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Neuronal migration during development and the amyloid precursor protein

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The Amyloid Precursor Protein (APP) is the source of amyloid peptides that accumulate in Alzheimer's disease. However, members of the APP family are strongly expressed in the developing nervous systems of invertebrates and vertebrates, where they regulate neuronal guidance, synaptic remodeling, and injury responses. In contrast to mammals, insects express only one APP ortholog (APPL), simplifying investigations into its normal functions. Recent studies have shown that APPL regulates neuronal migration in the developing insect nervous system, analogous to the roles ascribed to APP family proteins in the mammalian cortex. The comparative simplicity of insect systems offers new opportunities for deciphering the signaling mechanisms by which this enigmatic class of proteins contributes to the formation and function of the nervous system.

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Introduction: neuronal migration and the formation of the insect nervous system

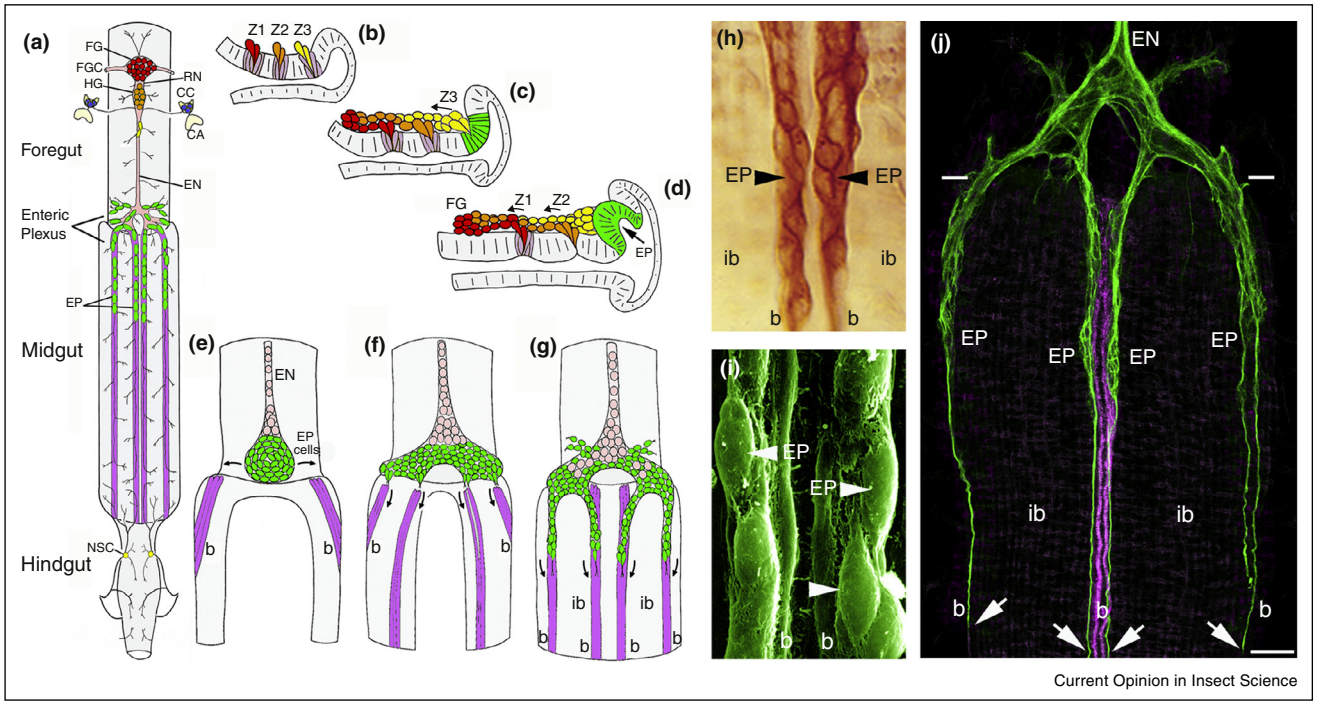
The directed migration of neurons and glia along specific pathways is a universal feature of developing nervous systems [1,2], during which cells navigate through a dynamic environment of potential guidance cues. The phenomenon of neuronal migration was first recognized in vertebrate development, where it is critical to the formation of both the central nervous system (CNS) and peripheral nervous systems (PNS) [3,4], and more modern methods have revealed extraordinary complexity in the modes of migration that give rise to the mammalian cortex [5••,6•]. The initiation, extent, and termination of migration must be precisely regulated, and a variety of evolutionarily conserved guidance cues have been identified that influence particular aspects of migratory behavior [7,8•]. The significance of the migratory process has been underscored by the numerous developmental defects and neurological diseases arising from errors in migration [9,10••], although the precise mechanisms underlying many of these defects have proven more difficult to ascertain.

Neuronal migration also plays important roles in invertebrate nervous systems, including mollusks [11], crustaceans [12], and nematodes [13,14], where the molecular pathways regulating the migratory process can be investigated within intact organisms. Until recently, however, the contribution of migration to the formation of insect nervous systems was under-appreciated. Although the differentiation of the embryonic CNS in insects typically involves relatively small displacements of newly generated neurons from their neurogenic niches [15,16•], more dramatic patterns of neuronal and glial migration have now been documented in both the embryonic PNS [17] and the developing adult CNS [18,19,20•]. A particularly striking example of migration was recently identified in the developing adult visual system of Drosophila, during which streams of newborn neurons travel into the optic lobes of the brain to establish discrete layers of interneurons with position-specific characteristics [21•,22••,23••]. Intriguingly, this process involves Notch-dependent cell fate selection and Slit/Robo-dependent cell positioning (both of which also regulate neurogenesis in the mammalian cortex), providing an elegant illustration of how evolutionarily conserved mechanisms controlling migration play analogous roles in both insect and vertebrate nervous systems [2].

The insect enteric nervous system: a dramatic example of neuronal migration

The most dramatic examples of neuronal migration in insects have been described in the developing enteric nervous system (ENS). Analogous to the vertebrate ENS, the insect ENS represents a distinct division of the PNS that provides innervation to the gut and regulates digestion and metabolism [24], as well as modulating a variety of endocrine functions [25,26]. As in other organisms, the insect ENS consists of interconnected peripheral ganglia and nerve plexuses that innervate the gut musculature. In contrast to vertebrates, however, the insect ENS lies superficially on the gut, making it more amenable to direct experimental manipulations. In general, the

Figure 1



Embryonic development of the insect Enteric Nervous System (ENS) involves extensive patterns of neuronal and glial migration. **(a)**, Schematic drawing of the ENS and associated neurosecretory organs in the larval stage of the tobacco hornworm *Manduca sexta* (modified from [27]). The primary ganglion on the foregut is the frontal ganglion (FG; red), connected to the overlying brain lobes by paired frontal ganglion connectives (FGC). Several nerve branches extend anteriorly onto the pharynx, while the recurrent nerve (RN) extends posteriorly to the hypocerebral ganglion (HG; orange), situated below the brain. In Manduca, the hypocerebral ganglion initially forms during embryogenesis but then becomes closely opposed to the frontal ganglion and is no longer readily distinguished in later stages. The HG is also connected to the paired *corpora cardiaca* (CC; blue), the primary neurosecretory organs of the brain, which are adjacent to the *corpora allata* (CA; the source of Juvenile Hormone). From the HG, the esophageal nerve (EN) extends posteriorly along the length of the foregut, giving rise to short nerve branches that innervate the foregut musculature. Near the foregut-midgut boundary, the esophageal nerve connects with the enteric plexus that spans the foregut-midgut boundary, which includes nerve branches extending along radial muscles on the foregut and major nerves that extend along eight well-defined muscle bands that lie superficially on the midgut (purple). The enteric plexus contains a population of ~300 distributed neurons (EP cells; green), which includes intermingled groups of neurons expressing a variety of morphological and transmitter phenotypes. The EP cells occupy positions along the anterior 20% of the midgut, and extend long axons posteriorly along the muscle bands with sparse lateral branches that provide a diffuse innervation of the interband midgut musculature. The hindgut is innervated by branches of the proctodeal and rectal nerves that originate in the terminal abdominal ganglion of the ventral nerve cord. Branches of the proctodeal nerve also extend onto the posterior midgut and contain several peripheral neurosecretory cells (yellow). Neurogenesis of the developing ENS in Manduca (after [31]). Panels **(b–d)** show lateral views of the foregut midline; anterior is to the left, dorsal is to the top. When raised at 25 °C, Manduca embryogenesis is complete in 100 hr (1 hr = 1 hour post-fertilization, or hpf). **(b)** By ~24 hpf, three neurogenic zones (Z1, Z2, & Z3) have formed in the dorsal foregut epithelium, which give rise to a series of mitotically active precursor cells via sequential delamination. Precursors giving rise to neurons typically divide only once (or occasionally twice) after delaminating, similar to midline precursors in the embryonic CNS. **(c)** By 28 hpf, streams of zone-derived cells have begun to migrate anteriorly along the foregut, while the remaining zone 3 cells delaminate as a group. The epithelium surrounding the original position of zone 3 subsequently differentiates into a distinct placode that will form the EP cells (green). **(d)** By 33 hpf, migrating zone cells have begun to form the frontal ganglion (FG), while the remaining zone 2 cells delaminate as a group. The EP cell placode has also begun to invaginate from the EP cell packet (described below). Zone 1 continues to generate cells until almost 40 hpf (not shown); late-emerging zone cells derived from all three zones tend to become glial precursors that remain mitotically active throughout much of embryogenesis and establish the glial sheath surrounding the foregut nerves and ganglia. Formation of the midgut enteric plexus; panels **(e–g)** show dorsal views of the developing ENS at the foregut-midgut boundary (after [88]). **(e)** By 40 hpf, the EP cells (green) have invaginated *en mass* from their neurogenic placode located within the posterior dorsal lip of the foregut (**d**, green). The neurons then commence a bilateral spreading phase of migration (arrows) that almost completely encircles the foregut, adjacent to the foregut-midgut boundary. Concurrently, subsets of longitudinal muscles on the midgut (magenta) begin to coalesce into eight well-defined bands as dorsal closure of the midgut proceeds. Anteriorly, the EP cell packet is in continuity with the developing esophageal nerve (EN), which contains populations of proliferating glial precursors (pink; derived from zone 3) that will subsequently ensheath the enteric plexus. **(f)** By 55 hpf, the EP cells have almost completely surrounded the foregut, and subsets of the neurons have aligned with each of the midgut muscle bands (only the dorsal four are shown). **(g)** By 58 hpf, subsets of EP cells have begun to migrate in a chain-like manner along the midgut muscle bands; smaller subsets also migrate onto radial muscles of the foregut (muscles not shown). Proliferating glial cells (pink) subsequently migrate along the pathways established by the neurons, thereby ensheathing the branches of the enteric plexus. **(h)** Magnified view of EP cell groups migrating on the mid-dorsal band pathways (at 58 hpf) of an embryo immunostained with an antibody recognizing all isoforms of the cell adhesion receptor Fasciclin II (Fas II). The migratory neurons and underlying muscle bands (b) express transmembrane Fas II (TM-Fas II), while the trailing glial cells express GPI-linked Fas II. The migratory EP cells and their processes remain