

Chordate Evolution and the Origin of Craniates: An Old Brain in a New Head

ANN B. BUTLER*

The earliest craniates achieved a unique condition among bilaterally symmetrical animals: they possessed enlarged, elaborated brains with paired sense organs and unique derivatives of neural crest and placodal tissues, including peripheral sensory ganglia, visceral arches, and head skeleton. The craniate sister taxon, cephalochordates, has rostral portions of the neuraxis that are homologous to some of the major divisions of craniate brains. Moreover, recent data indicate that many genes involved in patterning the nervous system are common to all bilaterally symmetrical animals and have been inherited from a common ancestor. Craniates, thus, have an "old" brain in a new head, due to re-expression of these anciently acquired genes. The transition to the craniate brain from a cephalochordate-like ancestral form may have involved a mediolateral shift in expression of the genes that specify nervous system development from various parts of the ectoderm. It is suggested here that the transition was sequential. The first step involved the presence of paired, lateral eyes, elaboration of the alar plate, and enhancement of the descending visual pathway to brainstem motor centers. Subsequently, this central visual pathway served as a template for the additional sensory systems that were elaborated and/or augmented with the "bloom" of migratory neural crest and placodes. This model accounts for the marked uniformity of pattern across central sensory pathways and for the lack of any neural crest-placode cranial nerve for either the diencephalon or mesencephalon. *Anat Rec (New Anat)* 261:111-125, 2000. © 2000 Wiley-Liss, Inc.

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How do highly complex biological structures evolve? Can we conceive of a series of intermediate stages, each of adaptive value in itself, that could be selected for over generations of organ-

and without precedent intermediate stages? When we examine the wide range of variation across multicellular animals, it is clear that complex biological structures have arisen many times and, in many cases, seemingly rather suddenly.

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A number of recent findings on the genetic bases for morphogenesis allow exciting new glimpses into both the embryological development and the evolution of complex structures. Eyes, for example, were previously thought by some to have evolved in various taxa many different times independently (Salvini-Plawen and Mayr, 1977). From the work of Gehring and his colleagues (Halder et al., 1995), we now know that the same single regulatory gene, *Pax 6* and its homologues, is responsible for initiating the genetic cascade that produces a whole eye in vertebrates (lampreys and jawed vertebrates) and invertebrates (protostomes and nonvertebrate deuterostomes) alike (see Table

isms and that would culminate in a complex structure such as an eye or a brain? Alternatively, how could such a complex structure appear suddenly

TABLE 1. Useful terms used in discussing comparative neuroanatomy and evolution

Alar plate	The dorsal half of the developing neural tube.
Arthropod	Taxon of animals with segmented bodies and jointed limbs that includes insects and crustaceans.
Basal plate	The ventral half of the developing neural tube.
Bipolar	Type of neuron characterized by a cell body with two processes, rather than only one process or more than two processes. In craniates, this type of neuron is sensory and has the cell body located in a ganglion near the central nervous system, into which it projects.
Caudal	The direction toward or pertaining to the tail of an animal.
Cephalopod	Taxon of animals with enlarged heads and tentacles that includes octopus and squid.
Chordate	Taxon of animals with a notochord during at least part of the life cycle that comprises urochordates (ascidians), cephalochordates (lancelets), and craniates.
Craniate	Taxon of animals with migratory neural crest derivatives that comprises myxinooids (hagfishes), petromyzontids (lampreys), and jawed vertebrates.
Deuterostome	Taxon of metazoa (multicellular animals with more than one type of tissue) in which the anus forms from the blastopore (invagination of the blastula), while the mouth forms from a secondary invagination of the archenteron (primitive gut cavity); comprises echinoderms (starfishes, brittle stars, etc.), hemichordates (acorn worms), and chordates.
Dorsal	The direction toward or pertaining to the back surface of an animal.
Grade	A particular level of development or organization shared by a set of species that may or may not be within a single phylogenetic lineage.
Multipolar	Type of neuron characterized by more than two processes. In craniates, this type of neuron occurs in the brain and spinal cord and also in motor ganglia of the autonomic nervous system.
Placode	A localized thickened area of epidermis that appears on the surface of an embryo during development.
Protostome	Taxon of metazoan organisms in which the mouth forms from the anterior part of the blastopore, and the anus forms from the posterior part of the blastopore; includes most invertebrates, such as annelids, arthropods, molluscs, platyhelminthes (including planaria), and nematodes.
Pseudounipolar	Type of neuron characterized by a cell body with one T-shaped process that develops from a bipolar neuron. In craniates, this type of neuron is sensory and has the cell body in a peripheral ganglion or, in one exceptional case, within the central nervous system.
Taxon	A group of species at any rank, such as species, class, genus, or family.
Ventral	The direction toward or pertaining to the belly of an animal.
Vertebrate	Taxon that comprises petromyzontids (lampreys) and ganthostomes (jawed vertebrates), as the term is used here, or, alternatively, a taxon that also includes hagfishes.

1 for a glossary of terms). The evidence is overwhelmingly strong that this gene evolved once in the common ancestor of all bilaterally symmetrical animals. Modifications have occurred within the downstream cascade of other genes initiated by *Pax 6*, such that eye spots are produced in planaria, ommatidial eyes are produced in the fruit fly *Drosophila*, cephalopod retinal eyes are produced in cephalopods, and vertebrate retinal eyes are produced in vertebrates (Halder et al., 1995).

Large brains with elaborate cytoarchitecture are a second example of complex biological structures that until very recently were thought to have evolved independently within various groups of protostomes and within craniates (hagfishes and vertebrates). As in the case of eyes, recent new findings on regulatory gene expression during the early stages of

neurogenesis have dramatically altered our view of nervous system evolution across animals (Arendt and Nübler-Jung, 1999). The enigma of brain evolution is beginning to yield its secrets, and scenarios of how complex brains evolve can be envisioned. Some protostomes—arthropods and cephalopods in particular—have complex nervous systems with large brains. Among deuterostomes, craniates likewise have large, elaborate brains with diverse peripheral sensory systems. Craniates also are characterized by a unique set of nonneural features. Comparative analyses of living craniates indicate that the large craniate brain, a host of peripheral sensory systems, a cranium, and other unique craniate features were all gained at or about the same time (Northcutt, 1996b; Wicht, 1996; Wicht and Northcutt, 1998), at the

transition from a cephalochordate-like common ancestor (Holland et al., 1994; Holland and Graham, 1995) to craniates.

This paper reviews some of the recent new findings that illuminate nervous system evolution across the major taxic transitions, with particular attention to the origin of craniates. Major taxic transitions were correlated with crucial alterations of early developmental events, while at the same time the continuity of most regulatory genes and morphogenesis of systems was preserved. The key features of organization across nervous systems and their surprisingly common genetic bases are surveyed in selected taxa in this context. The origin of craniates in particular included multiple seminal changes. The challenge of explicating how these changes all occurred in a mutually adaptive manner is addressed.

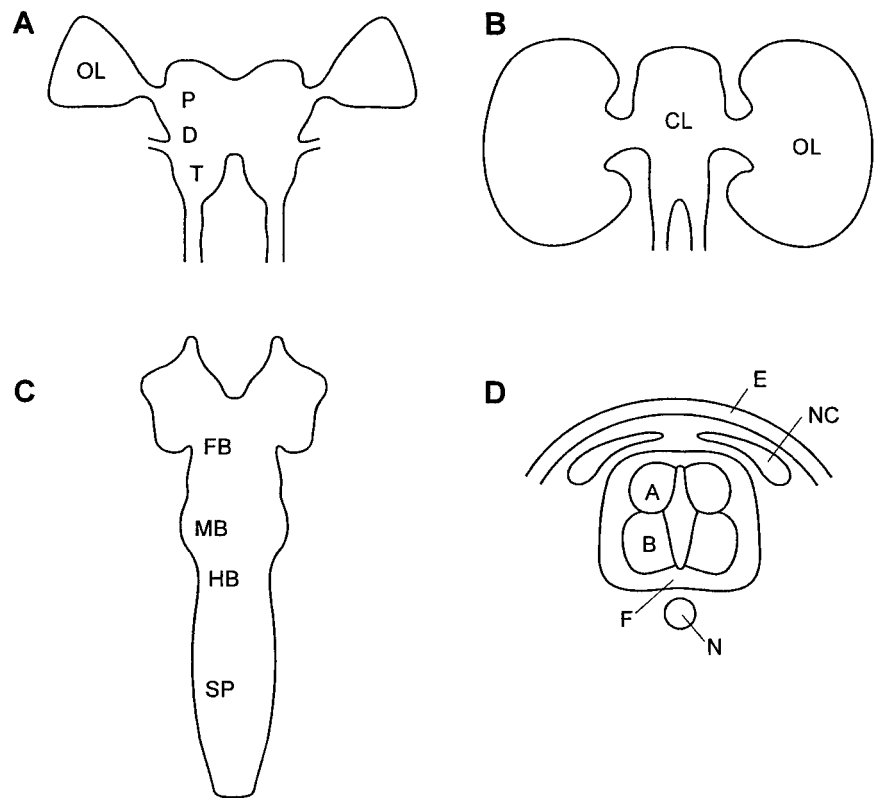


Figure 1. Schematic, generalized drawings of dorsal views of the brains of **(A)** an arthropod; **(B)** a cephalopod; and **(C)** a craniate. CL, circumesophageal lobes; D, deutocerebrum; FB, forebrain; MB, midbrain; HB, hindbrain; OL, optic lobe; P, protocerebrum; SP, spinal cord; T, tritocerebrum. **D**: Schematic drawing of a transverse section through the dorsal part of the body of a developing craniate to show the relationships of the alar (A), basal (B), and floor (F) plates in the neural tube and the positions of the notochord (N), neural crest (NC), overlying ectoderm (E). The neural crest migrates ventrolaterally.

PROTOSTOMES AND DEUTEROSTOMES: SAME GENES AND SAME BRAINS

Protostomes comprise a wide array of taxa including many different groups of worm-like organisms, molluscs (which include cephalopods such as the octopus and squid), arthropods (which include insects), and other diverse groups. Among protostomes variation in nervous system organization is extreme. In some protostome groups, such as planaria and nematodes, the nervous system exhibits a small degree of rostrocaudal differentiation and mainly comprises two nerve cords that are connected in a ladder-like pattern by a series of commissures (see Brusca and Brusca, 1990). In contrast, the nervous system has been particularly elaborated in some protostome taxa, such as arthropods and cephalopods. The rostral components of such elaborated nervous systems (Fig. 1*a,b*) comprise sets of ganglia that encircle the gut in the rostral part of the animal. These ganglia receive a variety of afferent sensory inputs, have populations of interneurons and in some cases cortical-like cellular architecture, and give rise to efferent motor projection systems

(see Brusca and Brusca, 1990). Many arthropods, for example, have rostrocaudally aligned ganglia called the protocerebrum (which receives visual input from the eyes via large optic lobes), the deutocerebrum, and the tritocerebrum. Cephalopod brains have a large number of circumesophageal lobes that are individually named, including an extremely large pair of optic lobes that receive visual input and project into the rostral part of the brain. The evolution of these collections of ganglia or lobes that can justifiably be referred to as brains has long been thought to have been completely independent of brain evolution within craniates, due in part to the great phylogenetic distance between these several groups of bilaterally symmetrical animals.

Deuterostomes comprise three major groups: echinoderms, hemichordates, and chordates (Fig. 2). The latter include craniates and the noncraniate chordates: urochordates, or ascidians (sea squirts), and cephalochordates, or lancelets (amphioxus). In deuterostome nervous systems, a nerve cord is present in the adult and/or larval forms. In chordates, which have been most extensively

studied, the nerve cord has a rostral specialization: the modestly sized cerebral (or sensory) vesicle of larval ascidians and lancelets and the large brain of craniates. Unlike the situation in protostomes, the rostral end of the nerve cord does not encircle the gut but instead lies dorsal to it.

During embryological development of the craniate brain, the hollow nerve tube comprises a ventrally situated basal plate and a dorsally situated alar plate (Fig. 1*d*). The basal plate overlies floor plate cells that play a role in the dorsoventral patterning of the brain. It contains motor neurons and interneurons and gives rise to some of the earliest longitudinal and efferent axonal pathways, or scaffolding, of the developing brain (Wilson et al., 1990). The alar plate constitutes the sensory-receptive part of the nervous system. It receives inputs from bipolar sensory neurons that for most sensory systems derive from the more laterally lying neurectoderm, the neural crest, or from placodes—thickened areas of epidermis (see Northcutt, 1996b). Neural crest consists of ectodermal cells and initially arises from the region of the lateral edge of the developing neural tube; these cells then mi-

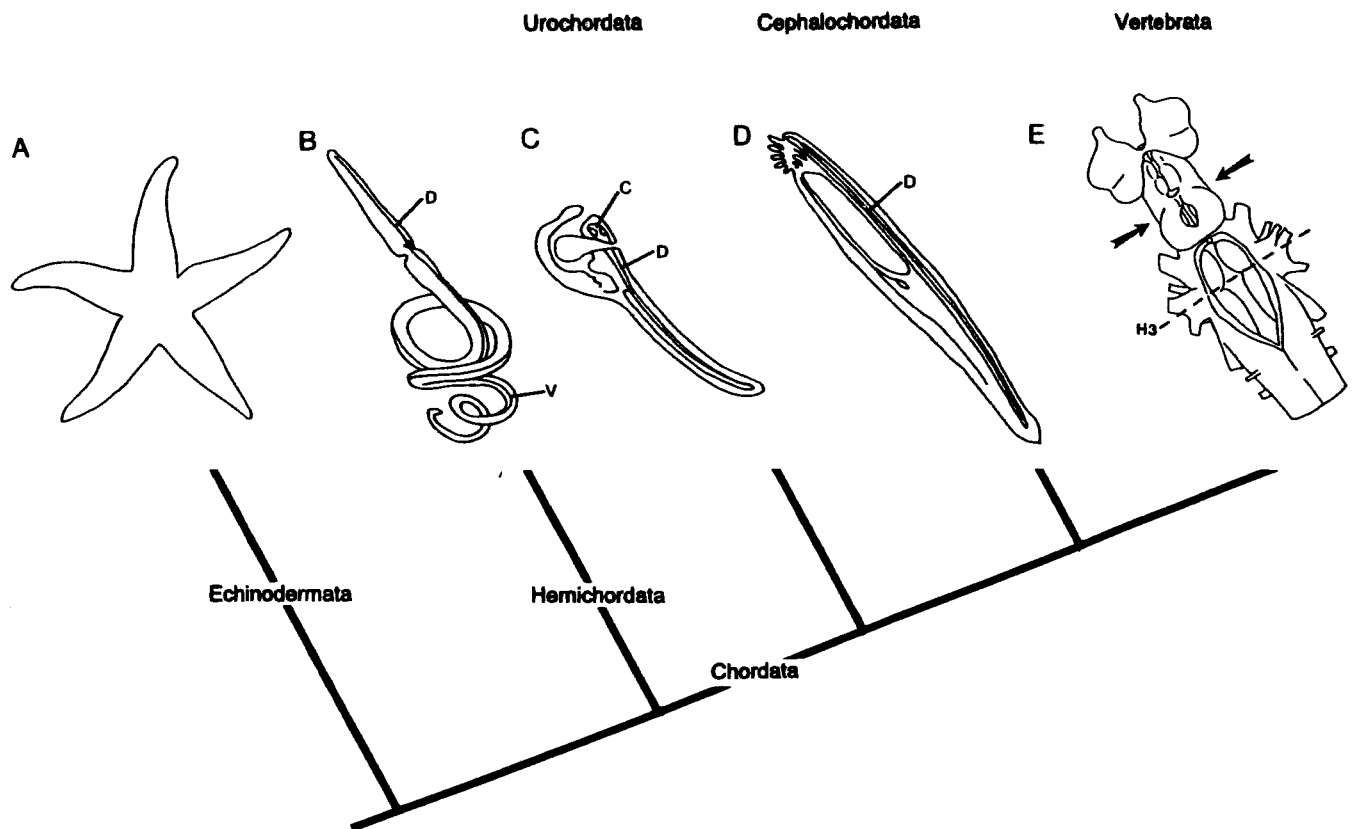


Figure 2. Dendrogram illustrating brain evolution in deuterostomes. **A:** a whole starfish (echinoderm), **B:** a whole acorn worm (hemichordate), **C:** a sagittally sectioned ascidian larva (urochordate), **D:** a sagittally sectioned lancelet (cephalochordate), and **E:** a dorsal view of the brain of a lamprey (vertebrate, i.e., representative of craniates) are shown. In the lamprey brain, the rostral expression boundary of *Hox-3* is indicated by the dashed line, and the rostral extent of the midbrain is indicated by the paired arrows. **C:** cerebral vesicle; **D:** dorsal nerve cord; **V:** ventral nerve cord. Reproduced from Butler and Hodos (1996) with permission of the publisher.

grate laterally and ventrally and contribute neurons to peripheral sensory ganglia in both the head and body as well as to the peripheral motor ganglia of the autonomic nervous system. Placodes, which are thickened patches of the surface ectoderm, also give rise to many of the neurons in the sensory ganglia in the head, just as does the surface ectoderm of both the head and body in protostomes.

The craniate brain also has three major rostrocaudal divisions: forebrain, midbrain, and hindbrain (Fig. 1c). The forebrain is subdivided into a rostral telencephalon, which includes the olfactory bulbs, and a more caudal diencephalon. The latter receives visual input via the optic nerves. It also has a visually-related dorsal-most part, the epiphysis, which in vertebrates includes the pineal apparatus. The midbrain is not divided rostrocaudally but has a more dorsal part, the tectum, which receives visual and other sensory inputs, and a more ventral part, the tegmentum, which in-

cludes some groups of motor neurons. The hindbrain comprises a rostral metencephalon (which includes the cerebellum in jawed vertebrates) and a more caudal myelencephalon, which

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is continuous caudally with the spinal cord. Until recently, little if any homologue of the craniate brain—a rudimentary hindbrain at best—was believed to be present at the rostral end of the nerve cord in any noncraniate deuterostome.

Protostomes

Recent new findings on protostome nervous systems mandate a major revision of some of our most fundamental perceptions of nervous system evolution. Until now, it has been widely believed that the elaborated nervous systems of arthropods, cephalopods, and craniates were evolved completely independently. We are now confronted with compelling evidence that not only the eyes but the whole nervous system itself is organized in essentially the same way across all bilaterally symmetrical animals and is specified by the same set of regulatory genes during development. As humans we essentially share the “same” brain not only with other primates, mammals, and craniates but also with fruit flies and octopuses.

Arendt and Nübler-Jung (1999) have recently reviewed these new findings in *Drosophila* and their stunning implications. While some basic differences do characterize nervous

system development in *Drosophila* and vertebrates, many similarities in rostrocaudal and mediolateral specification have been revealed. In *Drosophila*, the rostral part of the brain—the protocerebrum and part of the deutocerebrum—is specified by the regulatory gene *orthodenticle*, while the more caudal part is specified by *Hox* genes. This gene expression pattern corresponds to that of mammals and other craniates, where the *orthodenticle* homologues *Otx-1* and *Otx-2* specify the rostral part of the brain—the forebrain and midbrain—while *Hox* genes specify the hindbrain. As discussed below, these regulatory genes also identify comparable parts of the cerebral vesicle in ascidian larvae and lancelets.

As Arendt and Nübler-Jung (1999) discussed, the developing brain is also divided into mediolaterally aligned, longitudinal columns in both *Drosophila* and vertebrates. Some differences in regulatory gene expression occur between these two groups for the medial-most column of midline cells, although in both groups these midline cells serve as inductive centers for patterning the neurectoderm. The latter is divided into three columns in both groups—medial, intermediate, and lateral—which are, respectively, specified by homologues of the same regulatory genes. The medial column expresses *NK-2/NK-2.2*. It gives rise to the basal plate in vertebrates and to interneurons and motor neurons in *Drosophila*. In both groups, the medial column-derived cells pioneer early axonal scaffolding for long pathways within the developing nervous system. The intermediate column expresses *ind/Gsh* regulatory genes in both groups. It gives rise to the sensory-related alar plate in vertebrates and to a variety of cells in *Drosophila*, including some motor neurons. The lateral column expresses *msh/Msx*. It gives rise to neural crest lineages, including the sensory bipolar neurons and glial cells, in vertebrates and to a variety of glial cells as well as to some motor neurons in *Drosophila*.

The fates of the medial-, intermediate-, and lateral-column components, while not identical, thus have numerous and striking similarities in arthropods and craniates. The medial col-

umn motor neurons in *Drosophila* also express other regulatory genes that are the same as those expressed by a population of developing neurons in vertebrates that gives rise to the neurons of a long central tract, the medial longitudinal fasciculus, and to branchiomic motor neurons that innervate the muscles of the gill arches. As Arendt and Nübler-Jung (1999) noted, the chordate branchial apparatus and its innervation may thus have arisen from the ancestral body wall and its central motor control system, respectively. Similarly, the craniate neural crest, with its sensory neurons, glia, and numerous other derivatives, appears to share a lateral column derivation with glial and other elements in protostomes, while the intermediate column derivatives of various neurons in protostomes and the alar plate in craniates are likewise commonly inherited.

Most sensory neurons are derived from the surface ectoderm in insects, as Arendt and Nübler-Jung (1999) also discussed, and in craniates many of the sensory neurons for the cranial nerves of the head region are derived from ectodermal placodes (see Northcutt, 1996b). These populations of sensory neurons may thus also reflect a common heritage. The main difference between arthropods and craniates in terms of the peripheral nervous system would appear to be the derivation of sensory neurons for the body regions from surface ectoderm in arthropods and from neural crest cells in craniates. As discussed further below, Northcutt and Gans (Northcutt and Gans, 1983; Northcutt, 1996b) recognized the seminal role that migratory neural crest tissue played in the origin of craniates.

From the wide array of similarities in regulatory gene expression and other related data, a morphotype for the nervous system of the common ancestor of arthropods and craniates can be deduced (Arendt and Nübler-Jung, 1999). This ancestral nervous system would have had a nerve cord with a rostral brain that comprised at least a forebrain-midbrain rostral region, with visual input from paired eyes, and a caudal hindbrain region. The hindbrain region and the caudally extending spinal cord would have received non-visual sensory inputs from

a variety of sensory neurons derived from the surface ectoderm. Long axonal tracts to coordinate sensory inputs with motor outputs would have been present in the central nervous system, and motor neuronal systems for effector control of body wall muscles would also have been present.

While some of the taxa that evolved subsequent to this common ancestral form in both the arthropod and craniate lines, as well as in the cephalopod line, lacked phenotypic expression of these traits, the underlying genetic bases for their formation were nevertheless inherited from a common ancestor. The brains of fruit flies, octopuses, and humans are not homologous in the historical sense of phenotypic continuity from a common ancestor (Wiley, 1980). They are, however, the “same” brains. They are an example of syngeny, sharing the same genetic bases that have been inherited with continuity from a common ancestor (Butler and Saidel, 2000).

Chordate Origins

In early development, the process of gastrulation involves an invagination of the spherical ball of cells that form the blastula, so that an internal cavity—the archenteron, or primitive gut—with an opening, the blastopore, is formed. The protostome-deuterostome phylogenetic split involved changes in the early developmental fate of the blastopore. Nielsen (1995) postulated that while in the ancestral stock of protostomes, the blastopore divided to form both the mouth and the anus, in the deuterostome lineage a new mouth opening was acquired opposite the blastopore, with the latter then forming only the anus. Additionally, a new feeding structure, the ciliary band system, was added and has been retained in the larval forms of the descendant taxa. The latter structure consists of rows of ciliated, columnar cells that divide the surface of the organism into various domains. The beat of the cilia directs food particles toward the mouth, and the ciliary band also provides some structural support for the epithelium and for muscle attachment (Lacalli, 1996d).

With the change to a new mouth,

the position of the mouth with respect to the nerve cord shifted (see Arendt and Nübler-Jung, 1997; Nielsen, 1999). The new position of the mouth obviated the need for passage of the gut through the nerve cord, and the anatomical arrangement of ganglia encircling the gut as seen in protostome invertebrates was thereby eliminated. Arendt and Nübler-Jung (1996) noted a possible comparison of the preoptic-hypothalamic region and infundibulum of the brain of vertebrates with the stomatogastric nervous system (the part of the neuraxis that surrounds the gut) in arthropods. They suggest that the ancestral new chordate mouth would have been located in this infundibular region of the nervous system and that a prominent set of axons that encircle the stomodaeum anlage in protostomes marks this point.

A hypothesis that inversion of the dorsal and ventral surfaces of the body also occurred in the deuterostome line is supported by compelling evidence from gene expression patterns during development (see Nübler-Jung and Arendt, 1994; Lacalli, 1996a; Arendt and Nübler-Jung, 1994, 1997), confirming the original, 19th century idea of Geoffroy St. Hilaire. The gene *decapentaplegic* is expressed dorsally in *Drosophila*, while its orthologue *BMP-4* is expressed ventrally in vertebrates; thus, it is expressed on the abneural side of the animal, i.e., opposite to the nerve cord, in both groups. An antagonistic pair of orthologous genes, *short gastrulation* in *Drosophila* and *chordin* in the frog *Xenopus*, are both expressed on the neural side of the animal—ventral in insects and dorsal in vertebrates.

While arguments have been made that this inversion took place at the origin of deuterostomes, Nielsen (1999) has more recently proposed that it occurred at the origin of chordates. Nielsen (1999) postulated that a new anus was also acquired at this juncture, accounting for the anatomical relationships of the gut and the now dorsally positioned nerve cord in the chordates. This idea is supported by evidence that in echinoderms and hemichordates, the blastopore continues to give rise to the anus, as is the general case in protostomes, while a

new mouth opening to the archenteron (the cavity that will become the gut) forms as in the chordates (see Nielsen, 1999). Thus, the echinoderms and hemichordates exhibit an intermediate condition. In chordates, the formation of a new anus in addition to the new deuterostome mouth accounts for the perceived dorsoventral inversion of chordates as compared with insects, and the respective nerve tubes actually occupy comparable positions. This observation, coupled with the numerous similarities of regulatory gene expression during development as discussed above, makes a very strong case for the sameness of the nerve cord across all bilaterally symmetrical animals.

Chordates may have arisen from an ancestral larval form resembling the diplerula larvae of extant echinoderms and hemichordates, which

Chordates may have arisen from an ancestral larval form resembling the diplerula larvae of extant echinoderms and hemichordates, which have ciliary bands.

have ciliary bands. The nerve cord itself formed from fusion and infolding of part of the ciliary band in this ancestral stock (see Nielsen, 1995, 1999; Lacalli, 1996d). This idea is consistent with the hypothesis advanced by Garstang at the end of the 19th century, deriving the chordate nerve cord from converged ciliary bands of a diplerula larva. Lacalli (1996d) demonstrated how an invagination of the ectoderm at the midline between the ciliary bands in a diplerula larva is consistent with the process of vertebrate neurulation, with the ciliated cells of the band becoming incorporated into the neural tube of a chordate nervous system.

As noted above, longitudinally running axonal pathways, particularly for commissural and descending tracts, form a basic scaffolding in the early stages of chordate neural tube devel-

opment that is later used by other pathways as they grow and develop (Wilson et al., 1990). The initial axonal scaffolding of vertebrate brains is very similar in pattern to that in insects (see Arendt and Nübler-Jung, 1996; Reichert and Boyan, 1997). Below, I will discuss the idea that in the ancestral line that gave rise to craniates, these basic descending pathways, along with input from the diencephalic visual systems, served as the template for the nonvisual, ascending sensory systems.

The central nervous system in urochordate (ascidian) larvae has a so-called sensory vesicle at its rostral end. The ascidian homologue of *orthodenticle*, *Hroth*, is expressed in the anterior two thirds of the sensory vesicle (Katsuyama et al., 1996; Wada et al., 1998). As discussed above, the expression of *orthodenticle* and its homologues also characterizes the rostral part of the brain in *Drosophila* and in mammals. Based on the expression patterns of a number of genes, Wada et al. (1998) compared the ascidian sensory vesicle, "neck" region, and more caudal parts of the nerve cord to the mouse forebrain, midbrain, and hindbrain and spinal cord, respectively. Other work on *orthodenticle* homologues and other gene expression patterns by Williams and Holland (1998) compared the sensory vesicle to the forebrain and midbrain of mammals and the neck of the ascidian larval nervous system to the more caudal isthmal region between the midbrain and hindbrain of mammals. Thus, while the exact correspondence has not been resolved, there is clear evidence for forebrain vs. hindbrain regions of the rostral neural tube in ascidian larvae. Ascidiates also exhibit possible precursors of the craniate neural crest/or placodal tissues. Wada et al. (1998) postulated that the expression pattern of another patterning gene, *HrPax-258*, indicates that a sensory organ derived from a placode-like epidermal thickening in ascidiates may be a homologue of the craniate ear.

Lancelets, the sister group of craniates, appear to be a fairly close approximation of the mutual common ancestor (Garcia-Fernández and Holland, 1994; Holland et al., 1994; Holland and Garcia-Fernández, 1996).

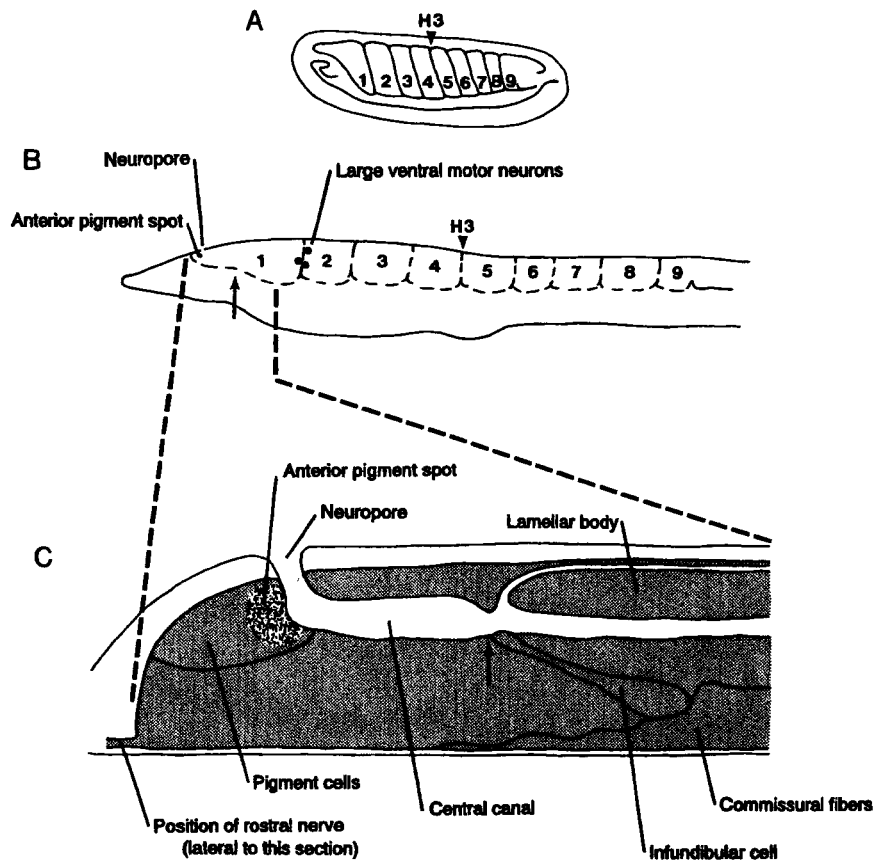


Figure 3. Semischematic drawings of parasagittal sections through (A) an early developmental stage of a lancelet and (B,C) a larval lancelet. Rostral is toward the left. Somites numbered 1–9 are shown in A and B, and H3 with arrowhead indicates the rostral boundary of *Hox-3* expression. An enlargement of the rostral part of the cerebral vesicle (shaded area), which lies medial to somite 1, is shown in C. Reproduced from Butler and Hodos (1996) with the permission of Wiley-Liss, Inc.

Noncraniate chordates were long thought to have at most a primordial hindbrain at the rostral end of their central nervous systems. The more rostral parts of the chordate neuraxis were thought to be unique to craniates, particularly the two major subdivisions of the forebrain, the telencephalon and diencephalon. In larval lancelets, a cerebral vesicle lies at the rostral end of the neuraxis, which corresponds to the ascidian sensory vesicle.

Several structures that lie within the cerebral vesicle have been identified by Lacalli and his co-workers (Lacalli et al., 1994; Lacalli, 1996b,c) as probable homologues of diencephalic structures of most craniates (Figs. 3, 4). An unpaired frontal organ, or eye, is a cluster of pigmented and associated cells that lies immediately rostral to a neuropore and marks the position of the original anterior margin of the neural plate. It appears to be the homologue of the paired, lateral eyes of craniates. The cells of the frontal eye may include elements homologous to both photoreceptors and some of the neurons of the retina of crani-

ates. The lamellar body, a set of cells that produce stacks of membraneous lamellae, appears to be homologous to the pineal of vertebrates [no epiphyseal structures have yet been identified in hagfishes (see Wicht, 1996)]. A set of infundibular cells appears to be homologous to the craniate infundibulum. Also, a balance organ, which consists of a small group of ciliated accessory cells located immediately rostral to the infundibulum, appears to be homologous to part or all of the hypothalamus of vertebrates (Lacalli and Kelly, 2000).

The above comparison of the various parts of the cerebral vesicle to the diencephalon of craniates is highly corroborated by recent findings on the expression of the homeobox gene *AmphiOtx* (the lancelet homologue of *orthodenticle*) in this region (Williams and Holland, 1996, 1998). The expression pattern supports homology of the region of *AmphiOtx* expression in the lancelet cerebral vesicle to the forebrain and midbrain of vertebrates (Simeone et al., 1993) as well as to the sensory vesicle of ascidian larvae and the rostral part of the brain in *Dro-*

sophila. This scenario is also consistent with the expression pattern of the *Distal-less* homologue *AmphiDll* in the developing lancelet (N.D. Holland et al., 1996). Cells near the anterior end of the neural plate that come to lie in the dorsal part of the neural tube express *AmphiDll*; these and another, additional group of *AmphiDll*-expressing cells lie within the anterior three fourths of the cerebral vesicle. This finding supports the homology of this part of the neural tube to the region of *Distal-less*-related gene expression in the vertebrate forebrain. Also, *AmphiDll* is expressed in laterally lying epidermal cells that migrate over the curling neural plate, suggesting a possible homology of these cells with craniate neural crest tissue.

In the putative lancelet midbrain, Lacalli (1996b,c) described a roof area, or tectum, that contains cells distinctive in their lack of an apical connection to the central canal and a ventral part that contains the anterior portion of a ventrally lying set of motor neurons, the primary motor center (PMC), that projects to the spinal cord. The latter neurons appear to

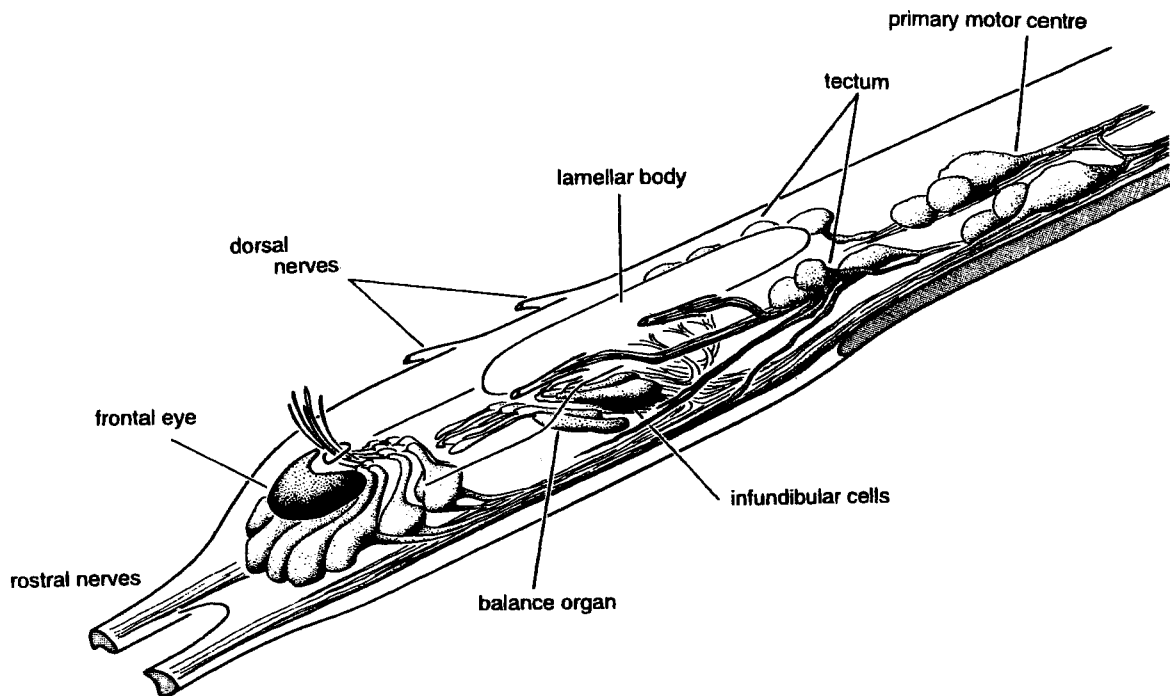


Figure 4. Semischematic drawing of a dorsolateral view of the anterior end of a 12.5 day lancelet larva, showing the rostral nervous system structures including the frontal organ (eye), infundibular cells, and lamellar body of the cerebral vesicle and the more caudally lying tectum and primary motor centre. Reproduced from Lacalli (1996b) with permission of the publisher.

correspond to the reticulospinal neurons in the midbrain and hindbrain of craniates (Fritsch, 1996) and presumably are involved in the production of undulatory swimming movements and startle responses (Lacalli, 1996b,c). Lacalli (1996b,c) described three pathways that link the frontal eye cells to PMC cells, including a “receptor-tectal” pathway from the receptor cells to tectal cells and hence to PMC cells.

In lancelets, the identification of a hindbrain region is strongly supported by the pattern of expression of *Hox* genes. The expression of *Amphi-Hox3* (Fig. 3), for example (Holland et al., 1992), is comparable to the expression of *Hox3* in vertebrates (Hunt and Krumlauf, 1991). Considering the expression pattern of the *Engrailed* gene in lancelets, which extends into the region of the caudal part of the cerebral vesicle (L.Z. Holland et al., 1996), Fritsch (1996) posited that the rostral-most motoneurons in the lancelet might be comparable to the trigeminal motor neurons of craniates. The weight of the current evidence strongly suggests that the craniate hindbrain is homologous to a region of the lancelet neural tube caudal to the cerebral vesicle (Holland, 1996)

and that a clear midbrain-hindbrain boundary is present caudal to the cerebral vesicle (Williams and Holland, 1998).

In the head region of lancelets, peripherally located sensory cells (Demski et al., 1996; Fritsch, 1996), a pair of rostral nerves (Lacalli, 1996b,c), and several small dorsal roots (Fritsch, 1996; Lacalli et al., 1994) are present. Fritsch (1996) found that the sensory cells project through the first two dorsal sensory nerves into the anterior part of the neuraxis as far as the caudal end of the lamellar body, i.e., that part of the rostral neuraxis that has been compared to the hindbrain region of craniates. He noted that the weight of current evidence favors a hypothesis that the anlagen of the various sensory organs and cells may thicken into placodes and give rise to sensory receptor and bipolar ganglion cells in craniates. Likewise, Rohen-Beard cells and other intramedullary dorsal cells are present in the lancelet spinal cord, pointing to the presence of nonmigratory neural crest tissue in cephalochordates (Fritsch and Northcutt, 1993; Fritsch, 1996). Fritsch and Northcutt (1993) proposed that the cranial and spinal nerves of craniates may be serial ho-

mologues derived from a lancelet-like dorsal spinal nerve pattern.

Lacalli (1996b,c) noted that the frontal eye and its links to the PMC may be involved in establishing and maintaining the orientation that lancelets assume in the water column for feeding, maximally shading the frontal eye, and possibly in increasing the startle response when illumination changes occur. He postulated that the midbrain may have become expanded in vertebrates in conjunction with the gain of image-forming eyes. Lacalli (1996b,c) also stated that the “expansion of the [vertebrate] forebrain during evolution could have involved the stepwise addition of blocks of tissue that would resemble segments, without being part of an actual segmental series,” an idea that anticipates part of the serial transformation hypothesis presented here.

Craniatic Brain

Each of the three rostrocaudal divisions of craniate brains—forebrain, midbrain, and hindbrain—has specific cranial nerves that are associated with it. The motor nuclei for these nerves lie within the basal plate, and sensory nuclei lie within the alar

plate. As many as twenty-two cranial nerves are now recognized in most aquatic craniates (Butler and Hodos, 1996; Hodos and Butler, 1997). Three of these cranial nerves have only motor components; these innervate the extraocular muscles that are present in lampreys and jawed vertebrates. Ten have only sensory components, and the remainder have both sensory and motor components. The latter mixed nerves innervate the muscles of the visceral arches—the mandibular, facial, and several branchial arches of the gill or throat region.

Of the purely sensory nerves, two are related to the visual system—the optic nerve of the retina and the epiphyseal nerve, which originates in the pineal and/or other epiphyseal component in the dorsal midline of the diencephalon. The additional sensory cranial nerves include chemical sense nerves for olfaction and taste, the trigeminal nerve for touch and related modalities of the head, several lateral line nerves for electrosensory and mechanosensory modalities, and the vestibulocochlear (statoacoustic) nerve for balance and hearing senses. The full set of cranial nerves—both motor and sensory—are complemented by a series of segmental spinal nerves that supply touch and related sensory modalities as well as efferent motor innervation for the body.

The receptors for the various sensory nerves of the head and body are diverse in their structure and their transduction mechanisms. This peripheral diversity contrasts with the striking similarity in the basic organization of the central multisynaptic sensory pathways. As modified from an original idea of Shepherd (1974) that compared olfactory and visual pathways, similar organization of central pathways (Fig. 5) can be recognized across all craniate sensory systems (see Butler and Hodos, 1996; Hodos and Butler, 1997). The similarity begins with the bipolar (or pseudounipolar) element in the neuronal chain, whether or not the receptor element is separate from it. In all sensory systems, the bipolar neurons terminate on groups of multipolar neurons within the central nervous system that in turn project to other groups of multipolar neurons. The various groups of neurons that receive

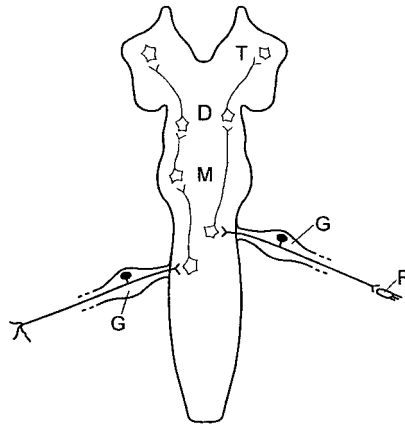


Figure 5. Schematic, generalized representation of a dorsal view of a craniate brain, with rostral toward the top. Two sensory ganglia (G) of the peripheral nervous system are shown containing the neuron cell body of a sensory bipolar neuron that either has its own sensory-receptive ending, as on the left, or innervates a separate sensory receptor cell (R), as on the right. Each type of bipolar neuron can give rise to either and/or both of the two types of central pathways illustrated. On the right a pathway that projects from the first-order multipolar neurons (FOMs) of the alar plate directly to the diencephalon (D) is illustrated. On the left a pathway that projects from the FOMs to the diencephalon via a relay in the midbrain (M) is indicated. In all cases, the diencephalic alar plate neurons, in turn, project to the telencephalon (T).

the bipolar neuron inputs are the first multipolar neurons in the sensory pathway and are thus referred to here as *first-order multipolar neurons*, or FOMs.

Most sets of FOMs project via one or two pathway formats—either directly to various parts of the diencephalon and/or to the diencephalon via a synaptic relay in the midbrain tectum. For example, the visual system bipolar neurons project to retinal ganglion cells, which are the FOMs of this system. The retinal ganglion cells then project to the diencephalon directly and also project to it via the roof of the midbrain. Likewise in the somatosensory system, the bipolar dorsal root ganglion cells project to their FOMs, the dorsal column nuclei, which in turn project to the diencephalon directly and also via the roof of the midbrain. In the auditory and lateral line systems, only midbrain roof pathways to the diencephalon are present. The olfactory system differs in one regard: the mitral cells that constitute its FOMs—comparable to the retinal

ganglion cells as Shepherd (1974) noted—project to the diencephalon via the olfactory cortex of the telencephalon rather than via the midbrain roof.

First-order multipolar neurons also constitute the sensory nuclei of other systems, including the vestibular, gustatory, and trigeminal (for face and jaw innervation) systems, as well as pain and temperature-sensing neurons within the spinal cord, and have similar ascending pathways to the diencephalon, either directly or via the midbrain roof. We can thus note that a fundamental principle of craniate sensory system design is the contrast between an extensive diversity of physical stimuli, receptor morphology, and transduction mechanisms in the peripheral parts of the systems and the remarkable uniformity in the organization of the central pathways (see Hodos and Butler, 1997).

For most sensory systems in craniates, the bipolar neurons and, where present, the specialized receptor cells, are both derived from migratory neural crest and/or placodes (see Northcutt, 1996b). A major advance in understanding the evolution of the nervous system and other major structures unique to craniates was made by Northcutt and Gans (see Northcutt and Gans, 1983; Northcutt, 1996b) with their insights on the origin and role of migratory neural crest and placodes in the transformation to the craniate grade. Based on findings by a number of workers, they recognized that most of the tissues of the head that were newly acquired by the first craniates arise embryologically from migratory neural crest and/or placodes, including special sense organs, the lens of the eye, and the bipolar (including pseudounipolar) neurons of nonvisual cranial nerve ganglia and spinal nerve ganglia. The special sense organs include the auditory, vestibular, and lateral line receptors, while the bipolar sensory neurons include the bipolar receptor cells for the olfactory and somatosensory systems, with their distally-modified receptor endings, as well as the bipolar neurons of the sensory ganglia of the auditory, vestibular, and lateral line systems. Among non-visual receptor cells, only the taste buds do not arise from migratory neural crest or

placodes but instead simply arise from the oral endoderm (see Northcutt, 1996b). Northcutt and Gans (1983) identified the gain of migratory neural crest and placodes as a fundamental and crucial evolutionary change that occurred at the origin of craniates.

From comparative analyses of craniate brains, a morphotype of the brain in the earliest craniate stock can be constructed (Wicht and Northcutt, 1998; Wicht, 1996). In marked contrast to cephalochordates, the ancestral craniate morphotype had a plethora of unique features, which included a telencephalon with pallial and subpallial parts, paired olfactory bulbs with substantial projections to most or all of the telencephalic pallium, paired lateral eyes and ears, a lateral line system for both electroreception and mechanoreception, spinal cord dorsal root ganglia, and an autonomic nervous system. In addition to ascending sensory pathways as discussed above, descending, motor-related pathways from various forebrain and midbrain areas were present. Comparison with cephalochordates (Lacalli, 1996b,c) suggests that the ancestral craniates also possessed a median epiphysis even though extant hagfishes lack this structure (see Wicht, 1996).

The many new features and extensive central pathways that constitute the craniate brain morphotype were acquired from a common ancestor shared with cephalochordates and resembling extant cephalochordates in many if not all features. The brain of ancestral craniates was newly elaborated, i.e., expanded and composed of multiple new cell types and neuronal groups, but noncraniate chordates have clearly homologous major divisions—including the diencephalon with both retinal and pineal visual systems, a putative midbrain region, and a hindbrain—and protostomes have similar forebrain/midbrain and hindbrain divisions under the same regulatory gene control. Thus, we now realize that most of the brain per se was not “new” in craniates. It was, in fact, not only shared with other chordates but also preceded by the brains achieved in other radiations of

bilaterally symmetrical animals, such as arthropods and cephalopods.

The single seminal change in nervous system evolution that occurred at the origin of craniates and that can now be identified as new was the derivation of most of the sensory components of the peripheral nervous system from migratory neural crest and thickened ectodermal placodes, rather than from general ectoderm. As Northcutt and Gans (1983) realized, the new head achieved with the gain of migratory neural crest and placodes was, indeed, the craniate hallmark, allowing the gain of the craniate type of peripheral nervous system along with the plethora of other derivatives of the migratory neural crest. The latter include large parts of the skull, the sensory capsules, branchial bars, chromaffin cells, melanocytes, and muscle of the aortic arches (see Northcutt, 1996b). Thus, craniates have an “old” brain in a new head.

CRANIATE TRANSITION: CONCURRENT GAIN OR SERIAL TRANSFORMATION?

The transition to the new craniate head was indeed a sudden event of considerable complexity. Whether this event occurred simultaneously with the elaboration of the brain is a question that has been little explored in the literature to date. That these two events were at least approximately concurrent (Holland and Graham, 1995) is a reasonable deduction. Northcutt (1996b) proposed that the origin of craniates was rapid and “without transitional forms.” One must indeed ask how an organism could derive any benefit from the gain of a peripheral sensory nervous system without the capacity to also generate the central nervous system cell groups and pathways that process the afferent information.

An explication of how these two events could have been linked and occurred simultaneously has not been offered, however. The regulatory genes that specify the central nervous system are different from those that specify the periphery and cannot be assumed to have upregulated as a unit. The alternative question to con-

sider is how an organism could derive any benefit from the elaboration of its brain in the absence of any peripheral nervous system with afferent sensory inputs. This question easily yields an answer. The elaboration of the brain across bilaterally symmetrical animals often includes elaboration of paired, enlarged eyes. In craniates, the retinas of the lateral eyes derive from the diencephalon¹ itself rather than from neural crest or placodes, or from surface ectoderm as in *Drosophila* (see Halder et al., 1995). An elaborated visual system with descending pathways to motor neuronal pools in the hindbrain could bestow a major selective advantage for an organism that was not yet a craniate but profoundly different from its immediate cephalochordate-like predecessor.

As Holland and Graham (1995) discuss, antagonism between a medially expressed, neural-inducing factor and a more laterally expressed, neural-repressing factor could have resulted in the formation of a neural plate and its derivatives in the ancestral line of chordates. A small shift in the medio-lateral gradient of this expression pattern might account for a serial transformation of the nervous system within the ancestral craniate lineage. Essentially, taking extant cephalochordates as an approximate ancestral model for craniates (Fig. 6A), I

¹The term diencephalon as used here includes the region identified as the ventral part of the secondary prosencephalon by Puelles and Rubenstein (1993), which predominantly comprises the hypothalamus and also gives rise to the eye stalks and the developing retinas. It is of note that in their prosomeric model of brain development in mammals, the eye stalk forms at the rostral-most part of the neuraxis except for the overlying telencephalon. Comparably in lancelets, as discussed in the text, the frontal organ, or eye, is located at the rostral-most limit of the neuraxis (Lacalli, 1996b,c), and a region that appears to be homologous to at least part of the craniate hypothalamus is present ventral to this frontal organ (Lacalli and Kelly, 2000).

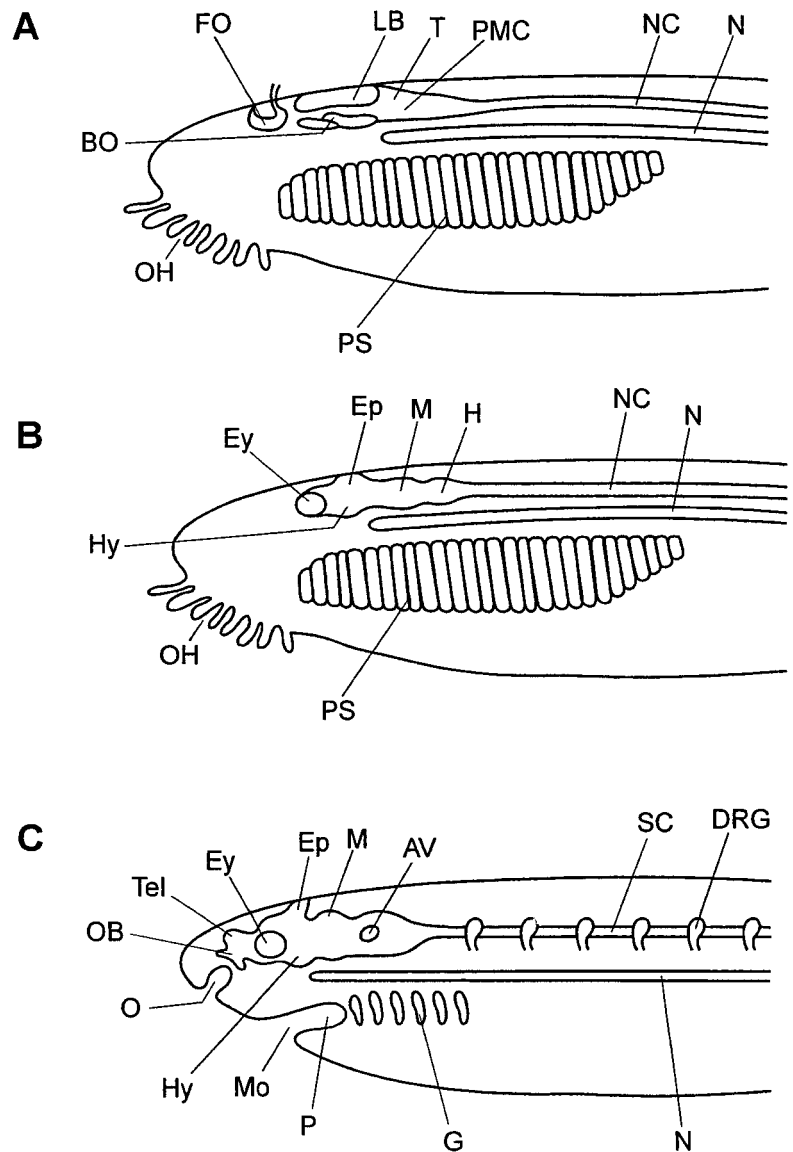


Figure 6. Lateral, schematic, generalized views, using the conventions of Walker and Liem (1994), of the rostral part of the body of (A) a hypothetical cephalochordate as a model of the common ancestor of modern lancelets and craniates; (B) a transitional "cephalate" with elaboration of paired eyes and the alar plate regions of the diencephalon and mesencephalon; and (C) a developing, extant craniate, with the addition of the telencephalon and craniate-type neural crest-placode peripheral sensory systems and other neural crest derivatives. In the hypothetical common ancestral cephalochordate, the notochord does not extend as far rostrally as in extant lancelets, based on comparison with the condition of the notochord in extant ascidian larvae; in all cases shown here, the notochord does not extend rostrally beyond the approximate midbrain-forebrain border. AV, cranial auditory-vestibular organ; BO, balance organ; DRG, dorsal root ganglion; Ey, lateral eye; Ep, epiphysis; FO, frontal organ; G, gill slit; H, hindbrain; Hy, hypothalamus; LB, lamellar body; M, midbrain; Mo, mouth; N, notochord; NC, nerve cord; O, olfactory organ; OB, olfactory bulb; OH, oral hood; P, pharynx; PS, pharynx with pharyngeal slits; PMC, primary motor center; SC, spinal cord; T, tectum; Tel, telencephalon.

propose that an initial transition occurred to a grade roughly approximating an insect or cephalopod brain in a noncraniate chordate body—a creature that one might call a "cephalate" (Fig. 6B). This stage would have had an elaborated alar plate such that the diencephalon would have been enlarged, and the paired eyes would form as evaginations from it. The alar plate of the midbrain roof would likewise have been enlarged to form a definitive midbrain, and existing descending visual pathways to motor centers of the midbrain and hindbrain would have been expanded upon. Lesser inputs from epidermally-derived sen-

sory neurons would also have been present. This "cephalate" condition would then have made the further transition to the craniate grade (Fig. 6C) with the bloom of the migratory neural crest and ectodermal, neurogenic placodes. This model of a serial transformation is an extension of the conclusions of N.D. Holland et al. (1996) and of Williams and Holland (1996), who postulated that "a distinct differentiated forebrain evolved before the separation of cephalochordates and vertebrates, predating skeletal tissues, migratory neural crest and elaboration of the vertebrate genome," and it is based on several lines of evidence.

Evidence for Serial Transformation

First, a simple observation is telling. Elaborated brains with paired eyes have occurred multiple times across bilaterally symmetrical animals, while the craniate-type of migratory neural crest and ectodermal placodes has occurred only once. While invertebrates clearly have precursors of the latter tissues, the elaboration of them into the craniate-type of peripheral nervous system with sensory nerve ganglia and into multiple new nonneural tissues is unique to craniates. Thus, elaborated brains with paired eyes, specified by the same set of regulatory

genes, can occur without the elaboration of craniate-type neural crest and placodes. Also of note, the converse condition—elaboration of neural crest and placodes absent an elaborated brain with paired eyes—has never been documented. Second, an equally fundamental observation is that in craniates, no populations of first-order multipolar neurons that receive input from neural crest/placode-derived sensory systems exist in the diencephalon or midbrain (see Butler and Hodos, 1996). This absence is remarkable in that such peripheral nervous system sensory systems occur throughout all other levels of the neuraxis: telencephalon, hindbrain, and spinal cord. This difference allows for the possibility that the retinal ganglion cells, the FOMs of the paired eye visual system, were established prior to the gain of the craniate-type of peripheral nervous system. When the latter arrived, the diencephalic and mesencephalic alar plate capacity to form FOMs was already spoken for by the visual system, resulting in the formation of FOM sites for the neural crest/placodally-derived systems only in the rest of the neuraxis.

Third, during development in craniates, the neural plate and the neural folds give rise to different structures. As Northcutt (1996b) has discussed, differences in neurulation between lancelets and craniates may account for the major differences in both alar plate and neural crest and placode derivatives in these groups. In lancelets, the neural plate overgrows to form the neural tube without folding of the tissue along the border of the neural plate with the adjoining epidermis. In contrast, vertebrate gastrulation is characterized by the formation of double-walled neural folds at the lateral and anterior aspects of the neural plate; the inner walls of these longitudinal and transverse neural folds give rise to portions of the alar plate as well as to neural crest cells, while the lateral walls of these folds give rise to part of the cephalic epidermis and to placodes. As demonstrated by Eagleston and Harris (1990), the alar plate components derived from the neural folds include most if not all of the telencephalon and, more caudally, parts of the brainstem and most of the cerebellum, while the neural plate it-

self gives rise to the retina, dorsal and ventral thalamus, hypothalamus, and most of the rest of the brainstem. As Northcutt (1996b) discussed, the parts of the vertebrate brain that are derived from the longitudinal and transverse neural folds, including the telencephalon, may be uniquely derived in craniates. In contrast, the neural plate gives rise to most of the diencephalon with the paired eyes as well as to most of the midbrain, hindbrain and spinal cord—structures that have syngenogues (corresponding structures with the same genetic specification) in insects and homologues in lancelets.

A transitional form that preceded craniates thus could have elaborated the neural plate tissue, similar to brain development in insects for example, without elaborating the more

**Evidence from
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laterally lying ectodermal region that forms the neural fold tissue in developing craniates. The known underlying contributions of regulatory genes to the formation of the neural plate and related structures (see Lumsden and Krumlauf, 1996; Kerszberg and Changeux, 1998; Rubenstein et al., 1998) allow for this possibility. Initially, neural tissue development is antagonized by a repressive influence of bone morphogenetic proteins (BMPs), which promote epidermal fate. In the medial region that will give rise to the neural plate, BMPs are inhibited by the expression of *chordin*, which is produced by cells in the underlying notochord, allowing the formation of the neural plate. An alteration of the mediolateral interaction of BMPs and *chordin* could thus contribute to a

more “medially restricted” nervous system, as in lancelets and insects, or a more “laterally expansive” one, with the addition of the craniate-type of elaboration of migratory neural crest and placodes. As Northcutt (1996b) has noted, small alterations in medio-lateral transduction events during neurulation may have been of crucial significance for craniate evolution.

Finally, evidence from regulatory gene expression studies allows for a common cephalochordate-craniate ancestor with either paired lateral eyes or a single, medial eye, as in extant lancelets. A notochord product that is produced by the floor-plate cells of the neural plate due to the expression of the gene *sonic hedgehog* (*Shh*) contributes to the dorsoventral differentiation of alar and basal plates and is also involved in the development of the paired eyes (see Rubenstein and Beachy, 1998; Rubenstein et al., 1998). While the homeobox gene *Pax 6* functions as a master regulator gene for initiating eye formation, as discussed above, interruption of the *Shh* signal results in the production of a single, median, cyclopic eye (Chiang et al., 1996). As Lacalli (1994) has pointed out, while the frontal organ, or eye (which incorporated the apical organ of nonchordate deuterostomes) is unpaired in lancelets, instances of both single and paired apical organs occur across various species of echinoderm larvae, and the latter develop by an initial midline outgrowth followed by a splitting process, as is the case for the paired eyes of vertebrates. Thus, paired eyes could already have been present in the common ancestor of extant cephalochordates and craniates.

Implications for Craniate Evolution

A serial transformation scenario has several fundamental implications for brain evolution in craniates. One such implication is that elaboration of visual system pathways previous to the elaboration of the neural crest-placodal peripheral nervous system would account for the uniformity of central sensory pathways. The scaffolding provided by *descending* visual system pathways—from diencephalon to midbrain to motor neuronal

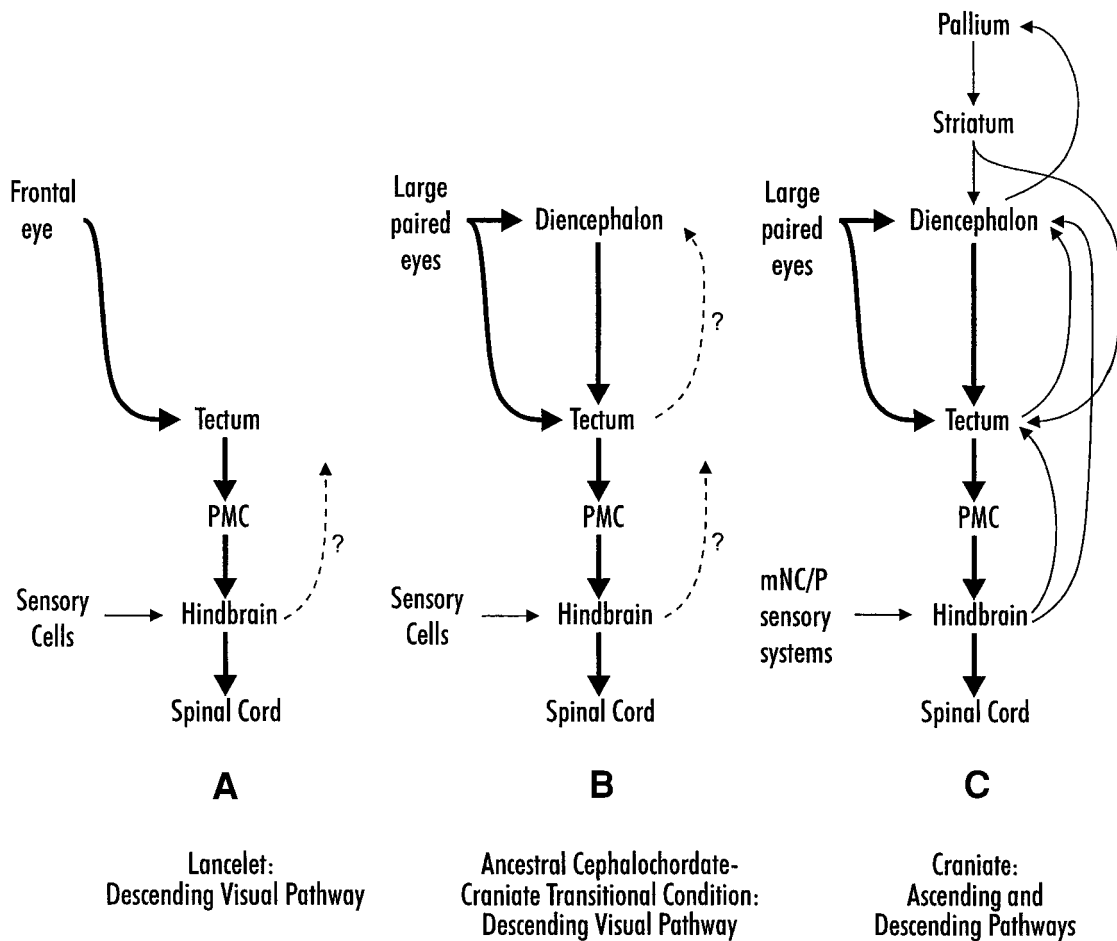


Figure 7. Schematic diagrams of known visual system connections in the (A) the lancelet brain with a descending visual pathway; (B) the hypothesized “cephalate” brain representing the ancestral cephalochordate–craniate transitional condition; and (C) extant craniates. In the “cephalate” brain, paired eyes are present, and the descending visual system pathway via the diencephalon and midbrain tectum is augmented, while in extant craniates the telencephalon (pallium and striatum) is added with afferent input from the diencephalon, and additional, craniate-type, neural crest–placode, sensory pathways are added that use the same alar-plate template as the descending visual pathways. mNC/P, migratory neural crest and placodes; PMC, primary motor center.

pools—could have served as a template for the patterning of the *ascending* pathways of the neural crest–placode systems (Fig. 7). For most of these pathways, the various sets of FOMs are located in the hindbrain and spinal cord rather than in the diencephalon, and their projections to the midbrain and diencephalon are thus regarded as “ascending.”

Lancelets have only a descending visual pathway, from the diencephalic frontal eye to the midbrain tectum and, via the PMC, to the spinal cord (Lacalli, 1996b,c). Such descending pathways are also present in some extant craniates: for example, within the diencephalon, the anterior nucleus of the dorsal thalamus and some of the pretectal nuclei project to the midbrain optic tectum in some teleost fishes (Northcutt and Wullimann,

1988) and in frogs (Neary and Wilczynski, 1979, 1980). A subsequent gain of the telencephalon and other structures derived from the neural crest and the elaboration of migratory neural crest and placodes (see Northcutt, 1996a,b) would have then provided the ultimate rostral destination for sensory projection systems (see Fig. 7) that were already established via the visual system to the penultimate site of the diencephalon.

The second implication involves homology of the various populations of alar plate first-order multipolar neurons. FOM-type circuits predate craniates. They can be identified in lancelets (Lacalli, 1996b) and arguably in various invertebrates. They represent a basic capacity of the chordate alar plate and comparable central nervous tissue in nonchordate invertebrates to

produce sensory-receptive neuronal pools. This capacity extends along the entire rostrocaudal extent of the alar plate and was of fundamental importance for the transition to craniates. The bipolar sensory neurons derived from migratory neural crest and placodes in craniates might not qualify as serial homologues of retinal bipolar neurons, due to the significant lateromedial difference in their ectodermal derivation. On the other hand, one can deduce that the FOMs for the neural crest/placode sensory systems are serial homologues of the retinal ganglion cells: all of these FOMs are alar plate, sensory-receptive neuronal populations that have the capacity to be generated and/or maintained given the presence of the sensory input.

That the craniate central nervous system has the potential to generate

and/or maintain several sets of alar plate, multipolar neurons to form an ascending sensory pathway for a new set of ingrowing bipolar sensory axons is elegantly demonstrated by the electrosensory lateral line system of fishes. Despite phenotypically independent evolution of electroreceptors and their afferent bipolar neurons and receptors at least several times among teleosts (Bullock et al., 1983), the central FOM target in these fishes—the electrosensory lateral line lobe—is similar in its position in the brainstem and in its ascending projections to the diencephalon via the midbrain roof. Further, these pathways mimic the corresponding electrosensory pathway in cartilaginous fishes (see Butler and Hodos, 1996). The FOMs in each case project rostrally to the diencephalon via a relay in the midbrain (and from the diencephalon to the telencephalon), just as auditory and other midbrain-relayed sensory systems do (see Hodos and Butler, 1997). In the many fishes that are not electroreceptive, no corresponding set of central cell groups is present. The similarity of pattern for “new” central pathways is exhibited for other modalities as well, such as in the unique trigeminal pathway that is present in infrared-detecting snakes (see Hodos and Butler, 1997). A possible explanation for being able to add on an additional sensory system in the same pattern as other sensory systems, i.e., serially homologous, alar plate FOMs projecting to their own midbrain and diencephalic targets, derives from postulating use of the same template established by the original visual system pathways.

The third implication is that a simple mediolateral shift in *BMP/chordin* expression can significantly contribute to the specification of nervous system morphology across all bilaterally symmetrical animals. Such a shift could successively produce nervous systems of the planarian-nematode grade, the cephalochordate grade, the arthropod-cephalopod grade, and the craniate grade. In the first of these grades, the nervous system is derived from the epidermis (see Brusca and Brusca, 1990). In the second and third grades, its components appear to correspond to the neural plate-derivatives of the craniate nervous system.

The fourth grade adds neural fold derivatives. In the second and perhaps even the first of these grades, the fundamental rostrocaudal divisions of the central nervous system are established, with the diencephalon being the most rostral division and the sensory neurons predominantly derived from simple surface ectoderm. In the arthropod-cephalopod grade, the central nervous system is enlarged and elaborated, and paired eyes are present. In the craniate grade, the migratory neural crest/placodally-derived peripheral nervous system with its sensory ganglia blooms, and the telencephalon, some components of the brainstem, and nonneural migratory neural crest derivatives are added. At least in these respects, the transition of the nervous system from the cephalochordate grade to the craniate grade may have involved a serial transformation through the arthropod-cephalopod grade.

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