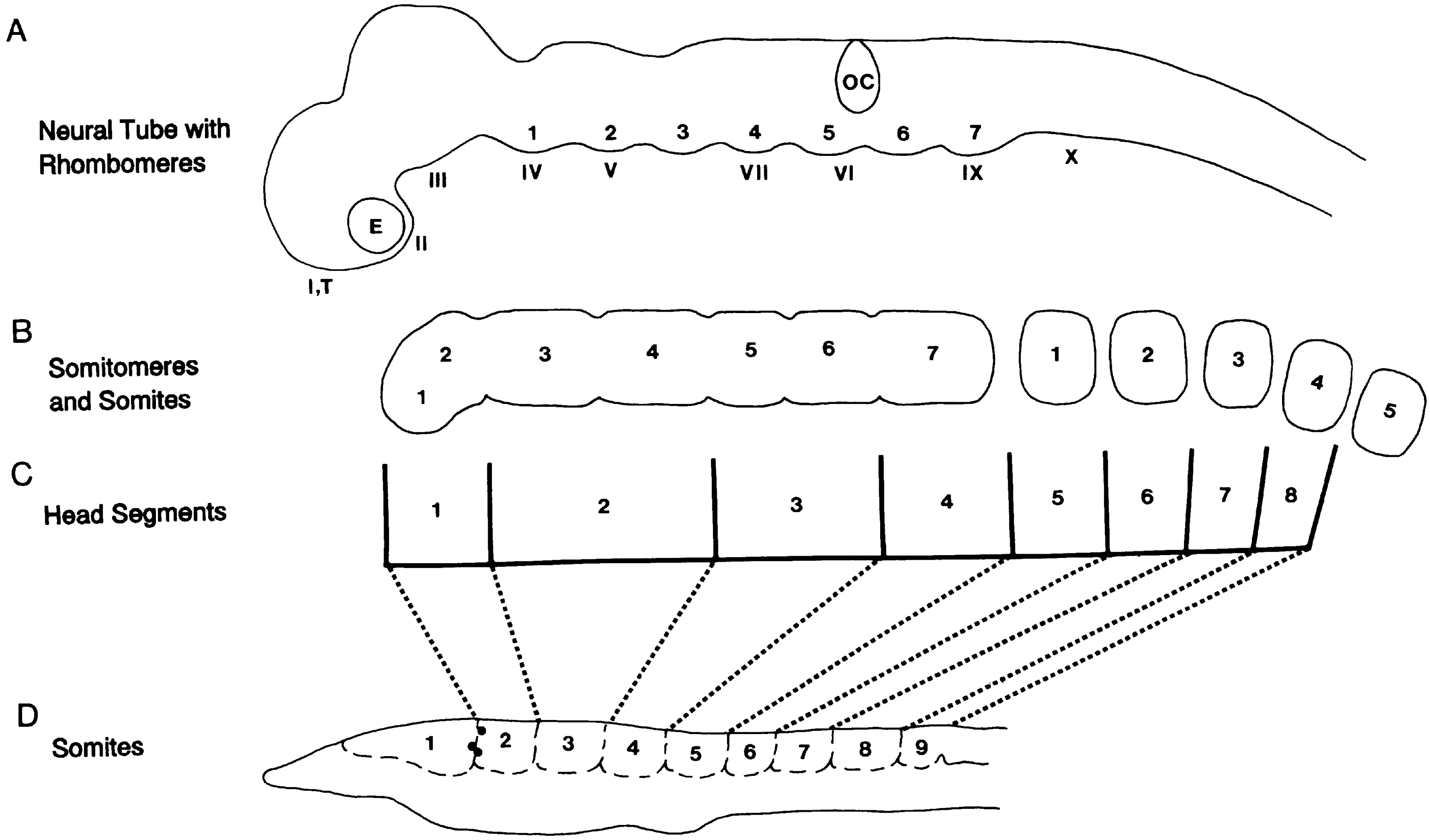

FIGURE 31-3. Speculative model of brain and head evolution. Schematic drawing of parasagittal sections in a developing vertebrate through (A) the neural tube and rhombomeres (1–7) and (B) the somitomeres (1–7) and somites (1–5), with corresponding head segments (1–8) indicated in (C). In A, the positions of some of the developing cranial nerves are indicated by Roman numerals and T (terminal nerve) and the position of the optic capsule by OC and the eye by E. A–C are similar to parts of Figure 9-9 (but with rostral to the left instead of to the right). (D) Schematic drawing of a parasagittal section through a *Branchiostoma* larva, with the somites numbered 1–9. Large dots at the border of somites 1 and 2 represent the position (more medially) of the most anterior of the large ventral motor neurons. The dotted lines indicate the correspondence of the somites in *Branchiostoma* with head segments and their respective somitomeres and somites in vertebrates, as hypothesized for this model.

TABLE 31-1. Speculative Correspondences in Chordate Brain and Head Evolution

Branchiostoma Somite	Vertebrate Head Segment	Vertebrate Somitomere or Somite	Vertebrate Cranial Nerves
1			I, T, VN, II, and Epiphyseal
2	1	Somitomeres 1, 2	Profundus, III, LL_{AD}
3	2	3, 4	IV, V, LL_{AV}
4	3	5, 6	VI, VII_{D}, VIII, Otic, VII_{VL}
5	4	7	IX_{D}, LL_{M}, IX_{VL}
6	5	Somites 1	X_{D}, XII, LL_{ST}, LL_{P}, X_{VL}
7	6	2	X_{D}, X_{VL}, Occipital
8	7	3	X_{D}, X_{VL}, Occipital
9	8	4	X_{D}, X_{VL}, Occipital

and particularly of the neurons of cranial nerve III, then the rostral end of the midbrain in *Branchiostoma* would be aligned with the rostral end of its second somite, which would then correspond to the rostral end of the first head segment and the somitomeric region in vertebrates. The position of the rostral expression limit of *Hox-3* is at the caudal border of the fourth somite. Thus, somites 2, 3, and 4 would correspond to the somitomeric part of the head in vertebrates that comprises the first three head segments and encompasses the three oculomotor cranial nerves.

In this hypothesized model, each of the somites 2, 3, and 4 in *Branchiostoma,* would be homologous to two somitomeres in developing vertebrates: 1 and 2, 3 and 4, and 5 and 6, respectively. Somites 2–9, as a group, in *Branchiostoma* would be homologous to the somitomeric region plus the first four somites of vertebrates, and somites 5–9 in *Branchiostoma* would be individually homologous to somitomere 7 and somites 1–4 in vertebrates, respectively. These relationships are indicated with the dotted lines in Figure 31-3.

By comparing the putative homologues of parts of the brain present in *Branchiostoma* with the brain in vertebrates, some of the features of the brain in the common ancestral stock of cephalochordates and vertebrates can be identified. The brain of the common ancestor would have had the four basic divisions of the central nervous system: forebrain, midbrain, hindbrain, and spinal cord. Whether a well-developed telencephalon was present in the forebrain, other than a small number of neurons in receipt of the rostral or terminal/olfactory nerve input, cannot be determined. A diencephalon would have been present, with at least a retinal apparatus, an infundibulum, and a photoreceptive pineal–parapineal complex. The retinal apparatus was probably unpaired (as will be further discussed below). Both a midbrain and hindbrain would have been present. The rostral extent of ventral motor neurons would have marked the rostral border of the midbrain. Whether the notochord would have extended rostral to the rostral border of the brain, as it does in *Branchiostoma,* or have ended caudal to the level of the forebrain, as it does in vertebrates, cannot currently be determined.

THE EARLIEST VERTEBRATES

Vertebrates are uniquely characterized by the presence of two ectodermal tissues, neural crest and ectodermal placodes, which directly give rise to or are crucial for the development of the anterior part of the head and the special sense organs for olfaction, vision, taste, hearing, and the lateral line system. The origin of vertebrates was an event that capitalized on the evolution of neural crest and placodes in conjunction with enlargement of the brain. The same tissue that gives rise to the epidermal nervous system of extant invertebrate chordates appears to give rise to the central nervous system itself and to the two additional novel tissues in vertebrates. Of these two new tissues, the neural crest may have been the first to have been evolved, and its presence may have been the defining event of the divergence of vertebrates from their invertebrate ancestral stock.

Two Novel Tissues: Neural Crest and Placodes

As discussed in Chapter 9, the neural crest arises during gastrulation in the neural fold that borders the neural tube (see Fig. 9-5). It not only gives rise to neural tissue but also gives rise to the muscles, bone, and connective tissues of the rostral (preotic) part of the head in vertebrates, which lies anterior to the anterior end of the notochord. The new head was correlated with changes in the propulsion system and with a shift to a more actively predatory mode of life. Thus formed, it was also available to house a rostrally expanded brain and special sense organs.

Placodes are the areas of surface ectoderm that overlie migrated neural crest tissue and produce neural tissue for most of the special sense organs. Different placodes make different contributions to different sense organs. Thus, the various placodes do not appear to simply be serially homologous derivatives of an initially continuous column of placodal tissue and may not have all evolved at the same time. Placodal tissue and the sensory cells to which it gives rise are thought, however, to be homologous to the epidermal nerve net of invertebrates, as derivatives of the same ectodermal nervous tissue. The sensory neurons of the invertebrate epidermal nerve net are ciliated, as are the cells that form the cerebral vesicle in *Branchiostoma,* and the receptors of the paired sense organs that derive from placodal tissue in vertebrates are ciliated during their development.

Development of the neural plate itself is induced by the notochord that forms from the archenteron roof, along with somites and the prechordal plate (mesoderm rostral to the notochord). The induced neural plate can in turn affect other tissue in an inductive capacity. Whether neural crest induces the development of the forebrain and the development of placodes remains to be established, but circumstantial evidence favors this possibility. Neural crest tissue is present in the region of the developing telencephalon, and removal of the neural folds early in development can preclude forebrain development. Neural crest cells migrate between the surface ectoderm and the deeper paraxial mesoderm and are present beneath the parts of the surface ectoderm that form placodes before placodal differentiation and production of neural elements begins.

Thus, a mutation that resulted in the formation of the novel tissue of neural crest during embryological development—as a differentiation of the dorsolateral part (neural fold) of the existing dorsal nerve cord—could have been selected for as a result of its contribution to head formation in correlation with a more mobile and actively predatory repertoire. The development of placodes and consequently of paired special sense organs for distance reception and the development of the forebrain for analysis, integration, and retention of the sensory inputs might thus be fortuitous side effects of the presence of neural crest during development.

Sensory System Evolution

From the model of a common ancestral chordate of both cephalochordates and vertebrates, we can postulate that the earliest vertebrates would have had a pair of rostral nerves terminating in the telencephalon. The identity of these nerves as either olfactory or terminal remains to be confirmed. While paired olfactory nerves are present in all extant vertebrate groups, paired terminal nerves with LHRH-positive (luteinizing hormone releasing hormone) neurons are present only in jawed vertebrates; terminal nerve-like neurons are present in lampreys but do not contain LHRH, and a terminal nerve has not been found in hagfishes. Determination of the identity of the rostral nerves in *Branchiostoma* will thus help to clarify the evolutionary history of the telencephalic nerves of vertebrates.

A retinal structure, either single or paired, and associated with the diencephalon, would have been present in the earliest vertebrates. Lacalli *et al.* suggested that the unpaired, retinal-like, frontal eye of *Branchiostoma* may have been derived from an unpaired apical organ such as that present in an auricularia—the larval form of one of the classes of echinoderms, the sea cucumbers. In this case, an unpaired retinal-like photoreceptor would be plesiomorphic for chordates and the paired retinal photoreceptors an apomorphy in the earliest vertebrates.

Structures associated with the retina in vertebrates, such as the cornea, lens, and iris, are present in lampreys and jawed vertebrates but absent in hagfishes and in all invertebrate chordates. Thus, they may have evolved in the common ancestral stock of lampreys and jawed vertebrates rather than in that of all vertebrates. Extraocular eye muscles and their cranial nerves are also present among extant vertebrates in the same distribution; however, evidence of the presence of these muscles and nerves in fossils of osteostracans and the presence of neurons in the brain of *Branchiostoma* that are the putative homologues of vertebrate oculomotor neurons raise the possibility that muscles associated with the retinal apparatus and their innervating ventral motor neurons were present in the earliest vertebrates and have subsequently been lost in hagfishes.

The earliest vertebrates had an unpaired, median, pineal–parapineal photoreceptor apparatus in the roof of the diencephalon. A pineal–parapineal complex is plesiomorphic for jawed vertebrates. Furthermore, this structure is present in lampreys and absent in hagfishes, and the putatively homologous lamellar body is present in *Branchiostoma*. This distribution suggests that a pineal–parapineal apparatus is plesiomorphic for at least the common ancestral stock of cephalochordates and vertebrates, and its absence in hagfishes is an apomorphy.

The lateral line senses of electroreception and mechanoreception were evolved early in vertebrate evolution. No evidence for these systems have been found in invertebrate chordates (although sensory papillae that detect vibrations and/or water flow are present in the invertebrate chaetognaths). The placodal tissue for both lateral line senses may have evolved in conjunction with the early vertebrate feature of the deposition of calcium salts in the dentine, which enhance electroreception. Furthermore, depressions and canal systems that could have effectively shielded lateral line electroreceptors have been found in the earliest fishes known from the fossil record. Such shielding is essential for perceiving the direction of the stimulus source. Extant hagfishes appear to lack electroreception and may thus have lost the apparatus for it over the course of their evolution.

Otic organs for vestibular sense and hearing characterize all major groups of living vertebrates, even though not all components, such as horizontal semicircular canals, are present in all vertebrates. No trace of any comparable sense is present in invertebrate chordates. Similarly, the chemosensory system of taste and the profundal and trigeminal sensory systems are common features of vertebrates. The timing of the evolution of these various senses relative to olfactory, retinal, and pineal–parapineal senses is unknown, but all placodal sensory systems clearly evolved relatively early in the vertebrate lineage.

Organization of the Brain

At this early stage in vertebrate evolution, most of the major divisions of forebrain, midbrain, hindbrain, and spinal cord were present, as were all of the major sensory and motor systems organized for active propulsion. Most of the neuron cell bodies in the brains of these early vertebrates would have been in a periventricular position, rather than migrated laterally (centrifugally) within the various parts of the brain.

Due to the influence of placodal tissue, the earliest vertebrates would very probably have had an expanded telencephalon. Recent evidence suggests that the presence of paired olfactory organs that are connected to the forebrain is necessary for the development of normal telencephalic lobes. The neural plate cells that give rise to the definitive telencephalon thus appear to require the influence of olfactory placodal tissue to develop normally. With the development of the olfactory inputs to the telencephalon, the presence of an olfactory pallium, as is present in extant vertebrates, can be postulated. That the entire pallium was olfactory in the earliest vertebrates (as it is in hagfishes) is probable, with olfactory projections being limited to the lateral pallial region only in gnathostomes.

In all vertebrates, a diencephalon is present that contains an infundibulum and also gives rise to the retina. A diencephalon with these two structures can also be recognized in cephalochordates and is thus plesiomorphic for the common ancestor of cephalochordates and vertebrates. A pineal–parapineal apparatus is present in all vertebrates except hagfishes and is present in *Branchiostoma*. This feature of the diencephalon is thus also plesiomorphic for the common ancestor of cephalochordates and vertebrates. Other portions of the diencephalon appear to be unique to vertebrates. These include an epithalamus with paired, asymmetrical habenulae, a dorsal thalamus, probably a ventral thalamus, and ventrally, a preoptic area and hypothalamus.

In jawed vertebrates, the dorsal thalamus is composed of two divisions, the lemnothalamus and the collothalamus. A nucleus anterior that may constitute the lemnothalamus has been identified in both lampreys and hagfishes, but further study of the dorsal thalamus of lampreys and hagfishes is needed to determine whether the two divisions were plesiomorphic for all vertebrates. However this question is resolved, a lemnothalamus–medial pallium system may have been one of the earliest ascending systems established to the telencephalic pallium. A striatal area in the telencephalon has been identified in both lampreys and hagfishes, implying that the striatum is plesiomorphic for vertebrates; thus, a collothalamus relaying visual and other sensory information from the roof of the midbrain to the striatum may have been present in the earliest vertebrates. Finally, the possible presence of cell groups homologous to the preglomerular nuclear complex in the caudal diencephalon of jawless vertebrates remains to be investigated, but the presence of receptors for the senses of taste and lateral line mechanoreception (and electroreception in lampreys) in these vertebrates suggests that cell groups relaying ascending information from these systems may have been present in the earliest vertebrates.

A midbrain containing both a roof (tectum) and a tegmental region is plesiomorphic for vertebrates. The only putatively homologous part of the midbrain yet identified in *Branchiostoma* is the ventral motor cells. The midbrain sensory roof may thus be unique to vertebrates.

The hindbrain is smaller in hagfishes than in lampreys and jawed vertebrates, and fossil evidence suggests that it was small plesiomorphically for vertebrates. As the lateral line and octaval sensory receptors evolved, they can be postulated to have entered the hindbrain and synapsed in a localized region within it. This hindbrain region would probably have projected rostrally to the roof of the midbrain. Since the roof of the midbrain is devoted to a spatially organized anlaysis of sensory information in all extant vertebrates, it is highly probable that such a spatial map was present in the midbrain roof in these earliest vertebrates. The lateral line and octaval systems contribute to the localization of predators and prey, and a spatial analysis of the sensory information in the midbrain roof would have provided the basis for the profitable use of the sensory information by the animal.

Little information is available on the early evolution of motor systems and the descending pathways that form them. A striatal region of the telencephalon and both the roof and tegmentum of the midbrain may have constituted some of the earliest motor-related parts of the brain rostral to the actual motor nuclei of cranial and spinal nerves.

In summary, olfactory (and/or terminal), retinal photoreceptive, and pineal–parapineal photoreceptive senses were probably the earliest senses established and occurred in the common ancestor of cephalochordates and vertebrates, as did the major subdivisions of the brain: a forebrain with a diencephalon and possibly a telencephalon as well, a midbrain, a hindbrain, and a spinal cord. In vertebrates, electroreceptive and mechanoreceptive lateral line, taste, auditory, vestibular, trigeminal, and profundal sensory inputs were established, although not all were evolved simultaneously. Some of the major ascending sensory pathways and descending motor pathways were established. Ascending serotoninergic projections from the raphe and descending projections to the spinal cord from the reticular formation and possibly also from vestibular, trigeminal, and solitary nuclei are among the pathways that characterized the brainstem in early vertebrates.

THE ADVENT OF JAWS

The evolution of jaws that could be used for the capture and initial processing of prey into the digestive system was of seminal significance in vertebrate history. In these animals, development of the postotic skull and true, bony vertebrae were also established. The forebrain, midbrain, and hindbrain in gnathostomes are all characterized by further developments and specializations related directly or indirectly to the advantages gained by the much more mobile and actively predatory lifestyle. We will survey a number of the features of the brain that evolved within the various radiations of gnathostomes and then consider the various mechanisms that underlie their evolution.

With increased mobility for both prey seeking and predator avoidance, changes that enhanced control of the motor system were strongly selected for. Such enhanced control was partly achieved through the development of the cerebellum in the roof, or rhombic lip, of the hindbrain. Early vertebrates had either only a small cerebellum or no cerebellum at all, with the rhombic lip poorly developed. This part of the brain may have consisted only of an emminentia granularis, a cell population associated with the cerebellum itself in gnathostomes, or of an emminentia granularis and a small cerebellum. A marked increase of cell proliferation in the rhombic lip occurs during development in gnathostomes and results in the formation of the cerebellum.

The midbrain in early vertebrates would already have been developed to the extent of relaying lateral line, octaval, and visual information to the forebrain. It would have been organized as a topographic map of external space and would also have played a role in the organization of oriented motor responses to the sensory stimuli. The midbrain roof did not undergo marked changes in organization with the development of jaws, but within different radiations of gnathostomes, this part of the brain was expanded markedly in size and was elaborated in terms of its cytoarchitectonic organization. Its usefulness for spatial analysis and orientation to stimuli continued to be selected for and thereby augmented in various groups.

Within ray-finned and cartilaginous fishes, the diencephalon is characterized more by development of the pretectum and posterior tuberculum than by development of the dorsal thalamus. The opposite condition—greater development of the dorsal thalamus than pretectal and posterior tubercular regions—characterizes amniotes, as we will consider below. The pretectum is elaborately developed particularly in some teleost fishes, in which a variety of pathways relay visual information through a varying series of pretectal nuclei to various sites in the brainstem. One pretectal pathway relays visual information to the inferior lobe of the hypothalamus, which participates in the motor control of feeding behavior.

In both cartilaginous and ray-finned fishes, the posterior tuberculum gives rise during development to a number of laterally migrated nuclei (the preglomerular nuclear complex of ray-finned fishes) that relay ascending lateral line and gustatory information to the forebrain, particularly to the (topologically) medial pallium. The dorsal thalamus in these groups relays some sensory information to the telencephalon but is more simply organized, consisting of only three periventricular nuclei.

While the dorsal thalamus is not markedly elaborated in cartilaginous and bony fishes, the telencephalon is greatly expanded in some groups within both of these radiations. The telencephalon is also large and complex in hagfishes. Within amniotes, both the dorsal thalamus and the telencephalon are expanded and complex in mammals and in some diapsid reptiles and birds. These increases in the size of the forebrain have occurred independently. Within each of these various groups of vertebrates, the increase in the size and complexity of the forebrain may be related to actively predacious lifestyles in some cases but may also be correlated with such functions as more complex analysis of sensory information, learning and memory, and social, conspecific interactive behaviors.

While the dorsal thalamus of fishes is not elaborated, it does consist of two parts, the lemnothalamus predominantly in receipt of lemniscal sensory inputs, and the collothalamus predominantly in receipt of sensory inputs relayed through the roof of the midbrain. The lemnothalamus projects to the (topological) medial pallium and to what has been identified as the dorsal pallium, while the collothalamus projects to the striatum. In some cartilaginous and ray-finned fishes, projections of both divisions of the dorsal thalamus also terminate in a pallial region that lies between the (topological) medial and lateral pallia. In sharks, this region is composed of at least two major parts, a dorsal laminar zone and a more ventrally lying zone called the central nucleus. Similarly located regions are present in the telencephalon of many teleosts, particularly in some of the euteleosts in which the telencephalon is strikingly enlarged and elaborated. That these dorsally lying pallial areas in cartilaginous and ray-finned fishes are homologous to the dorsal pallium of amniotes is dubious, however. Immunohistochemical studies in particular suggest that they have more probably evolved independently along with the independent expansion of the telencephalon.

ONTO THE LAND

The conquest of the terrestrial environment was, like the acquisition of jaws, a momentous event in vertebrate history. It allowed for a plethora of new selective pressures to operate on variations in sensory input systems, information processing areas, and motor control systems in the central nervous system and on their peripheral musculoskeletal counterparts.

In all tetrapods, a dorsal pallial region is present between the medial and lateral pallia, although the evolutionary relationship between the dorsal and lateral pallial areas in amphibians and what is recognized as the dorsal pallium in amniotes is unclear. In ancestral amniotes, two major changes occurred in the development of both the dorsal thalamus and the dorsal pallium that were strongly selected for. The dorsal thalamus underwent a dual elaboration, that is, in both the lemnothalamus and collothalamus, regionally specific cell proliferation was increased during development in correlation with the lateral (centrifugal) migration of neuron cell bodies. This change resulted in the presence of multiple, migrated nuclei within both parts of the dorsal thalamus. In ancestral amniotes, projections from the lemnothalamus to the medial pallium and to the dorsal pallium were present. Projections from the collothalamus to the striatum were also present. In addition, projections from the collothalamus to the dorsal pallium were acquired. Furthermore, ascending somatosensory projections via the dorsal column nuclei to the dorsal thalamus, both directly and relayed through the roof of the midbrain, were also either acquired or greatly enhanced at this time.

In correlation with the dual elaboration of the dorsal thalamus, a dual expansion of the dorsal pallium occurred, so that both the medial, lemnothalamic-recipient and the lateral, collothalamic-recipient divisions of the dorsal pallium were expanded by regionally specific increases in cell proliferation. In the synapsid line that led to extant mammals and in the common ancestors of diapsids and turtles, further expansions of these two dorsal pallial divisions continued independently.

In the synapsid line, an increase in the radial organization of the neurons in both divisions of the dorsal pallium occurred, resulting in an "inside-out sequence" in the centrifugal migration of neurons during development, with the consequent formation of the six layers present in most of the dorsal pallial cortical region. Increases in cell proliferation also resulted in the presence of new cell types as defined by their immunohistochemical profiles, particularly in layers II–IV of the isocortex. In various separate lineages of mammals, other mutational events produced repeated duplications of various sensory cortical areas, resulting in multiple sensory representations.

Further mutational events in mammals resulted in a number of new organizational features and structures. The medial pallium was further expanded. A number of ascending connections from the dorsal thalamus were lost, particularly some of those from the contralateral part of the lemnothalamus. Long descending projections from the isocortex and interhemispheric connections via the corpus callosum were gained.

In the nonsynapsid line, marked increases in the area of the lateral division of dorsal pallium occurred, with the consequent formation of the anterior dorsal ventricular ridge. Expansion of the medial division was relatively minor. An increase in radial organization of the proliferated neurons did not occur in either division, and thus the dorsal ventricular ridge is predominantly characterized by a single cell lamina or by nuclear groups rather than by multiple cortical laminae.

In the diapsid reptilian stock that gave rise to birds, an independent expansion of the medial division of the dorsal pallium occurred, resulting in the formation of the Wulst. Cells with immunohistochemical phenotypes similar to some of those found in layers II–IV of mammalian isocortex were also independently evolved in the dorsal pallium. Regional increases in cell proliferation during embryological development that resulted in an enlarged medial pallium were selected for in birds as well; this phenomenon is particularly evident in birds that have sequestered stores of food for the winter to which they must repeatedly return to stock and to feed from.

The dual elaboration of both parts of the dorsal thalamus and the dual expansion of both divisions of the dorsal pallium that occurred in ancestral amniotes was strongly selected for. The massive increase in the amount of sensory information reaching the dorsal pallium was of great advantage for survival in a terrestrial environment. In correlation with the increased analysis of sensory information, the value of learning and memory is reflected in the further development of the medial pallium, particularly in mammals.

In ancestral amniotes, a new set of selective pressures also affected the evolution of somatosensory and motor control systems for survival in the terrestrial environment. These systems have been elaborated to some extent independently in the synapsid line and in birds. In mammals, sensorimotor cortex, a part of the medial (lemnopallial) division of the dorsal pallium, is well developed and distinct from other cortical areas. Similarly, in birds, the somatosensory part of the Wulst is well developed, and a more caudal, superficially lying region in the telencephalon may play a major role in motor control via influences on the striatum.

Other motor control pathways also vary among amniotes as a consequence of differential selective pressures. In mammals, selective pressures have favored motor control mediated by pathways from the striatum to the sensorimotor cortex via the dorsal thalamus and by long descending pathways to the brainstem and spinal cord from sensorimotor cortex. Pathways from the striatum to the optic tectum via the pretectum and substantia nigra are relatively minor. In nonsynapsid amniotes, selective pressures have favored striatal pathways to the optic tectum via the pretectum and/or the substantia nigra. Adaptation of the central nervous system in amniotes also encompasses examples of specialized evolution within a restricted group of species, such as has occurred in the development of complex descending motor pathways for vocal control in songbirds.

THEORIES OF VERTEBRATE BRAIN EVOLUTION

The invasion hypothesis of vertebrate brain evolution dominated the first half of the twentieth century. This hypothesis held that changes in central nervous system connections occur as a result of axon collaterals invading and forming new connections with a given group of neurons. In particular, the telencephalon was thought to have been dominated ancestrally by olfactory input and that other sensory systems later invaded the telencephalon and competed with olfactory fibers for synaptic sites, eventually establishing their own areas of pallial territory. This hypothesis may well contain at least some correct elements but for the wrong reasons. It was based on the belief that the brains of most extant anamniote vertebrates are predominantly in receipt of olfactory input and do not have the ascending sensory inputs from the nonolfactory senses that amniotes do. While olfaction was one of the earliest senses to evolve in vertebrates, the rest of the major sensory pathways to the telencephalon were also established relatively early in vertebrate history.

A more recently proposed hypothesis, Ebbesson's parcellation hypothesis, is in some respects the mirror image of the invasion hypothesis. The parcellation hypothesis holds that the brain has changed over evolution by the selective loss of connections and the concomitant segregation of neuronal populations. As opposed to new neuronal groups and connections being added in the brain over time, the parcellation hypothesis suggests that a more diffusely organized amalgam of neurons and connections goes through a process of attrition and sorting out over time, resulting in the discrete nuclei and connections present in extant vertebrate brains.

The equivalent cell hypothesis of Karten created a revolution in comparative neuroanatomy in the 1960s. This hypothesis derived from studies of ascending sensory pathways in birds and focused on the evolution of the telencephalon in amniotes. It holds that various cell populations that form nuclear groups within the dorsal ventricular ridge in birds and other nonsynapsid amniotes are comparable to groups of neurons within specific layers of mammalian isocortex that have similar respective connections. Furthermore, these cell populations in nonsynapsids and their respective comparable cell populations within isocortex in mammals were inherited from the common ancestral stock of amniotes and are thus respective homologous cell populations.

The problem of whether or not part of the dorsal pallium of ancestral amniotes was developed into a dorsal ventricular ridge or had an isocortical structure or neither has been the subject of continuing debate. Northcutt argued that expansion of the dorsal pallium occurred independently in synapsids and nonsynapsid amniotes and that parts of mammalian isocortex and the dorsal ventricular ridge are thus homoplastic.

A resolution of this question has been recently proposed by both Reiner and Butler. Each noted that, based on their distribution in extant amniotes and their absence in out-groups to amniotes, neither the dorsal ventricular ridge nor the lateral parts of isocortex were present in the common ancestral stock of amniotes. On the other hand, expansion of the dorsal pallium and the presence of certain ascending sensory pathways to specific parts of the dorsal pallium are common features of all amniotes and can thus be presumed to have characterized the common amniote stock. Thus, particular regions of the dorsal pallium in any given amniote are homologous to the respective comparable regions in other amniotes as derivatives of specific embryonic fields. The dorsal ventricular ridge and the lateral parts of isocortex are homoplastic as pallial derivatives with specific morphologies and some specific cell types.

HOW VERTEBRATE BRAINS EVOLVE

In this book, a multitude of differently evolved parts of the brain in diverse groups of vertebrates has been discussed. We can now generate at least a partial list of the variety of ways in which vertebrate brains evolve.

Induction is one of the most basic mechanisms involved in the evolution of the vertebrate central nervous system. The most salient example of this phenomenon is the origin of the vertebrate central nervous system *per se* from the nerve net-like condition of the earliest deuterostome ancestral stock. The localized condensation resulting from increased proliferation of ectodermal neural tissue along the dorsal sector of the rostrocaudal axis occurs as a result of induction by the mesoderm (the roof of the archenteron), and the caudorostral progression of the inductive process contributes to the regional specification of the nervous system. The differentiation of the neural crest, the formation of placodes, and the sensory system structures consequently induced account for some of the most momentous events in vertebrate central nervous system evolution.

A second basic mechanism of vertebrate brain evolution involves the rostrocaudal and dorsoventral specification of regions within the brain. How homeobox genes, present in the ancestral invertebrate chordate stock, shifted or extended their functional influence to specify a detailed neuromeric organization within the newly evolved central nervous system is one of the most important remaining questions in brain evolution. The neuromeric patterning established in the earliest vertebrates has been preserved in all descendant groups.

Invasion has occurred in various instances. In the earliest vertebrates, some of the new sensory systems that were developed as a result of the evolution of neural crest and placodes projected into the hindbrain and were relayed via the midbrain and diencephalon to the telencephalon. These new incoming, ascending projections and the synaptic territories that they established are perhaps the ultimate example of invasion. The evolutionary development in ancestral amniotes of new projections from the collothalamus to the dorsal pallium in addition to the existing projections to the striatum is a second example of invasion, and evidence suggests that this invasion occurred as a result of collateralization, which is one of the originally hypothesized mechanisms for invasion.

Parcellation has occurred in some instances. One of the best examples of this process may be in some of the changes associated with the elaboration of the lemnothalamus in ancestral amniotes. The single nucleus, nucleus anterior, present in anamniotes appears to be homologous as a field to multiple nuclei in the dorsal thalamus in amniotes. These multiple nuclei do not each have all of the afferent and efferent connections that the nucleus anterior has in anamniotes. The embryological development of the lemnothalamus in amniotes is such that connections and cell groups are segregated relative to the condition in anamniotes.

Loss of connections *per se,* that is, in the absence of the parcellated segregation of cell groups, has also occurred. The lemnothalamus gives rise to bilateral projections to the pallium in anamniotes. In amniotes, some of the projections to the contralateral side are maintained, but some have been lost. This loss has been most extensive in mammals.

Developmental differentiation of a specific embryonic field into multiple nuclei instead of just one nucleus has occurred in some instances. The evolution of the lemnothalamus in amniotes mentioned above is one example of this phenomenon. A second example occurs in the pretectum of acanthopterygian teleosts, where two nuclei, nuclei pretectalis superficialis pars intermedius and glomerulosus, are present instead of the single nucleus, nucleus posterior, which is present in most other groups of ray-finned fishes. Other examples of this phenomenon are the presence of new, unique nuclei within particular species or groups, such as the electromotor control systems of some electric fishes and the elaborate, descending motor pathways for vocal control in songbirds.

Duplication of neural regions has occurred in a number of instances, particularly in the evolution of isocortical sensory areas in various groups of mammals. Mutational events have occurred that have resulted in the production during development of multiple "copies" of both the lemnothalamic (VI) and collothalamic (VII) visual areas present in ancestral synapsids. Similar duplications may have occurred independently in birds, particularly in the collothalamic visual pallium.

The most frequent mechanism of central nervous system evolution may be regionally specific changes in neuron proliferation. While the specification of dorsoventral and rostrocaudal parts of the brain is regulated by homeobox gene function, differences in local neural proliferation may be under the control of other mutational events. Regional increases in proliferation usually occur in association with one of several related developmental phenomenon.

The continuation of proliferation paired with lateral migration of neurons away from the periventricular matrix accounts for the evolution of both the lemnothalamus and the collothalamus in amniotes and of the enlargement of the dorsal ventricular ridge in some diapsid reptiles and in birds. The evolutionary elaboration of the cerebellum in jawed vertebrates is a third example of this process.

The continuation of proliferation paried with migration of neurons in the presence of increased radial organization accounts for the change from an "outside-in" developmental sequence to the "inside-out" developmental sequence that produces the six isocortical layers present in most of the mammalian dorsal pallium. With a lesser degree of radial organization, nuclear groups result from neuronal migration, as is the case in the dorsal thalamus of all amniotes and in the dorsal ventricular ridge of nonsynapsid amniotes.

The continuation of proliferation paired with differentiation, as a result of mutational events, of the migrated neurons accounts for the presence of new phenotypes of neurons. An example of this phenomenon is the presence of neurons in some layers of mammalian isocortex that have neurotransmitter- and neuropeptide-specific profiles not found in the dorsal pallium of most nonsynapsid amniotes. Some neurons with mammalian-like phenotypes are present in birds, having been independently evolved as the result of similar mutational events.

Thus, evolution of the vertebrate central nervous system has occurred by the phenomena of:

- Induction.
- Homeobox gene patterning.
- Invasion.
- Parcellation.
- Loss of connections *per se.*
- Developmental differentiation of multiple nuclei
- Duplication of neural areas.
- Regionally specific changes in neuron proliferation paired with lateral or centrifugal migration, changes in the degree of radial organization, and/or differentiation of new neuronal phenotypes.

These phenomena can all be influenced by relatively simple mutational events that can thus become estabished in a population as the result of random variation. Selective pressures acting on a given population then determine whether the pheontypes produced by these random mutations increase their proportional representation within the population and eventually become established as the normal condition. The behavioral phenotypic expressions of central nervous system organization are the abilities for sensory processing, information storage, retrieval, and analysis, and motor response repertoires of the animal. The adaptive advantages conferred by an organized nervous system as opposed to a nerve net, by a variety of specific sensory input systems, by the gain of some new connections and the loss of some established connections, by the formation of multiple new nuclei through elaboration or duplication, and by regionally specific increases in cell proliferation in many different parts of the brain have determined the course of brain evolution among vertebrates.

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