REVIEW

The neuroendocrine system of invertebrates: a developmental and evolutionary perspective

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Abstract

Neuroendocrine control mechanisms are observed in all animals that possess a nervous system. Recent analyses of neuroendocrine functions in invertebrate model systems reveal a great degree of similarity between phyla as far apart as nematodes, arthropods, and chordates. Developmental studies that emphasize the comparison between different animal groups will help to shed light on questions regarding the evolutionary origin and possible homologies between neuroendocrine systems. This review intends to provide a brief overview of invertebrate neuroendocrine systems and to discuss aspects of their development that appear to be conserved between insects and vertebrates.

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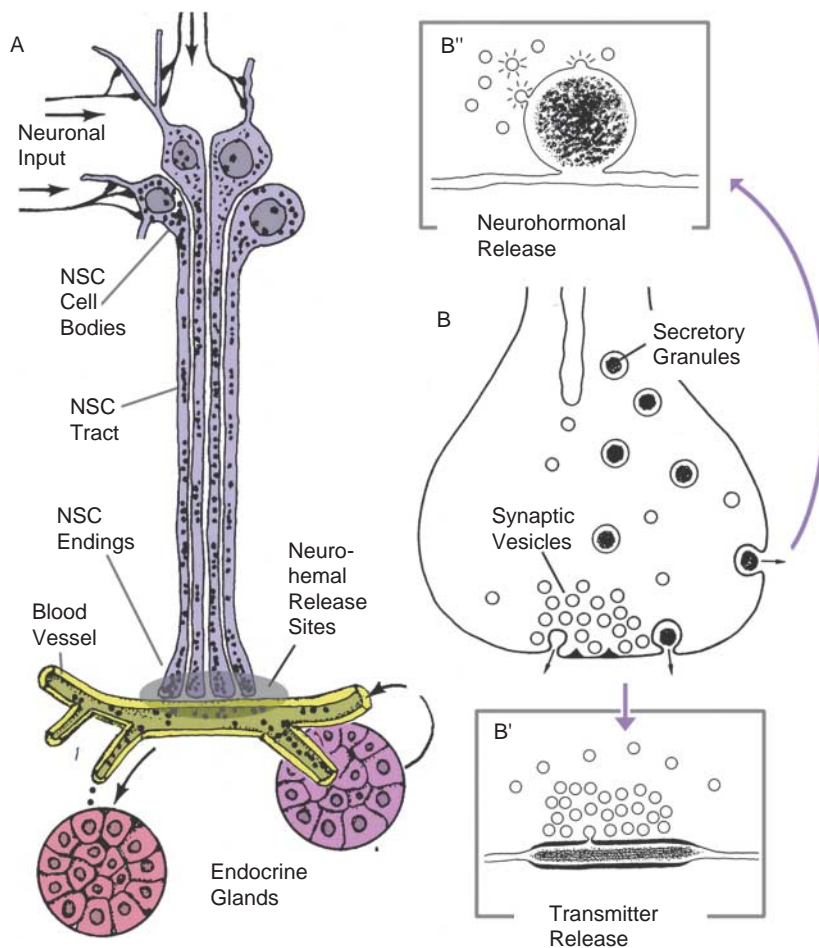
Endocrine and neuroendocrine cells

Cells in multicellular animals communicate through signaling mechanisms that take place at direct intercellular contacts, or that involve signals released systemically into the extracellular space where they diffuse over large distances and are able to affect targets far removed from the signaling source. The first mechanism, communication of cells that are in direct contact, is developed to a state of high complexity in the nervous system. Here, a multitude of signals in the form of neurotransmitters chemically couple networks of neurons at specialized cell–cell contacts, the synapses. The second mechanism of cell–cell communication defines the endocrine system. It involves secreted signals, hormones that affect target cells in a less directed way, since all cells expressing receptors for a given hormone will react when that hormone is released. The endocrine system in bilaterian animals consists of multiple specialized cell populations, sometimes compacted into glands that are found in all parts of the body, and are derived from all three germ layers (Tombes 1970, Highnam & Hill 1977, Gorbman *et al.* 1983, Laufer & Downer 1988). Endocrine glands regulate a large number of homeostatic mechanisms. They include the activity of neurons, muscles, and pigment cells during specific behaviors (food intake, fight and flight, and reproduction), the activity of visceral muscle and exocrine glands (digestion), the control of major metabolic pathways (synthesis, storage, and release of carbohydrates and lipids), the control of the ionic milieu through absorption and excretion, the formation and maturation of gametes, and growth and regeneration of the body. In many instances, endocrine glands form an integrated system in which hormonal production and release is controlled through feed back loops.

Most hormones found throughout the animal kingdom are short polypeptides, produced by proteolytic cleavage from larger precursor proteins, called prohormones. Similar to other secreted proteins, peptide (pro)hormones are produced in the rough endoplasmic reticulum, processed through the Golgi apparatus, and stored in membrane-bound vesicles. These vesicles, 100–300 nm in size, give peptide hormone-producing cells their characteristic granular appearance (Golding & Pow 1988, Thorndyke & Georges 1988). Peptide hormone receptors belong to the class of seven pass transmembrane, G-protein-coupled receptors. Beside peptides, lipids and amino acid derivatives act as hormones. The steroid hormones (e.g. cortisone or estrogen in vertebrates and ecdysone in arthropods) are derived from the lipid cholesterol. Juvenile hormone in insects is an ether derivative of a polyunsaturated fatty acid. Like other lipids, these hormones are synthesized in the smooth ER and are not stored in vesicles. Steroid hormone receptors belong to a class of transcription factors, called nuclear receptors that are localized in the cytoplasm in their inactive state; upon ligand binding, they will enter the nucleus and bind to DNA, thereby modulating gene expression (Schulster *et al.* 1976).

In addition to endocrine glands, many neurons of the central and peripheral nervous system produce hormones which are released locally into the extracellular space, as well as into the blood stream (Thorndyke & Georges 1988). In most cases, hormones (all of them of the peptide class) synthesized by neurons are the same that are also produced by non-neuronal endocrine cells. Examples are provided by the large number of peptides formed in both the nervous system and the intestinal endocrine cells, including the pancreas (brain–gut peptides; Walsh & Dockray 1994): glucagon, gastrin, cholecystokinin, tachykinin, and many others. Neurons that produce hormones are called neurosecretory cells (NSCs). NSCs, and the structures their axons target, form the neuroendocrine system (Fig. 1). In vertebrates, the neuroendocrine system includes the hypothalamus and pituitary, as well as peripheral neurons of the autonomic nervous system that target endocrine cells in the adrenal medulla, the intestinal wall, and the pancreas. NSCs form a distinct population of nerve cells, which are recognized by their content of large peptide-storing vesicles. Vesicles are distributed throughout the cell body, axon, and synapse of the NSC, rather than being restricted to the synapse, like regular neurotransmitters (Thorndyke & Georges 1988). Furthermore, release of neurohormones, occurring through fusion of the vesicles with the cell membrane, occurs not only at synapses but also anywhere along the soma and axon (Fig. 1B). In this way, the released neurohormone affects multiple cells which are within reach of the NSC.

Figure 1 Structure of the neuroendocrine system. (A) Somata of neurosecretory cells (NSCs) are located in the central nervous system and receive neuronal input from presynaptic neurons. NSC axons project to peripheral neurohemal release sites that are frequently in close contact with endocrine cells targeted by the neurohormones released at the NSC terminals (after Scharrer & Scharrer 1963). (B) Ultrastructural aspects of neurotransmitter release (B') and neurohormonal release (B''). Neurotransmitter release occurs exclusively at presynaptic sites from 50 nm vesicles. Neurohormones are stored in large vesicles found throughout the NSC and released outside synapses (after Golding & Pow 1988).

Important aspects of endocrine system evolution

Cell communication through secreted, diffusible signals is phylogenetically older than neural transmission. Animals without nervous system (e.g. sponges and placozoa) and even protists produce a wide array of hormones, which are in some cases identical to the corresponding compounds found in highly derived taxa (Robitzki *et al.* 1989, Schuchert 1993, Skorokhod *et al.* 1999). The general hypothesis put forward in classical reviews and textbooks assumes that in primitive multicellular animals, specialized epithelial cells integrated into the epidermis and the intestinal lining reacted to certain stimuli, chemical or physical, by secreting metabolites that diffused throughout the body and evoked adaptive responses in other tissues (Fig. 2A). These primitive endocrine cells then underwent further specializations during the course of evolution. They separated (delaminated) from the epidermis, neuroectoderm, and intestinal epithelium; many became neurons of the peripheral and central nervous system (e.g. hypothalamus in vertebrates), others formed specialized endocrine glands (e.g. pituitary and endocrine pancreas; Fig. 2B and C).

For most of the peptidergic endocrine systems, we start to recognize phylogenetic relationships that span far across phyletic boundaries (Fig. 2C and D). First and foremost, one might think of the neuroendocrine system that develops from the neuroectoderm of the head in bilaterian animals, and that includes: (1) populations of NSCs that are integrated into the brain; (2) NSCs that migrate and form a nerve plexus in the walls of inner organs (autonomic nervous system); and (3) peptidergic endocrine glands or cell clusters (e.g. anterior pituitary in vertebrates and corpora cardiaca in insects), usually spatially close to the brain, and controlled through neurosecretory mechanisms by the central NSCs. As discussed later, we can recognize these neuroendocrine elements in many bilaterians, which suggests that they already existed in the bilaterian ancestor. Among the protochordates and chordates, further specializations occurred in the endocrine cell populations of the pharynx and gut. We see the formation of endocrine glands, from the pharyngeal endoderm (thyroid and parathyroid) and the midgut (endocrine pancreas), which apparently have no counterparts in other phyla (Fig. 2D).

One striking trend that can be observed at multiple instances in the evolution of endocrine systems is the interpolation of novel steps into endocrine pathways. For example, GnRH is a peptide hormone that plays a role in reproduction, acting on neural circuits controlling reproductive behavior and on gamete differentiation in the gonads alike (Rastogi *et al.* 2002, Gorbman & Sower 2003). In chordates, GnRH (via other peptide hormones) acts on steroidogenic cells in the gonads, and it is the steroid hormones that in these animals profoundly affect gametogenesis and reproductive behavior.

In the following, a brief overview of the endocrine system of invertebrate animals will be given, emphasizing those
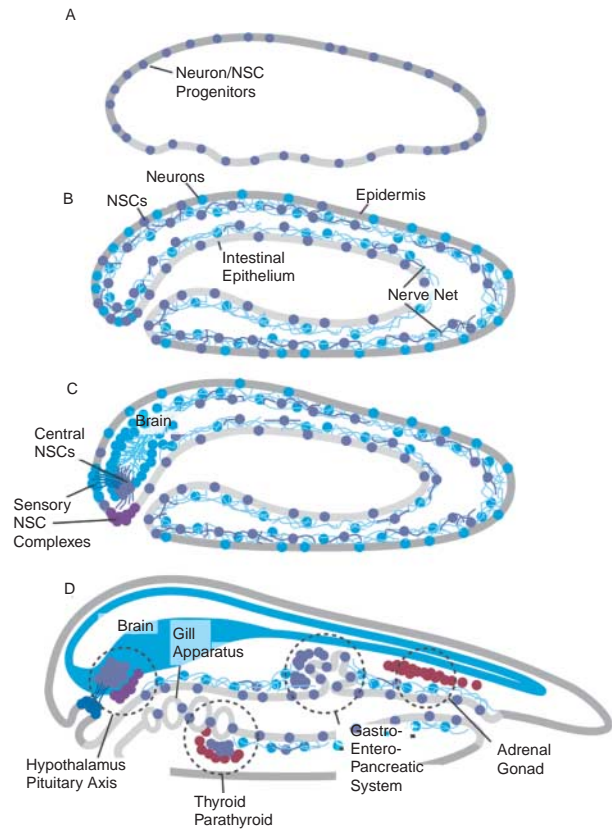
Figure 2 Hypothetical stages in the evolution of the endocrine and neuroendocrine systems. Cells releasing endocrine signals are likely to predate the appearance of a nervous system, since they can be found in extant metazoa lacking nerve cells (A). The first nervous system is thought to have possessed the structure of a basi-epithelial nerve net, similar to the one still found in present day cnidarians (B). At this stage, neurons and NSCs/endocrine cells most likely had evolved into distinct lineages of sensory cells integrated into the epidermis, the gastrodermis and the nerve net. A central nervous system integrating multimodal sensory input evolved in bilaterian animals (C). Populations of sensory NSCs involved in the regulation of fundamental biological processes, such as feeding and reproduction may have formed specialized complexes in the brain, pharynx, and gut of early bilaterians. During later stages of evolution (shown in (D) for the chordate lineage), NSCs and endocrine cells in general show the tendency of losing their sensory function, delaminating from the surface epithelium (epidermis, pharynx, and intestinal epithelium), and undergoing morphogenetic changes that produced dedicated endocrine glands, such as the pituitary, thyroid/parathyroid, and pancreatic islets.

aspects that tie together evolution and development. In view of this objective, only the populations of peptidergic cells that form the neuroendocrine system associated with the brain and intestinal tract, and that can be recognized in one form or another in all animals, will be covered. I will begin with a look at the cnidarians, the simplest animals that possess a nervous system containing groups of fairly well-characterized neuroendocrine cells. From there, the survey will proceed to the two large lophotrochozoan phyla, annelids, and mollusks, to the ecdysozaoans, arthropods, and (very briefly)

nematodes. The last section of the review will look in a comparative manner at the genetic mechanism controlling neuroendocrine system development in the model system *Drosophila* and in vertebrates.

Structure of the neuroendocrine system in invertebrate phyla

Origins: the neuroendocrine system of cnidarians

In cnidarians, endocrine cells occur as scattered neurons and epithelial cell in the epidermis and gastrodermis (Lesh-Laurie 1988, Thomas 1991, Grimmelikhuijzen & Westfall 1995). NSCs comprise both sensory cells (i.e. neurons integrated into the epidermis, with modified cilia acting as stimulus-receiving apparatus), as well as subepidermal ganglion cells. Cnidarians possess almost the full range of neurotransmitters, neurohormones, and non-neuronal hormones present in chordates or arthropods (Grimmelikhuijzen *et al.* 1996). A considerable fraction of both sensory and ganglion cells are neurosecretory. For example, in the planula larva, more than 40% of the neurons express the neuropeptide FMRFamide (Martin 1992).

Neuropeptides in cnidarians act as transmitters mediating communication of neurons within the nerve net and stimulating effector organs (Grimmelikhuijzen & Westfall 1995, Holtmann & Thurm 2001, Pernet *et al.* 2004). Peptides act as stimulators or inhibitors; no specific behavioral responses have been associated with any particular peptide. For example, FMRFamide-expressing cells, mostly bipolar sensory neuron, are concentrated in the tentacles of *Aglantha*. These neurons control the feeding response: tentacular movement leading to prey capture and ingestion (Mackie *et al.* 2003). FMRFamidergic neurons in the planula larvae of the anthozoan (coral) *Hydractinia echinata* exert a tonic effect on motility (Katsukura *et al.* 2004). Planulae settled on a substratum migrate toward light and then initiate metamorphosis into polyps. Migration occurs in rhythmic bursts of active movement interrupted by resting periods. The peptide LWamide extends the active periods longer, thereby speeding up migration, whereas RFamide has the opposite effect.

Beside their role as neurotransmitters, peptides have been shown to systemically act like true hormones on reproduction, development, and reproduction. Cnidarians reproduce sexually (haploid gametes released in the seawater) and asexually by budding. Development typically undergoes multiple phases where small larval forms (planula) give rise to polyps which then change into medusae. Cnidarians, like many other simple invertebrates, show a pronounced capacity of regeneration, where a small piece of the body can regenerate into the full organism. Each of these reproductive and growth phenomena is under the control of neurohormones released by the NSCs (Lesh-Laurie 1988). For example, the same RFamides introduced earlier as stimulators of migration induces metamorphosis, whereas LWamides inhibit the same process (Katsukura *et al.* 2003).

The neuroendocrine system in lophotrochozoans: annelids and mollusks

Scattered NSCs, similar to those described for cnidarians in the previous section, can be found among central and peripheral neurons, as well as the gut epithelium, of all animal phyla. Many cells undergo further specializations that add to the complexity of the neuroendocrine system. In the brain, NSCs cluster into several 'nuclei' whose neurites innervate specific compartments of the neuropile, and whose neurosecretory peripheral axons form specialized endings in association with the glial sheath covering the brain, with blood vessels, or with peripheral endocrine glands.

Variable clusters of NSCs have been identified in representatives of all annelid taxa in both larval forms and adults (Tombes 1970, Baid & Gorgees 1975, Aros *et al.* 1977, Highnam & Hill 1977, Orchard & Webb 1980, Jamieson 1981, Porchet & Dhainaut-Courtois 1988). Besides, largely unknown neurite terminations in the neuropile of the brain and ventral nerve cord, axons of many NSCs terminate in the pericapsular organ, a neurohemal structure at the ventral surface of the brain (Bobin & Durchon 1952, Highnam & Hill 1977; Fig. 3A and B). The pericapsular organ is formed by a glial (connective tissue) sheath, a layer of epithelial cells some of which also appear to be neurosecretory and blood vessels. Specialized endings of NSCs are clustered next to the glial sheath and among the epithelial cells, suggesting that the pericapsular organ represents a site of active neurohormonal release. NSCs of the ventral nerve cord also terminate in neurohemal release sites associated with the glial sheath; some produce axons that leave the CNS and terminate among epidermal cells (Jamieson 1981, Gardiner 1992).

NSCs and neurohemal structures located in the glial sheath of the nervous system have been described in detail for several mollusk species. Within the brain cortex of terrestrial snails (pulmonates), several peptide hormone producing 'nuclei' have been described (Geraerts *et al.* 1988, Joosse 1988, de Lange *et al.* 2001). Among these are the caudo-dorsal cells (CDCs), bag cells (BCs), latero-dorsal cells (LDCs), medio-dorsal cells (MDCs), and BGCs (Fig. 3C). All of these cell groups produce axons terminating underneath the glial sheath and releasing their hormonal content into the hemolymph. The CDCs, controlling ovulation and egg laying behavior, produce complex recurrent axons terminating in several glial-bounded neurohemal 'compartments' located in the brain commissure. The LGCs form a large, bilateral cluster of peptidergic NSCs in the dorsal brain. They control body growth and receive synaptic input from peripheral sensory neurons located in the epidermis of the head (Roubos & van der Wal-Divendal 1982).

Outside the populations of NSCs, several non-neuronal populations of endocrine cells, have been described (Fig. 3C). They are located within or close to the glial sheath around the brain, are possibly of mesodermal origin (Boer *et al.* 1968), and are innervated by brain neurons. Among these endocrine structures are the dorsal bodies and lateral lobes (in pulmonates)
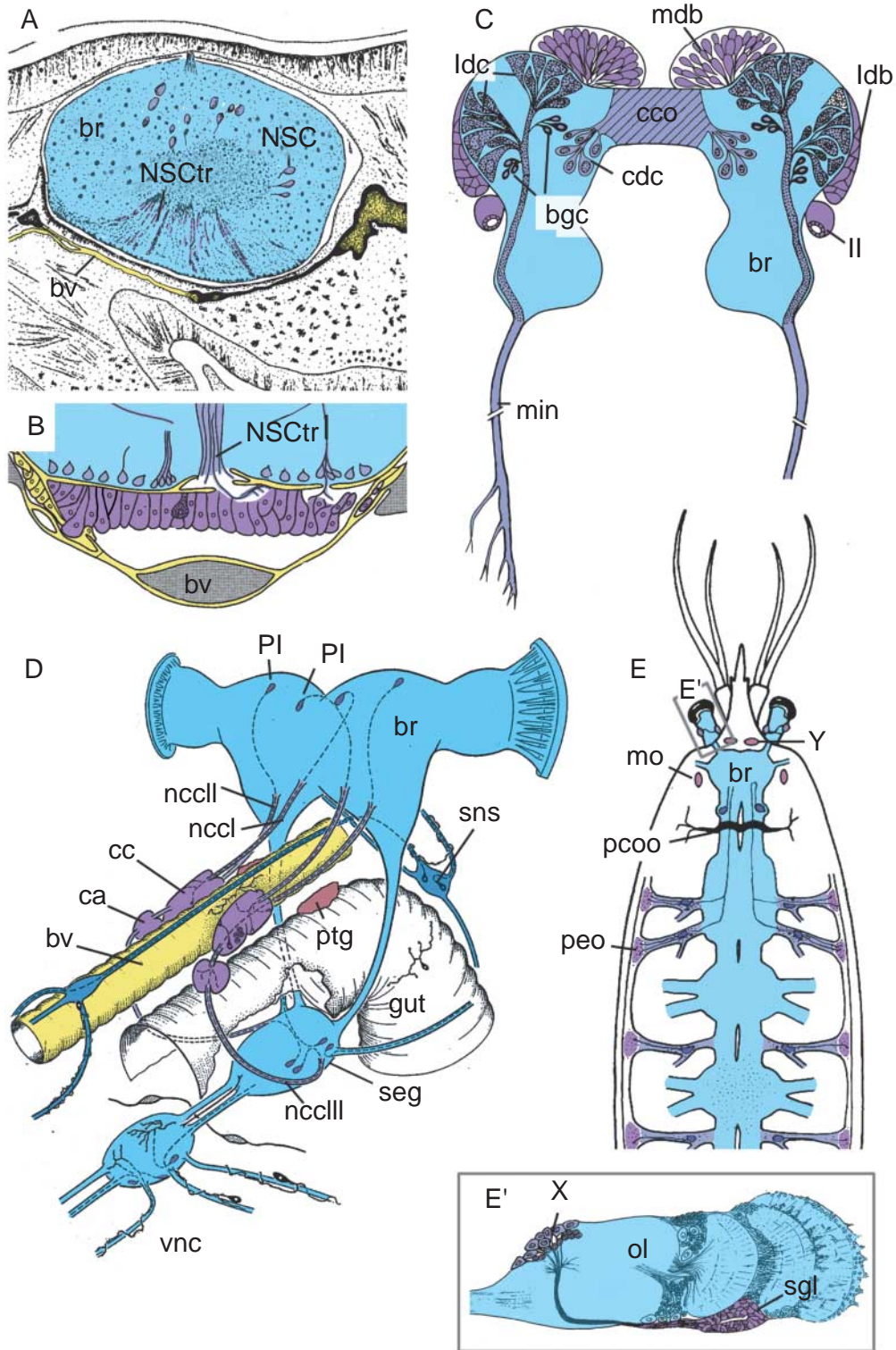
and optic glands (in cephalopods). The lateral lobes are functionally related to the LGCs and influence body growth; the dorsal bodies produce a female gonadotropic hormone, as well as ecdysteroid hormones (de Jong-Brink *et al.* 1986, Marchand & Dubois 1986, Wiens & Brownell 1994, Wayne 1995, Wayne *et al.* 2004). The optic gland in cephalopods produces gonadotropic hormones and receives inhibitory input from neurons of the brain (Di Cosmo & Di Cristo 1998, Iwakoshi-Ukena *et al.* 2004).

Neuroendocrine system of arthropods

The neuroendocrine system of arthropods shows strong homologies among different taxa of this phylum. The arthropod brain contains a wide variety (in regard to location, projection, and peptide content) of NSCs. Most are scattered cells with largely uncharacterized projections within the neuropile. In addition, subsets of NSCs form conspicuous clusters, whose axons leave the neuropile and project to neurohemal release sites and non-neuronal endocrine glands.

Insects The neurosecretory system in insects consists of several sets of neurosecretory cells located in the brain and ventral nerve cord. The majority of NSCs are found in the dorso-medial protocerebrum, the so-called pars intercerebralis (PI) and pars lateralis (PL; Pipa 1978, Raabe 1989, Schooneveld 1998, Veelaert *et al.* 1998, Siegmund & Korge 2001). These NSCs project their axons toward a set of endocrine glands, the corpora cardiaca (CC) and corpora allata (CA; Fig. 3D). In *Drosophila*, the CC and CA, along with a third neuroendocrine gland, the prothoracic gland (PTG), are fused into a single complex, the ring gland, which surrounds the anterior tip of the dorsal blood vessel (Fig. 4D). Containing release sites for neurosecretory products, the CC and CA act as neurohemal organs. At the same time, neuropeptides that reach the CC and CA from the brain

may act locally on the glandular cells of these organs and control the release of their hormones.

The pars intercerebralis comprises an unpaired cluster of neurons located along the anterior brain midline, flanked by the mushroom body on either side and the central complex ventrally. The architecture of the NSCs has been the object of many studies, describing them as monopolar neurons with dendrites spreading in the hemispheres and axons joining the first nerve to the corpora cardiaca (nccI; Geldiay & Edwards 1973, Rowell 1976, Koontz & Edwards 1980, Zaretsky & Loher 1983, Homberg *et al.* 1991*a,b*, Fig. 3D). NSCs of the PI secrete insulin-like peptides, FMRFamide-like peptides, *Locusta*-diuretic hormone, pigment-dispersing hormone, *Manduca sexta*-allatostatin, ovary ecdysteroidogenic hormone, and myomodulin (reviewed in Nassel 2002). The NSCs forming the PL of the brain produce FMRFamide-like peptides, pigment-dispersing hormone, corazonin, and *M. sexta*-allatostatin. Their axons form the second nerve of the corpora cardiaca (nccII), which in most insects travels alongside the nccI (Fig. 3D); in *Drosophila*, both nerves are enclosed by a single perineurial (glial) sheath.

Outside the PI and PL, the tritocerebrum and the ventral nerve cord, as well as the ganglia of the stomatogastric nervous system (SNS) contain neurosecretory cells. NSC axons of the tritocerebrum and subesophageal ganglion projecting toward the corpora cardiaca form the nccIII nerve (Penzlin 1985, Kim *et al.* 1998, Schooneveld 1998, Nassel 2002); neuro-secretory axons from the SNS also form a compact axon bundle connecting the hypocerebral ganglion with the corpora cardiaca (Penzlin 1985). NSCs of the ventral nerve cord have release site associated with the dorsal glial sheath of the cord and the segmental peripheral nerves (Duve *et al.* 1988, Nassel *et al.* 1988, Schooneveld 1998).

Peripheral neuroendocrine glands in insects: the CC of insects consist of two distinct zones, an unpaired ventral storage lobe, containing the terminals of NSCs located in the PI and PL,

Figure 3 Comparative overview of important elements of the neuroendocrine system in ((A) and (B)) annelids, (C) mollusks, (D) insects, and ((E) and (E′)) crustaceans. In all panels, the central nervous system is colored light blue; central NSCs are shown in violet, peripheral endocrine cells (targeted by the NSCs) in magenta, and vascular cells in light green. (A) Section of annelid brain (br). NSCs form fiber tracts (NSCtr) that terminate in contact with the glial/connective tissue layer covering the ventral brain surface. Other NSC axons penetrate the glial layer (B) and contact the pericapsular organ (pco), a presumed endocrine structure located between the ventral brain and the blood vessel (bv). (C) Schematic dorsal view of gastropod cerebral ganglion. Multiple populations of central NSCs are found in the brain (bgc, bag cells; cdc, caudo-dorsal cells; and ldc, latero-dorsal cells). In some cases, neurohemal release sites have been identified (cco, commissural neurohemal organ; and mln, median lip nerve). The medio-dorsal body (mdb), latero-dorsal body (ldb), and lateral lobe (ll) form endocrine structures closely associated with the brain and targeted by NSCs. (D) Posterior–dorsal view of insect neuroendocrine system. Central NSCs are located in the pars intercerebralis (PI) and pars lateralis (PL) of the protocerebrum, the tritocerebrum and subesophageal ganglion (seg), and the ventral nerve cord (vnc). Peripheral axons of these cells innervate the retrocerebral complex of endocrine glands via the nccI nerve (from PI), nccII (from PL), and nccIII (from subesophageal ganglion/tritocerebrum). Secretory axons of NSCs located in the ventral nerve cord terminate at neurohemal release sites associated with the glial sheath surrounding the nerve cord and peripheral nerves. The retrocerebral complex receiving NSC axons consists of the corpora cardiaca (cc) and corpora allata (ca), both of which are located close to the dorsal blood vessel (bv). The corpora allata produce juvenile hormone which, together with the steroid ecdysone produced and released by the prothoracic gland (ptg), control growth and molting. The stomatogastric nervous system (sns) contains further NSCs and is functionally closely connected to the corpora allata and corpora cardiaca. (E) and (E′) dorsal view of crustacean brain and neuroendocrine system. Central NSCs are located in the brain, particularly in the 'X-organ' (X) found in the optic lobe (ol in (E′)). Endocrine glands controlled by central NSCs are the sinus gland (sgl), postcommissural organ (pcoo), and pericardial organ (peo), the latter possibly homologous to the insect corpora cardiaca. The Y-gland (Y) produces ecdysone and represents a homolog of the insect prothoracic gland; likewise, the mandibular organ (mo) secretes methyl farnesoate which is chemically and functionally similar to insect juvenile hormone.
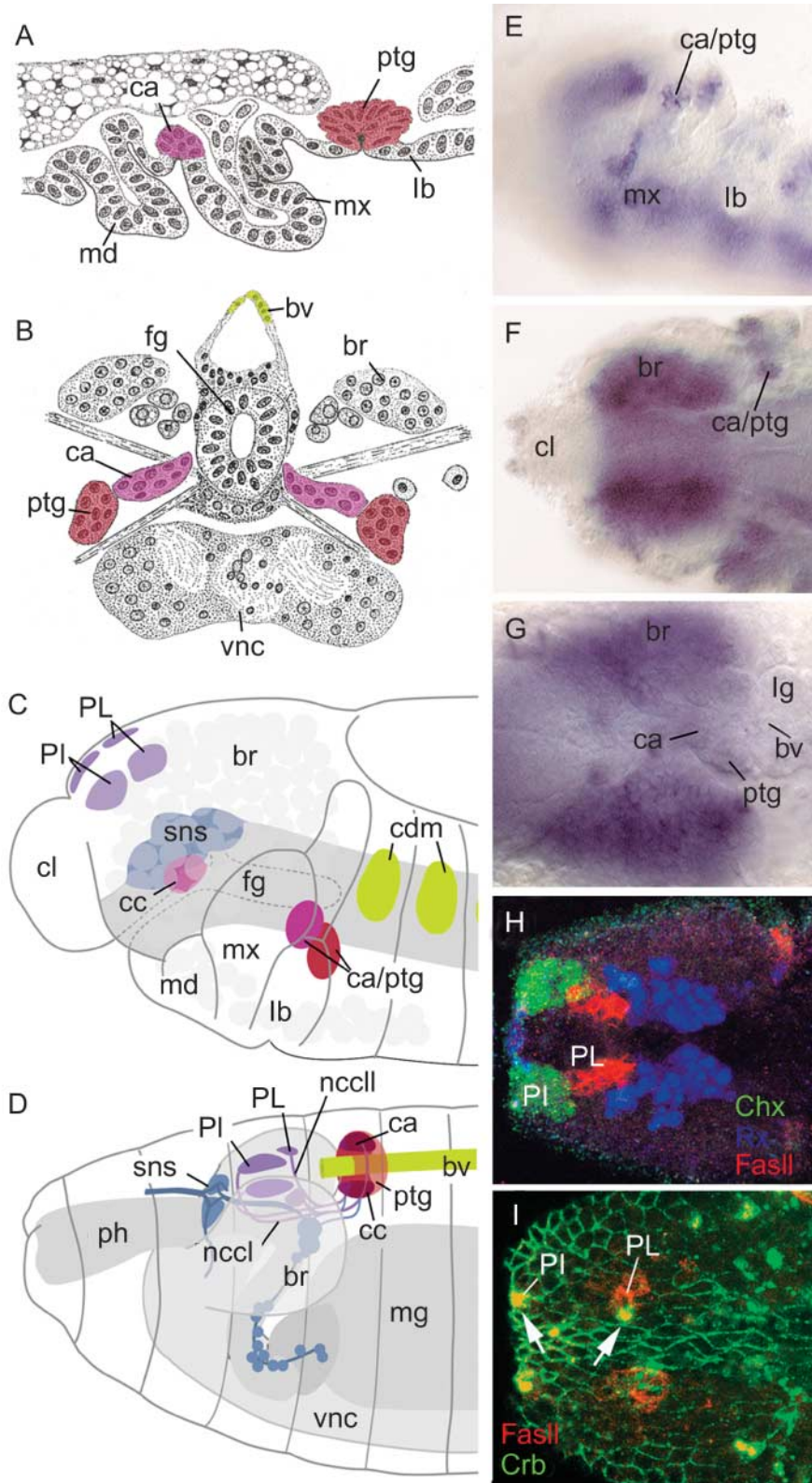
and a more lateral glandular lobe that is formed by NSCs in its own right (Gupta 1990, Dai & Gilbert 1991, Dorn 1998, Schooneveld 1998). Some insects, among them flies, lack a storage lobe; here, neurosecretory axons that would terminate in the CC in locusts and other insects pass through the CC and end in contact with the aorta (King *et al.* 1966, Schooneveld 1998). The glandular lobe of the CC produces several hormones, including AKH, certain glycemic factors, cardiac–accelerating factors, and melanin–inducing factor. The AKH hormones are the major products of the CC, which are secreted into the hemolymph to mobilize lipids and carbohydrates during flight (O'Shea & Rayne 1992, Noyes *et al.* 1995, Veelaert *et al.* 1998, Nassel 1999, Oudejans *et al.* 1999).

The CA produces juvenile hormone (JH), a fatty acid derivative which has profound effects on larval growth, metamorphosis, egg development, and sexual behavior (Veelaert *et al.* 1998, Vullings *et al.* 1999, Gilbert *et al.* 2000). The pars lateralis in the brain via its projections to the CA is the source of positive and negative control over JH production (Stay *et al.* 1996, Stay 2000, Siga 2003). One of the neuropeptides reaching the CA was identified as allatostatin, which inhibits JH release.

The prothoracic gland (PTG) derives its name from the fact that in most insects it is situated in the prothoracic segments. In dipterans, the PTG consists of bilateral clusters of large glandular cells that form the lateral wings of the ring gland. The PTG synthesizes and secretes a polyhydroxylated steroid prehormone, which is then converted to the major molting hormone, 2O–hydroxyecdysone, by peripheral tissues (Bollenbacher *et al.* 1975, Gilbert *et al.* 1997). Ecdysone triggers the transition from larval to pupal molts. It is also responsible for the complex metamorphic–remodeling processes that shape the adult organs of the insect body. The level of ecdysone is controlled by numerous humoral and neural pathways. One of the factors that controls ecdysone release is prothoracicotropic hormone (PTTH), a peptide that has been isolated in several insect species, including *Drosophila* (Gilbert *et al.* 1997, Kim *et al.* 1997). Axon tracts that funnel PTTH (and other factors) directly to the PTG stem from the ventral nerve cord (prothorax!); in addition, PTTH–secreting NSCs are located in the PI, send their axons through the NCCI to the CA where they release PTTH into the hemolymph (Westbrook & Bollenbacher 1990, Dai *et al.* 1995, Aizono *et al.* 1997).

Crustaceans Numerous groups of NSCs with specialized neurohemal projections outside the neuropile have been identified in the brain and ventral nerve cord of crustaceans (Tombes 1970, Cooke & Sullivan 1982, Beltz 1988, Fingerman 1992, Keller 1992). Compared with insects, where the PI, PL, and tritocerebrum form a relatively uniform central neuroendocrine system, the diversity of central neuroendocrine cells in crustaceans is considerable. A schematic map is shown in Fig. 3E/E′. A conspicuous group of NSCs with no obvious counterpart in insects, called the X–organ, forms part of the proximal optic lobe. Axons of the X–organ and most other NSCs of the brain project toward the ventral surface of the optic stalk where they terminate in a large neurohemal structure called the sinus gland (Tombes 1970, Beltz 1988). Two other neurohemal structures, called the postcommissural and the pericardial organs, receive projections from NSCs in the brain and ventral nerve cord. A large variety of neuropeptides influencing pigmentation, carbohydrate levels, osmoregulation, growth/molting, and reproduction are released from each of these sites (Bulau *et al.* 2004, Serrano *et al.* 2004).

Whereas the sinus gland/X–organ system associated with the crustacean optic lobe has no obvious counterpart in insects,

Figure 4 Embryonic development of the insect neuroendocrine system. ((A) and (B)) Sections of the anterior part of *Oncopeltus* embryo (after Dorn 1972). Parasagittal section in A illustrates the topology of the invaginating primordia of prothoracic gland (ptg, in ectoderm of labium (lb)) and corpora allata (ca, in ectoderm of maxilla (mx)). Transverse section in (A) shows later embryonic stage. Primordia of corpora allata and prothoracic gland form mesenchymal cell clusters migrating dorso-medially toward the dorsal blood vessel (bv). ((C) and (D)) Schematic drawings of heads of *Drosophila* embryo, dorso-lateral view, anterior to the left. (C) Depicts late extended germ band embryo (stage 11/12; corresponding to the stage shown for *Oncopeltus* in (A)). Primordia of the neuroendocrine centers of the brain, the pars intercerebralis (PI) and pars lateralis (PL), form placodes in the antero-medial neuroectoderm of the head. Primordia of the corpora allata (ca) and prothoracic gland (ptg) originate from the lateral ectoderm of the gnathal segments (lb, labium; mx, maxilla; and md, mandible). Primordia of corpora cardiaca (cc) are associated with the stomatogastric placodes (sns) which invaginate from the roof of the foregut (fg). At later stage (stage 16, depicted in (D)), the corpora allata, prothoracic gland, and corpora cardiaca have coalesced into the ring gland that surrounds the anterior end of the dorsal blood vessel (bv). Neurosecretory axons from the PI and PL reach the ring gland via the nccI and nccII nerves respectively. (E)–(G) Micrographs of heads of *Drosophila* embryos ((E) stage 11, lateral view; (F) stage 13, dorsal view; (G) stage 15, dorsal view) labeled with RNA probe against DN-cadherin (A Younossi-Hartenstein, F Wang & V Hartenstein (unpublished observations)). DN-cadherin is expressed in a cluster of cells that can be seen to delaminate from the maxillary ectoderm and migrate dorsally. At later stages, DN-cadherin labeling occurs in the prothoracic gland and, to a lesser extent, the corpora allata. (H) and (I) Micrographs of heads of *Drosophila* embryos (both stage 12, dorsal view, anterior to the left; from B De Velasco, T Erclik, D Shy, J Sclafani, HD Lipshitz, RR McInnes & V Hartenstein (unpublished observations)). (H) Primordia of the PI and PL are labeled with antibodies against Dchx1 (green) and FasII (red; Grenningloh *et al.* 1991). The *Drosophila Rx* gene (Eggert *et al.* 1998) is expressed in a large dorso-medial domain posterior of the PL primordium. (I) Labeling with the apical membrane marker anti-Crumbs (Tepass *et al.* 1990) reveals the placodeal nature of the PI and PL primordia. Arrows point at strongly Crumbs-positive pits which demarcate the centers of the invaginating placodes. Other abbreviations: br, brain; cdm, cardiogenic mesoderm; cl, clypeolabrum; fg, foregut; lg, lymph gland; md, mandible; mg, midgut; ph pharynx; and vnc, ventral nerve cord.

the pericardial organ may be considered homologous to the insect corpora cardiaca. Beside nerve terminals from the brain and ventral cord, the pericardial organ contains intrinsic endocrine cells which produce, among others, crustacean hyperglycemic hormone (CHH), which controls hemolymph sugar and fatty acid levels, similar to AKH produced in the insect corpora cardiaca (Beltz 1988, Fingerman 1992, Keller 1992, Dircksen *et al.* 2001). CHH also affects heart beat and molting. Beside the pericardial organ, the X-organ/sinus gland complex is another source of CHH (Fu *et al.* 2005).

Homologs of the insect growth/molting controlling non-neural endocrine glands, the corpora allata and prothoracic gland, exist in crustacean and appear to develop in a similar fashion from ectodermal invaginations of the head segments. One gland, called the Y-organ, produces ecdysteroids; the other gland, the mandibular organ, releases a hormone (methyl farnesoate, MF) similar to juvenile hormone in insects (Beltz 1988). MF not only controls growth and morphogenesis, but also reproduction and sex determination.

Both Y-organ and mandibular organ, similar to their PTG/CA counterparts in insects, are controlled by hemo-lymph born neurohormones (Beltz 1988, Han *et al.* 2006). Notable among the peptides released from the sinus gland and acting on the Y-organ is molting-inhibiting hormone (MIH), which decreases ecdysone production (Nakatsuji & Sonobe 2004). Sinus gland-derived peptides acting on juvenoid production in the mandibular organ are mandibular organ-inhibiting hormone (MO-IH) and gonad-inhibiting hormone (GIH; De Kleijn & Van Herp 1995).

Neuroendocrine system of nematodes

A significant number of peptidergic neuroendocrine cells occur in the CNS of nematodes. The genome of *Caenorhabditis elegans* contains 41 genes encoding peptide hormones, 21 of which represent FMRF-like peptides with multiple functions in neural transmission (Li *et al.* 1999). A neuroendocrine network that has been characterized in detail in *C. elegans* regulates growth, metabolism, and lifespan (Kimura *et al.* 1997, Gerisch *et al.* 2001, Jia *et al.* 2002, Tatar *et al.* 2003, Gissendanner *et al.* 2004, Kurz & Tan 2004, Mak & Ruvkun 2004). Central neurons producing insulin-like peptide act on a group of cells, among them a pair of sensory neurons and a set of epidermal cells in the head, which express a cytochrome P450 enzyme (encoded by the *daf-9* gene) suspected to be involved in the synthesis of a steroid hormone. This suspected hormone acts on a widely expressed nuclear receptor (encoded by the *daf-12* gene), which promotes molting. The insulin and steroid pathway, similar to their function in other animals, control growth, metabolism, and lifespan. One might speculate that the epidermal cell cluster expressing cytochrome P450 are evolutionarily related to the ectodermally derived cells of the prothoracic gland in insects, or the Y-organ in crustaceans.

Development of the insect neuroendocrine system

Formation of the peripheral endocrine glands

The ontogeny of the neuroendocrine system has been followed for a number of insect species; little is known about this process outside of the insects. According to Dorn's (1972, 1998), careful histological studies in *Oncopeltus* and other taxa, the anlage of the prothoracic gland (PG) arises in the ectoderm of the labial segment, lateral of the salivary gland. Following invagination cells of the PG anlage become mesenchymal and migrate dorsally. They are in contact with the first segmental tracheal branch that permeates the prothoracic segment. Mitosis within the PTG primordium ceases after blastokinesis (germ band retraction); at this stage, the number of cells approximates 300. This number remains constant throughout development until the adult stage.

The anlage of the corpora allata (CA) makes it appearance in a manner similar to that of the PTG. In this case, a group of cells invaginates from the ventro-anterior ectoderm of the maxillary segment. Adopting a solid, mesenchymal organiz-ation, the primordium of the CA migrates dorsally where it comes in contact with the third endocrine gland, the corpora cardiaca (CC). This structure derives from cells that can be first detected adjacent to the primordium of the esophagus. The roof of the esophagus of the early insect embryo contains three large, unpaired placodes, aligned antero-posteriorly, which give rise to the neurons of the stomatogastric nervous system (Hartenstein 1997). Following invagination, these cells dissociate and differentiate as neurons, which move along the elongating foregut and anterior midgut and eventually aggregate into the ganglia of the SNS. As mentioned earlier, the SNS (very similar to the vertebrate intramural autonomic ganglia) contains numerous NSCs, but their projection and function is largely unknown. Precursors of the CC can be first detected on either side of one of the SNS placodes (Dorn 1972, 1998, Copenhaver & Taghert 1991), and it has been stated that CC precursors invaginate, or delaminate, from the same esophageal epithelial domain that also gives rise to the SNS. As the esophagus primordium stretches posteriorly, the cells of the SNS and CC precursors move along until they reach the CA primordium.

In *Drosophila*, the peripheral endocrine glands appear to develop along similar lines as in other insects, although the conspicuous invaginating ectodermal placodes that give rise to these glands in *Oncopeltus* and other species have not been observed in the fly. Molecular markers, among them the transcriptional regulator Glass, are expressed in the precursors of the CC at a time when these are aligned with the SNS placodes. However, the origin of these cells from one of the placodes has so far not been confirmed; instead, mutant analysis suggests that the CC precursors originate from the anterior ventral furrow, which is adjacent to, yet separate from, the esophagus primordium (De Velasco *et al.* 2004). The precursors of the *Drosophila* PTG and CA can be traced to the dorsal region of the gnathal segments (maxilla,

labium; A Younossi-Hartenstein, F Wang & V Hartenstein (unpublished observations), Fig. 4C and E), which corresponds to the location identified as the site of origin of the corresponding structures in other insects (discussed earlier). The *Drosophila* adhesion molecule DN-cadherin is expressed in this domain, first in the ectoderm, and then (after an inconspicuous delamination event transporting the cells into the interior of the embryo) in a mesenchymal cluster of cells that migrate dorsally, following the elongating tracheal primordium to which they become attached at an early stage. In the late embryo, these cells merge with the CC precursors arriving from anteriorly and become arranged as a ring-shaped cluster around the anterior end of the dorsal vessel (Fig. 4D–G).

Development of the central neuroendocrine system

The PI/PL originate as placodes from the dorso-medial neuroectoderm of the head (Younossi-Hartenstein *et al.* 1996, B De Velasco, T Erclik, D Shy, J Sclafani, HD Lipshitz, RR McInnes & V Hartenstein (unpublished observations) in a way that is similar to the formation of a few other structures of the nervous system of the head, including the optic lobe (Green *et al.* 1993) and the stomatogastric nervous system (Hartenstein *et al.* 1994). In all of these cases, shortly after gastrulation, small domains of the neuroectoderm adopt the shape of placodes (Fig. 4G and H), with cells elongating in the apico-basal axis and expressing a higher level of apical markers (such as the Crumbs protein) at their apical surface. Eventually, all of these placodes invaginate, dissociate, and directly turn into neural cells (as in the case of the PI placode, or the SNS placodes), or give rise to neuroblasts (as for the optic lobe). In the dorso-medial head, one can recognize four bilateral pairs of placodes aligned along the antero-posterior axis. The anterior pair gives rise to the PI and the second pair to the PL. In the late embryo, following their invagination, both placodes become part of the dorso-medial brain cortex. A subset of neurons formed from these placodes express neuropeptides and send out axons that innervate the CC and CA.

The origin of the PSCs forming the central neuroendocrine system from epithelial placodes is atypical for insects. Most neurons of the insect brain are formed by the proliferation of stem cell-like neuroblasts, which delaminate as individual cells from the neuroectoderm. It seems probable that the neuroblast-mode of neural cell birth and proliferation is a derived feature because it appears not to be present in taxa considered basal in the arthropods, and taxa outside the arthropods. In chelicerates and chilopods, for example, the neuroectoderm produces a large array of small placodes, which subsequently invaginate, dissociate, and differentiate into the neurons and glial cells of the ventral nerve cord and brain (Stollewerk *et al.* 2001, Dove & Stollewerk 2003, Kadner & Stollewerk 2004). Regarding their pattern, the placodes are comparable to the array of neuroblasts in insects. One might speculate that at the root of arthropods, the

neuroectoderm gave rise to an array of small placodeal domains, which invaginated and produced a specific part of the CNS. In later stages of evolution leading towards insects, this mode of neurogenesis was replaced by the 'invention' of stem cell-like neuroblasts. According to this hypothesis, one would have to conclude that the occurrence of placodes along the head midline, giving rise to the PI and PL, of insects represents a vestige of the phylogenetically older mode of neurogenesis. Similarly, one could argue that molecular mechanisms at work in these placodes, or the function of brain parts derived from them, is phylogenetically more ancient compared with structures developing from neuroblasts. This makes further research on the formation of the neuroendocrine placodes an important area in developmental neurobiology.

Genetic control of neuroendocrine development: a comparison between *Drosophila* and vertebrates

### Similarities in structure and function

Many previous studies have emphasized similarities between the neuroendocrine system of vertebrates and arthropods on the structural, functional, and developmental levels (e.g. Veelaert *et al.* 1998), despite the fact that these taxa are separated by more than 500 Mio years of evolution. In both vertebrates and arthropods, the highest command center of the neuroendocrine system is comprised of groups of NSCs located in the brain; these cells, beside innervating brain centers and thereby influencing neural circuits as 'neuromodulators', send their axons to peripheral neurohemal glands in which the hormones produced by the NSCs are stored and released. In vertebrates, neurosecretory cells are located in the hypothalamus. The endocrine gland they act upon is the pituitary. The corresponding structures in arthropods would be the PI/PL and their peripheral targets, the CC/CA respectively. The main hormone produced by the CC, adipokinetic hormone (AKH), mobilizes lipids and carbohydrates from the fat body (O'Shea & Rayne 1992, Oudejans *et al.* 1999, Van der Horst *et al.* 2001, Diederen *et al.* 2002) and thereby resembles vertebrate glucagon that is produced in endocrine cells of the pancreas, as well as peptidergic neurons in the brain (Han *et al.* 1986). AKH also shows some sequence similarity with the N-terminus of glucagons (Scarborough *et al.* 1984). The relationship between *Drosophila* insulin-like peptides and AKH (Kim & Rulifson 2004) is most likely homologous to the antagonism between glucagon and insulin in vertebrates. There exist a number of other neuropeptides, among them FMRFamides (Rastogi *et al.* 2001, Nassel 2002), tachykinins (Nussdorfer & Malendowicz 1998) and CRF/CRF-like diuretic hormone (Schoofs *et al.* 1997, Nassel 2002) found in vertebrate hypothalamus and insect PI.

Signaling pathways affecting neuroendocrine development

The vertebrate and *Drosophila* neuroendocrine systems show significant similarities during early development. Both structures arise within the anterior neural plate where the anlage of the pituitary/CC is anteriorly adjacent to the cells, which will become the hypothalamus/pars intercerebralis (Couly & Le Douarin 1990, Eagleson & Harris 1990, De Velasco *et al.* 2004). At the time when the fate map of the neuroendocrine system and other structures associated with the brain is established, Shh is expressed near the midline of the vertebrate neuroectoderm and is required to promote the expression of determinants of hypothalamus and pituitary fate (Fig. 5A; Rosenfeld *et al.* 2000, Herzog *et al.* 2003, Roessler *et al.* 2003, Sbrogna *et al.* 2003). At a corresponding

early stage of development, *Drosophila* Hh plays no role yet in specifying the anlagen of the PI/PL or the neuroendocrine glands. However, Dpp (the *Drosophila* BMP2/4 homolog) is expressed in the dorsal midline and is involved in delineating the fate map of the brain, including the PI/PL (Fig. 5B; B De Velasco, T Erclik, D Shy, J Sclafani, HD Lipshitz, RR McInnes & V Hartenstein (unpublished observations)).

At a later stage when the morphogenesis of the neuroendocrine system is under way, precursors of the pituitary/CC become closely associated with the primordium of the foregut. During this stage, Shh/Hh is expressed posteriorly adjacent to the CC/Rathke's pouch in the primordium of the foregut/oral epithelium in both vertebrates and *Drosophila* (Fig. 5C and D). At the same stage, expression of BMP2/4 is initiated in the mesenchyme
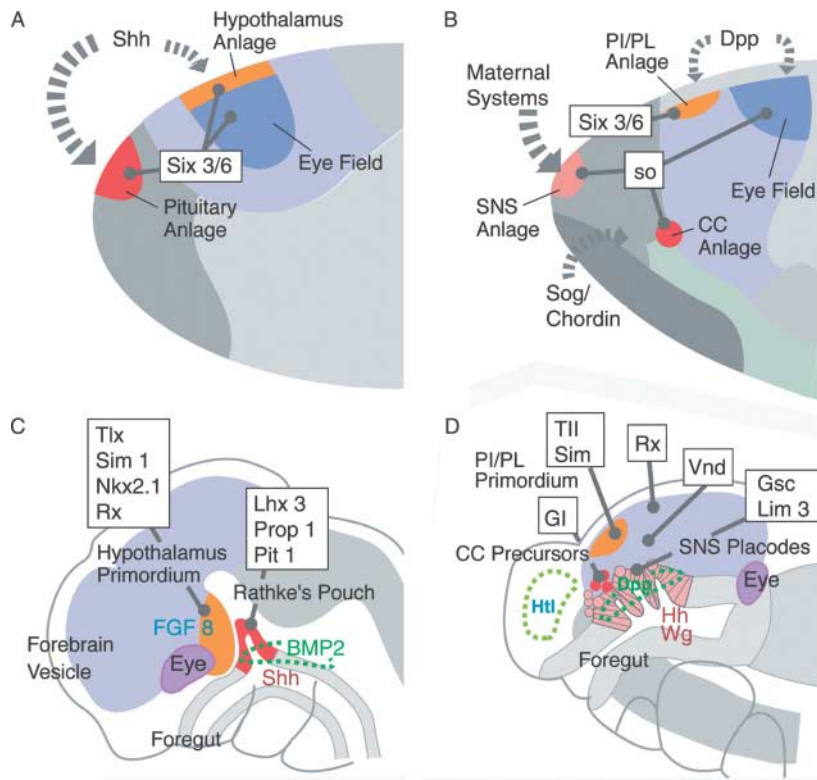
Figure 5 Molecular determinants of embryonic neuroendocrine system development in vertebrate ((A) and (C)) and *Drosophila* ((B) and (D)). All panels show schematic lateral views of anterior part of embryos (anterior to the left, dorsal up). ((A) and (B)) Postgastrula stage embryos. The eye field forms in the anterior domain of the neural plate. The anlage of the hypothalamus represents the medial part of the eye field; the anlage of the pituitary (anterior lobe) is located anteriorly adjacent to the hypothalamus. In *Drosophila*, the anlage of the pars intercerebralis/pars lateralis is located near the midline of the head neuroectoderm, anteriorly adjacent to the eye field. The anlagen of the corpora cardiaca and stomatogastric nervous system (SNS) map anterior to the head neuroectoderm. In the later stage vertebrate embryo (C), hypothalamus and anterior pituitary are seen in their primordial state. The primordium of the anterior pituitary, called Rathke's pouch, invaginates from the roof of the stomodeum and comes into contact with the primordium of the hypothalamus. In a *Drosophila* embryo of a corresponding stage (D), the primordium of the SNS forms three invaginating placodes in the roof of the foregut. Precursors of the corpora cardiaca are associated with the SNS primordium. The expression pattern of relevant signaling pathways and transcription factors (boxed) involved in neuroendocrine system specification is indicated.

surrounding the base of Rathke's pouch (Fig. 5C). Similarly, in *Drosophila*, Dpp appears in the mesoderm flanking foregut primordium, CC and SNS (Fig. 5D). A third signaling pathway active in pituitary development is the FGF pathway. FGF8 and FGF3 are secreted from the hypothalamus primordium in vertebrates (Fig. 5C; Ericson *et al.* 1998, Dasen & Rosenfeld 2001, Burgess *et al.* 2002, Herzog *et al.* 2003). The expression of FGF homologs in the *Drosophila* head has not yet been analyzed; however, the FGFreceptor homolog *heartless* (*htl*) is expressed in the head mesoderm anteriorly adjacent to the CC/SNS primordium, indicating a role of FGF signaling in the morphogenesis of these structures (De Velasco *et al.* 2004). In vertebrates, the ventral-to-dorsal BMP gradient and dorsal-to-ventral FGF8 gradients control the differentiation of pituitary cell types. Shh is required in the proliferation and differentiation of the pituitary primordium (Treier *et al.* 2001). The role of these signaling pathways in *Drosophila* has so far not been defined as clearly. The CC is still present in *dpp* and *hh* or *htl* mutant embryos, although it exhibits abnormalities in shape and location (De Velasco *et al.* 2004). One can hope that the use of additional markers for subsets of CC cell types will further elucidate the role of the Hh- and Dpp-signaling pathways in neuroendocrine development.

Similarities in transcriptional regulators controlling neuroendocrine cell fate

Shared regulatory genes switched on by the signaling pathways mentioned in the preceding section add to the overall similarity between neuroendocrine development in vertebrates and flies. One example is the expression pattern of genes of the *sine oculis/six* group. In *Drosophila*, *sine oculis* (*so*) appears in a fairly restricted manner in the eye field, the stomatogastric anlage, and the anterior lip of the ventral furrow that gives rise to the CC (Cheyette *et al.* 1994, Chang *et al.* 2001, De Velasco *et al.* 2004, B De Velasco, T Erclik, D Shy, J Sclafani, HD Lipshitz, RR McInnes & V Hartenstein (unpublished observations) Fig. 5B). Another gene of the same family, *optix*, the ortholog of vertebrate *six3/6*, is expressed in an anterior unpaired domain close to the SNS and PI anlage (Seimiya & Gehring 2000). In the early vertebrate embryo, *six3/6* is specifically expressed in the eye field and the anlage of the pituitary (Jean *et al.* 1999, Ghanbari *et al.* 2001, Fig. 5A); *six1/2*, orthologs of *Drosophila sine oculis*, are expressed in sensory placodes of the vertebrate head, although no pituitary expression has so far been reported. Thus, in both *Drosophila* and vertebrates, a *sine oculis/six* gene plays an early and essential role in the specification of the CC and pituitary respectively. In *Drosophila*, both CC and SNS are absent in *so* mutants; in vertebrate loss of *six3/6* causes severe reduction and posteriorization of the forebrain region (Lagutin *et al.* 2003).

Other transcriptional regulators that are expressed during development of the hypothalamus of vertebrates (Fig. 5A and C) include *Rx* (Mathers *et al.* 1997, Deschet *et al.* 1999), the paired-box genes *pax6* (Kioussi *et al.* 1999) and *Nkx2.1/2*

(Takuma *et al.* 1998), the PAS-bHLH gene *sim1* (Michaud *et al.* 1998), and the orphan nuclear receptor Tlx (Monaghan *et al.* 1995, Hollemann *et al.* 1998). Homologs of all of these transcription factors also appear in or adjacent to the anlage of the *Drosophila* PI/PL (Fig. 5D): Rx is expressed posterior to the PL placode (Eggert *et al.* 1998, Fig. 4H); the Nkx2.1/2 homolog *vnd* (Nirenberg *et al.* 1995) appears laterally adjacent to the PI placode (B De Velasco, T Erclik, D Shy, J Sclafani, HD Lipshitz, RR McInnes & V Hartenstein (unpublished observations)); the Sim1 homolog *sim* and the Tlx homolog *tailless* (*tll*) are both present in the PI placode (B De Velasco, T Erclik, D Shy, J Sclafani, HD Lipshitz, RR McInnes & V Hartenstein (unpublished observations)). Loss of *tll* function results in the absence of the PI; the role of the other transcription factors in PI development awaits further study.

Members of the LIM family (Lhx 3, Pit-1, and Prop-1) of transcription factors play an early and essential role in the vertebrate pituitary (Ericson *et al.* 1998, Dasen & Rosenfeld 2001, Burgess *et al.* 2002). *Drosophila lim3* is expressed at a later stage in part of the SNS primordium, but not the CC primordium (Thor *et al.* 1999, De Velasco *et al.* 2004). No structural phenotype associated with the SNS or CC has been noted in *lim3* mutants. Two additional factors, Glass (Gl) and Giant (Gt), are centrally involved in *Drosophila* CC development, since loss of either of them results in the absence of this structure (De Velasco *et al.* 2004). Vertebrate counterparts with similar function have so far not been described.

In conclusion, there is evidence for a number of conserved properties in the way the progenitors of the neuroendocrine system in vertebrate and *Drosophila* embryos are spatially laid out, and employ cassettes of signaling pathways and fate determinants. This suggests that fundamental elements of a primordial 'neuroendocrine system' were already present in the Bilaterian ancestor. Among such elements could have been populations of neurosecretory neurons from which the central neuroendocrine compartments of extant taxa (e.g. vertebrate hypothalamus, insect PI) evolved. Current ideas on pituitary evolution (reviewed in Gorbman 1995) are also compatible with the notion of a primitive neuroendocrine system in the bilaterian ancestor. Thus, sensory structures that may constitute homologs of the vertebrate pituitary exist in lower deuterostomes (cephalochordates, urochordates, and hemichordates). These data support the idea, discussed in the beginning section of this review, that the pituitary and comparable invertebrate endocrine glands originated early in bilaterian evolution as a chemosensory structure involved in reproductive behavior, feeding, and control of fundamental metabolic functions. In later stages of evolution, this 'ancestral pituitary forerunner' was internalized and placed under the control of NSCs located in the CNS. It is possible that this 'centralization' of the ancestral pituitary occurred in several phyla independently. To shed light on this issue, we can eagerly await more molecular comparisons between the neuroendocrine systems of 'model systems', such as *Drosophila*, mouse, and zebrafish, as well as comparative analyses of

neuroendocrine development in the multitude of invertebrate taxa about which fairly little is known at present.

Acknowledgements

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