REVIEW ARTICLE

Invertebrate Versus Vertebrate Neurogenesis: Variations on the Same Theme?

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INTRODUCTION

The morphology of a vertebrate body appears very different from that of, for example, a worm or a fly. However, it has become obvious from molecular, genetic, and developmental studies that this apparent diversity does not necessarily reflect fundamental differences in the molecular mechanisms that underlie pattern formation in these different species [for review, see Laufer and Marigo, 1994]. Indeed, many gene products that are conserved in structure and function throughout evolution have been identified and the animals that we study seem more similar every day [for review, see Bodmer, 1995; Laufer and Marigo, 1994; Littleton and Bellen, 1995; Bonhoeffer and Sanes, 1995]. Most recently, another striking example was added to a fast growing list of genes, as the Drosophila eyeless gene and its mammalian homologues Small eye/Aniridia play similar key roles in eye development of fruitfly, mouse, and human [for review, see Hanson and Van Heyningen, 1995; Halder et al., 1995]. Here, we review and compare recent knowledge about the molecular mechanisms underlying nervous system development in vertebrates and invertebrates.

The molecular mechanisms that underlie early neurogenesis have been best characterized in Drosophila [for review, see Hassan and Vaessin, 1996 (this issue); Schweisguth et al., 1996 (this issue)] and C. elegans [for review, see Duggan and Chalfie, 1995; Sengupta and Bargman, 1996 (this issue)]. In recent years, homologues of many invertebrate genes involved in neurogenesis have been cloned in vertebrates [for review on vertebrate neurogenesis, see Calof, 1995; Kuwada, 1995; Groves and Anderson, 1996 (this issue)], and it is now possible to initiate a critical and more systematic comparison of neurogenesis in these different phyla. This review focuses mainly on a comparison of neuronal determination and early differentiation in the peripheral nervous system (PNS) of invertebrates (flies and worms) and vertebrates (mice, chicken, zebrafish). The PNS is a more tractable system than the central nervous system (CNS) due to its simpler structure; our knowledge about PNS development is therefore more advanced. However, it should be noted that many of the genes that are involved in the development of the PNS are also involved in CNS development (A. Salzberg and H. Bellen, unpublished data); hence the separation of CNS versus PNS is somewhat arbitrary.

The PNS of worms, flies, and mice differ considerably in their anatomical features. In C. elegans, most neurons are generated in reproducible positions in the periphery. They arise from invariant cell lineages, and cell ancestry determines their fate [reviewed by Sulston, 1988]. The strict classification into sensory receptors, inter neurons, or motor neurons is often not possible in C. elegans because single neurons can combine several functions [Ward, 1975]. However, a mature PNS organ or sensillum (mechano- and chemoreceptors) consists of three or more peripherally located cells: a neuron (or set of neurons) ensheathed by a sheath cell (glia-like cell), and a socket cell that surrounds the shaft of the dendrite(s) [Perkins et al., 1986]. The precise function of many sensilla is unknown but some have specialized dendritic projections beneath the cuticle and may mediate mechanosensation. Others communicate with the outside through a hole in the cuticle and are thought to function as chemoreceptors [reviewed by Chalfie and White, 1988]. The cells of a single sensillum are closely related by
lineage [for examples, see Figure 1 in Sengupta and Bargman (this issue)]. In addition to the sensilla, there are three touch receptor neurons in C. elegans that are not organized as sensilla and that have multiple dendrites [Chalfie and White, 1988]. These neurons control the response of the worm to touch. A simple touch assay has been used to isolate mutants that respond abnormally to touch [for review, see Duggan and Chalfie, 1995]. Other screens that focused on cell lineages have also allowed identification of mutations that affect PNS development [for review, see Chalfie and White, 1988].

The PNS of the fruitfly embryo is somewhat similar to that of the worm. Most notably, the cell bodies of the neurons are located in the periphery (unlike many neurons of the PNS in vertebrates), and many sensory organs consist of few cells, e.g., a neuron, a sheath or glial associated cell, and two other accessory cells. The lineages of the different PNS organs in Drosophila embryos have recently been re-analyzed and are reviewed by Brewster and Bodmer (this issue). A sensory organ precursor cell divides twice or thrice to give rise to several cells which constitute a sensory organ (see Figs. 1–2, in Brewster and Bodmer). Different types of sensory organs are thought to play a role in mechanosensory, chemosensory, or stretch transduction. In addition, as in the worm, the PNS of the fly contains multiple dendritic neurons that are not associated with sensory organs and may be involved in touch perception.

The PNS of adult flies is more elaborate than the embryonic PNS. However, as in embryos and larvae, the adult PNS consists of a stereotyped array of sensory organs. The molecular mechanisms directing the ontogeny of embryonic and adult sensory organs are probably quite similar, although clearly not identical [for review, see Jan and Jan, 1993]. Adult flies, like most insects, are covered with bristles secreted by hair cells. These cells are part of external sensory organs which most often function as mechanoreceptors. Morphological changes of these hairs are easily identifiable and many genes that affect the PNS in the fruitfly were isolated on the basis of altered bristle patterns in adult flies (e.g., achaete, scute, Hairless, extra macrochaetae; see Lindsley and Zimm, 1992). More recently, genes involved in PNS development were isolated primarily because they are expressed in the PNS cells or their precursors (e.g., prospero, tramtrack) [Vaessen et al., 1991; Guo et al., 1995]. Systematic searches to identify genes based on phenotypic alterations in embryos or larvae have only been carried out fairly recently [Salzberg et al., 1994; Kania et al., 1995].

The anatomical features of vertebrate PNS are quite different from those of invertebrates. The cell bodies of PNS neurons involved in touch, cold, pain, and proprioception are not positioned in the periphery as described for invertebrates, but are grouped in the dorsal ganglia along the spinal cord. This is obviously not the case for all the neurons of the PNS in vertebrates as the cell bodies of photoreceptors, chemo sensory neurons and auditory neurons are situated peripherally, as is also the case in insects. A substantial portion of the vertebrate PNS neurons arise from the neural crest prior to closure of the neural tube. These neurons migrate laterally and populate the dorsal root ganglia where they send out neurites to the periphery. Recently, Sharma et al. (1995) showed that a second migratory wave of PNS neurons takes place from the dorsal tube, long after the primary migration from the neural crest. These neurons migrate from the dorsal side of the neural tube via the dorsal root into the dorsal ganglia, where they join the neurons that previously migrated there from the neural crest. Hence, the ontogeny and anatomical features of the mature vertebrate PNS appear quite different from those of invertebrates. Relatively little is known about the molecular mechanisms underlying vertebrate PNS development, and genetic approaches to isolate genes that affect PNS development have not been feasible in vertebrate species until recently. The work presented by Henion et al. (this issue) is a first in this respect.

SIMILAR GENES, SIMILAR DEVELOPMENTAL PATHWAYS?

Many vertebrate genes exhibiting structural similarity to Drosophila genes required for neuronal determination, differentiation, and growth cone guidance have been identified in recent years. Table 1 lists Drosophila genes known to be involved in neurogenesis and their homologues identified in other species. Owing to space limitations, this Table corresponds only to some aspects of neurogenesis and does not include pre-pattern genes [Patel et al., 1989; Condron et al., 1994] and genes required for growth cone guidance, fasciculation, and synaptogenesis [Kolodkin et al., 1993; for reviews, see Goodman and Shatz, 1993; Goodman, 1994; Fernandes and Keshishian, 1993; Muller and Kypka, 1995]. The sequence conservation found between Drosophila genes and their vertebrate cognates suggests that vertebrate and invertebrate animals share at least some of the mechanisms that control neurogenesis. Recently, in vivo evidence to support the involvement of three vertebrate homologues, MASH1, X-Delta1, and X-Notch1, in neurogenesis has surfaced. Similar data are still lacking for most vertebrate homologues (e.g., MATH-1 [atonal] CDP, Cux [cut]), but this may change rapidly, given the speed at which targeted mutations in mice are being generated.

SIMILAR SEQUENCES, SIMILAR ROLES?

In the simplified model shown in Figure 1, the onset of neurogenesis is marked with the specification of neuronal precursors. In Drosophila, the precursors of both the PNS and CNS emerge from domains of ectodermal cells termed proneural clusters. All the cells in the cluster that express the proneural genes are competent
TABLE 1. *C. elegans* and Vertebrate Homologues of *Drosophila* Genes Implicated in Neurogenesis

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<tr>
<th>Positive regulators of neurogenesis</th>
<th>Putative roles and functions</th>
<th>References</th>
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<tr>
<td><em>Drosophila</em> genes involved in neurogenesis and homologues from other species (%) identity</td>
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<td><em>achaete</em> and <em>scute</em></td>
<td>Proneural genes for external sensory organs</td>
<td>Cabrera et al., 1987; Villares and Cabrera, 1987; reviewed by Campuzano and Modolell, 1992</td>
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<tr>
<td><em>Xenopus</em> <em>XASH-1</em> and 3</td>
<td>Activates neural gene expression, promotes neurogenesis and causes neuronal hyperplasia when ectopically expressed</td>
<td>Zimerman et al., 1988; Ferreiro et al., 1993; Ferreiro et al., 1994</td>
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<td><em>Zebrafish</em> <em>ZASH-la, -1b</em></td>
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<td><em>Chicken</em> <em>CASH-1</em></td>
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<td><em>Mouse and rat MASH-1, 2</em> (80% in HLH domain)</td>
<td><em>Mash-1</em>— mice exhibit loss of neurons, mainly from the olfactory epithelium and sympathetic ganglia</td>
<td>Johnson et al., 1990; Guillemot et al., 1993; Lo et al., 1991; reviewed by Joyner and Guillemot, 1994; Franco del Amo et al., 1993</td>
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<td><em>Human</em> <em>hASH1</em> (80% in HLH domain)</td>
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<td><em>atonal</em></td>
<td>Proneural gene for chordotonal organs and photoreceptors</td>
<td>Jarman et al., 1993, 1994, 1995</td>
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<td><em>C. elegans</em> <em>lin-32</em> (63% in bHLH domain)</td>
<td>Specifies neuroblast cell fate; loss of function causes loss of sensory organs</td>
<td>Zhao and Emmons, 1995</td>
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<td><em>Mouse</em> <em>MATH-1</em> (70% in bHLH domain)</td>
<td>Activates E-box-dependent transcription in collaboration with the <em>daughterless</em> homologue E47</td>
<td>Akazawa et al., 1995</td>
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<td><em>daughterless</em></td>
<td>Loss of <em>da</em> removes all peripheral neurons; <em>Da</em> can form heterodimers with AS-C proteins</td>
<td>Caudy et al., 1988a,b</td>
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<td><em>Chicken</em> <em>GbHLH1.4</em> (76% in bHLH domain)</td>
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<td><em>Human</em> <em>E12/E47</em> (76% in bHLH domain)</td>
<td>Bind as dimers to E-boxes</td>
<td>Murre et al., 1989</td>
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| Negative regulators of neurogenesis (lateral inhibition) | | |
| *Notch* | Receptor in lateral signaling and other inductive signals | Wharton et al., 1985; reviewed by Artavanis-Tsakonas and Simpson, 1991; Heitzler and Simpson, 1993; Artavanis-Tsakonas et al., 1995 |
| *C. elegans* *lin-12* | Function as receptors in cell–cell interactions which specify cell fates (in a manner analogous to *Drosophila* Notch) | Greenwald et al., 1983; Yochem and Greenwald, 1989; reviewed by Greenwald and Rubin, 1992; Mello et al., 1994 |
| *C. elegans* *glp-1* | | |
| *Xenopus* *X-Notch-1* (47% overall, 51% in EGF-like repeats, 70% in cdc10 repeats) | May inhibit differentiation and keep undetermined cells competent for receiving inductive signals. Expression of activated Notch causes neural and mesodermal hypertrophy and loss of dorsal structures. | Coffman et al., 1990, 1993 |
| *Zebrafish* *Notch* | | |
| *Mouse* *Notch 1, 2, 3*; *int-3* | Mice lacking one of their *Notch* genes die as embryos and exhibit extensive regions of cell death | Bierkamp and Campos-Ortega, 1993; Gallahan et al., 1987; Robbins et al., 1992; Franco del Amo et al., 1992, 1993; Swiatek et al., 1994; Conlon et al., 1995 |
| *Rat* *Notch 1, 2* (47% overall, 51% in EGF-like repeats, 70% in cdc10 domain) | Expression of activated int-3 in transgenic mice leads to lack of differentiation and hyperproliferation of glandular epithelia | Jhappan et al., 1992 |
| *Human* *Notch 1, 2, 3* | Notch-1 (also called TAN-1) truncation is related to tumor formation. Notch-2 and 3 also map to chromosomal regions of neoplasia-associated translocations | Weinmaster et al., 1991, 1992 |
| | | |
| (continued) | | |
Drosophila genes involved in neurogenesis and homologues from other species (% identity) | Putative roles and functions | References
---|---|---
**Delta** | Mediates lateral signaling through its interaction with Notch. Loss of DI causes hyperplasia of the nervous system. | Vassan et al., 1987; Parody and Muskavitch, 1993; Muskavitch, 1994
*C. elegans lag-2* (another similar protein is axp-1 which is closer to the Drosophila Serrate protein) | A signaling ligand for the LIN-12 receptor | Tax et al., 1994; Henderson et al., 1994; Wilkinson et al., 1994
**Xenopus X-Delta-1** | Mediates lateral inhibition | Chitnis et al., 1995
**Chicken C-Delta-1** | Acts downstream of Notch in the neurogenic pathway | Delidakis and Artavanis-Tsakonas, 1992; Knust et al., 1992; Jenings et al., 1994
**Enhancer of Split (and hairy)** | Binds preferentially to N boxes. Persistent expression of HES-1 in mice perturbs neuronal and glial differentiation. HES-3 is expressed exclusively in cerebellar Purkinje cells | Sasai et al., 1992; Takebayashi et al., 1994; Ishibashi et al., 1994; Sakagami et al., 1994
**Mouse and rat HES-1, HES3** | Mediates lateral inhibition | ND
HES-1 shows 70% and HES-3 50% identity to hairy in the bHLH domain and only 40% to E(Spl) | Furukawa, 1992; Schweiguth and Posakony, 1992, 1994
**Suppressor of Hairless** | Sequence-specific DNA binding transcription regulator. Involved in the establishment of alternative cell fates | Matsunami et al., 1989
**Mouse RBP-JK (82%)** | Sequence-specific DNA binding | Brou et al., 1994; Dou et al., 1994; Hsie and Hayword, 1995
**Human RBP-JK (CBF1)** | Acts as a transcription regulator by binding to specific DNA sites | Successful in a given gene (e.g., AS-C, Notch) | Blochlinger et al., 1988

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<th>Neural identity genes</th>
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**cut** | Specifies external sensory organ identity | Andres et al., 1992
**Dog Clox (48% in HD)** | Shown to repress MEF2-mediated cardiac myosin gene activation | Valarche et al., 1993
**Mouse Cux (50% in HD)** | Inhibits expression of neural cell adhesion molecule (NCAM) DNA binding | Yoon and Chikaraishi, 1994
**Rat CDP2 (50% in HD, ~70% in CD)** | Repressor of developmentally regulated genes | Neufeld et al., 1992; Dufort and Nepveu, 1994; Lievens et al., 1995
**Human CDP/cut** | Represses transcription from c-myc promoter | |

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<th>Neuronal precursor genes</th>
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**Prospero** | Regulates expression of neuronal precursor-specific genes | Chu-lagraff et al., 1991; Vaessin et al., 1991; Doe et al., 1991; Matsuzaki et al., 1992
**C. elegans prospero (79% in HD)** | | Bürglin, 1994
**Mouse Proxl (65% in HD)** | | Oliver et al., 1993

To become neuronal precursor. However, only one or a few cells in each cluster are singled out to become neuronal precursors whereas the remaining cells adopt the epidermal fate. The binary switch between epidermal and neuronal fate has been extensively studied in embryonic and adult PNS, and many of the genes that function as positive and negative regulators of neurogenesis have been identified. As shown in Table 1 (and references therein), many of these genes have been conserved during evolution, and many mammalian cognates have been identified. Nevertheless, the function of a single gene, or a discrete molecular event specified by the action of a small group of genes, is in a way a modular unit that can be used differently in different developmental contexts. Thus, conservation of amino acid sequences does not necessarily imply conservation of developmental role. Similarly, the same protein may function in different developmental pathways in different tissues of the same organism. In addition, vertebrate genes have diverged during evolution, and often multiple genes with sequence similarity can be identified for a given Drosophila gene (e.g., AS-C, Notch). Thus, it is necessary to determine in each case which of the vertebrate homologues exhibit functional homology to the Drosophila gene and how similar their roles are. Recent knockout experiments in mice and in vivo manipulations of Xenopus oocytes (for review, see Joyner and Guillemot, 1994; Calof, 1995) provide an op-
Fig. 1. Steps in Drosophila and vertebrate neurogenesis. Schematic diagram depicting the different stages of PNS development in Drosophila (leftmost column) and vertebrates (rightmost column). Drosophila genes implicated in neurogenesis are listed near the developmental stage in which they are thought to be involved (open and shaded rectangles). Vertebrate genes that were implicated in neurogenesis based on their mutant phenotypes are listed near the earliest developmental step for which they are thought to be required (ellipses). Drosophila genes for which vertebrate homologues have been identified are shaded in gray.

CONSERVED ROLE FOR THE PRONEURAL GENES?

The Drosophila proneural genes, the genes of the achaete-scute complex (AS-C) and atonal, are basic helix-loop-helix (bHLH) transcription factors that function as positive regulators of neuronal determination (Campuzano and Modolell, 1992; Jarman et al., 1993). Loss-of-function mutations in these genes cause a loss
of specific sensory organs, whereas ectopic expression leads to overproduction of sensory organs [Campuzano et al., 1986; Rodrigues et al., 1990; Jarman et al., 1993]. The bHLH domain of theachaete-scute genes is highly conserved and achaete-scute homologues have been identified in fish, amphibians, avians, and mammals. atonal homologues have recently been identified in mouse and nematodes (see Table 1 and references therein). Phenotypic analysis of loss-of-function mutations and overexpression of the nematode atonal homologue, lin-32, demonstrate that the lin-32 gene product is necessary and sufficient for the specification of neuroblast versus epidermal fate [Zhao and Emmons, 1995]. As was previously demonstrated for the AS-C and atonal genes in flies, loss of lin-32 function causes loss of sensory organs in the worm, whereas overexpression in neural crest cells as they arrive at sites of peripheral neurogenesis [Lo et al., 1991; Guillemot et al., 1993; reviewed by Groves and Anderson, 1996 (this issue)]. The expression of MASH-1 in the PNS is restricted to precursor cells of the autonomic lineages and its transient pattern (it appears prior to markers of differentiated neurons and is down-regulated shortly after their appearance) is reminiscent of that of AS-C genes in the fly. MASH-1 −/− mice die shortly after birth and exhibit neuronal hypoplasia which correlates well with the expression pattern of the gene. These mice lack olfactory, sympathetic, parasympathetic, and enteric neurons. The expression pattern of MASH-1 and phenotypes associated with its loss of function suggest an early role in neurogenesis, similar to that of the Drosophila AS-C genes.

In the absence of proneural genes in Drosophila, neuronal precursors fail to differentiate and expression of neuronal markers is abolished in affected neuronal lineages. However, recent data show that some markers such as snail [Ip et al., 1994] and scute [Vaessin et al., 1994], are expressed in neuroblasts or SOPs, even in the absence of some proneural genes. These data place the achaete–scute genes somewhere at the top of the hierarchy of genes required for neural determination/differentiation but also suggest that an as yet uncharacterized set of genes is involved in the specification of neuronal precursors. This may be quite similar to what has been observed in MASH-1 mutant mice in which several neuronal markers continue to be expressed by undifferentiated cells derived from the neural crest [Groves and Anderson, 1996]. These data also suggest that more than one pathway of gene interactions govern neuronal differentiation in neural crest cells and that gene(s) other than MASH-1 play a role in its regulation. Whether these yet unidentified regulators function higher in the hierarchy of gene interaction, or function in parallel to MASH-1 or the AS-C genes, is currently an open question.

NEGATIVE REGULATORS
OF NEUROGENESIS

All the cells in a proneural cluster express the AS-C genes (or ato) and are considered equipotent in their ability to become neural precursors. In a second phase, one or a few cells in the cluster accumulate higher levels of the proneural protein and start expressing neuronal precursor-specific markers. The gradual refinement of proneural gene expression pattern, and the consequent selection of a single precursor cell, are mediated through cell–cell communications between the cells of the proneural cluster. This signaling process is referred to as lateral or mutual inhibition [Ghyson et al., 1993] or lateral specification [Artavanis-Tsakonas, 1995] and is mediated by the products of the genes of the neurogenic group. Loss-of-function mutations in the neurogenic genes lead to a neuronal commitment of all or most cells of the proneural cluster.

Two of the neurogenic genes, Delta and Notch, encode, respectively, a cell surface ligand and its receptor. These proteins mediate some key steps in lateral signaling in Drosophila. Cells expressing Delta activate Notch in neighboring cells. This inhibits the cells that receive the signal from becoming neural precursors. Recently, many vertebrate homologues of Notch have been cloned (see Table 1), but the roles of the corresponding Notch proteins are still unclear. Targeted disruption of Notch-1 in mice has neither confirmed nor disproved a role of Notch in vertebrate neurogenesis [Swiatek et al., 1994; Conlon et al., 1995]. A truncated form of Notch lacking the extracellular domain (which functions in Drosophila as a constitutively active protein [Fortini et al., 1993]) suppresses neurogenesis when expressed in PC12 cells, as expected [Nye et al., 1994]. However, overexpression of a similar Notch protein in Xenopus causes an increase in neural tissue and muscles [Coffman et al., 1993]. Hence, it has clearly been difficult to ascertain the role of Notch proteins in vertebrate neural development.

Recently, Chitnis et al. [1995] and Henrique et al. [1995] have provided evidence that vertebrate Notch and Delta play a similar role in neural development as their homologues in invertebrates. Injection of X-Delta mRNA inhibits production of primary neurons, and interfering with Delta activity by using an antimorphic X-Delta gene stimulates neurogenesis. In addition, in contrast to the results obtained by Coffman et al. [1993], injection of an activated X-Notch suppresses neurogenesis. On the basis of these results, Chitnis et al. [1995] propose that the "Delta/Notch signaling pathway is a universal device for controlling fine-grained patterns of cell differentiation in animal tis-
suces.” This suggests that the other genes/proteins that are involved in this cascade in Drosophila (e.g., Suppressor of Hairless, Hairless, and genes of the E(Spl) complex) are also likely to play a similar role in vertebrates. Indeed, as shown in Table 1, homologues of some of these genes have been identified. However, despite the conservation of molecular features [Brou et al., 1994; Tannahill et al., 1995], genetic or other in vivo evidence to support the role of these genes in vertebrate neurogenesis is still missing.

Finally, it should be noted that many important questions remain to which no satisfactory answers can be formulated at the present time. For example: why is the position of SOP in the proneural cluster so highly stereotyped? Are proneural cell clusters really domains of equivalent cells, or do some cells have more potential than others to become SOPs? Do Delta/Notch amplify a pre-existing difference between competent but not equipotent cells? How does Notch transduce the signal (binding of Delta) to the nucleus? Hints to some of these answers can be found in the reviews of Schweisguth and colleagues and Hassan and Vaessin (this issue).

SELECTOR GENES AND GENES REQUIRED FOR NEURONAL DIFFERENTIATION

The lineages that give rise to different types of sensory organs in the PNS of Drosophila have been well characterized [for review, see Brewster and Bodmer (this issue)]. The stereotyped lineages and the availability of numerous cell-type specific markers allowed the identification of selector genes required for the specification of correct cell identities in each step of the neuronal lineages. The cut gene encodes a homeobox protein, which is required to specify the identity of external sensory organs as a whole, and in its absence external sensory organs are transformed into chordotonal organs [Bodmer et al., 1987; Blochlinger et al., 1991]. cut homologues have been identified in vertebrates (see Table 1 and references therein) and were shown to act as repressors of developmentally regulated genes such as the neuronal adhesion protein NCAM [Andres et al., 1992]. However, as none of the vertebrate cut homologues has been manipulated in vivo, it is not known whether these homologues actually affect cell identity in vertebrate neuronal lineages.

Many features are common to all PNS neurons. Thus, in addition to the lineage specific developmental programs, it is likely that a pan-neuronal program exists. These genes may confer a general neural identity to neuronal precursor cells and hence actively participate in the initiation or maintenance of neural differentiation. Several genes in Drosophila are thought to participate in this pan-neural developmental pathway. One of these genes is prospero. In the absence of the Prospero protein, neural differentiation is aborted, leading to profound defects in the nervous system. Recently, Oliver et al. [1993] isolated the mouse homologue, Prox-1 and demonstrated that the Prox-1 message is found mainly in young post-mitotic differentiating neurons in the spinal cord and the brain. Based on the similar expression profiles in Drosophila and mice the authors suggest that both proteins may play similar roles. However, no other data on the in vivo function of Prox-1 have been published.

NEURONAL SURVIVAL

Most if not all neurons in the mammalian nervous system seem to depend on growth factors for their survival [for review, see Silos-Santiago et al., 1995]. Neuronal numbers seem to be much larger early in development than late and many neurons are thus thought to die during development. Similarly, in invertebrates, neuronal death and apoptosis in the nervous system have been extensively documented [Hengartner and Horvitz, 1994; Steller and Grether, 1994; Zhou et al., 1995]. The genetics of programmed cell death has been studied extensively in vertebrates and invertebrates and the mechanisms by which apoptosis occurs seem to rely on a similar basic molecular machinery [Hengartner and Horvitz, 1994]. Yet, whereas the signals that induce apoptosis in the nervous system of vertebrates have been well documented, the signals that trigger cell death in the invertebrate nervous system are unknown. Many neurotrophic factors required for neuronal survival and their receptors have been extensively characterized in vertebrates (Fig. 1) [for review, see Silos-Santiago et al., 1995; Slack and Miller, 1996 (this issue)]. However, to our knowledge, none of these factors has known homologues in invertebrates. Hence, here may lie a basic difference between vertebrate and invertebrate neural development.

EPILOGUE

This review has touched on the few known key aspects of neurogenesis that seem to be conserved between invertebrates and vertebrates. Some of the differences have been highlighted as well. The scope of this review is necessarily limited, and many topics such as cell cycle and the role of glia in nervous system development have not been covered. The review by Slack and Miller (this issue) provides an in depth coverage on the function of one of the key proteins that participate in the regulation of cell division in the CNS. Finally, the paper by Klambt et al. (this issue) illustrates the essential role of glia in the development of the CNS in Drosophila.

In summary, the preliminary data reviewed here suggest that major developmental pathways are conserved in PNS and CNS development of species as different as Drosophila and mouse. It is quite likely that a much clearer picture of the similarities between vertebrate and invertebrate nervous system development will emerge in the very near future. The next years
promise to be exciting and the interplay between vertebrate and invertebrate biologists promises to be fruitful. Comparative developmental biology is alive again.

ACKNOWLEDGMENTS

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