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Eph proteins and the assembly of auditory circuits

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Abstract

Many kinds of information are carried in the acoustic signal that reaches auditory receptor cells in the cochlea. The analysis of this information is possible in large part because of the neuronal architecture of the auditory system. The mechanisms that establish the precise circuitry that underlies auditory processing have not yet been identified. The Eph receptor tyrosine kinases and their ligands are proteins that regulate axon guidance and have been shown to contribute to the establishment of topographic projections in several areas of the nervous system. Several studies have begun to investigate whether these proteins are involved in the formation of auditory system connections. Studies of gene expression show that Eph proteins are extensively expressed in structures of the inner ear as well as in neurons in the peripheral and central components of the auditory system. Functional studies have demonstrated that Eph signaling influences the assembly of auditory pathways. These studies suggest that Eph protein signaling has a significant role in the formation of auditory circuitry.

Keywords: Auditory pathways; Auditory nerve; Axon guidance; Eph receptor; Ephrin

1. Introduction

Neuronal connections in the auditory system convey detailed information about the timing, intensity, and frequency of sounds. These features are used to compute more complex aspects of acoustic input, such as interaural phase and intensity differences, which are used to determine the location of sound sources. The ability of the auditory nervous system to make these computations depends on precision in the arrangement of auditory circuitry.

One of the principal features of this circuitry is tonotopy. The orderly arrangement of best frequency in the cochlea is preserved at the level of the cochlear ganglion, which sends tonotopic projections peripherally to hair cells, as well as centrally, to the cochlear nucleus of the brainstem (Rubel and Fritzsch, 2002). Within the brainstem, the cochlear nucleus in turn makes tonotopic connections with its targets. A second feature is that contralateral targets differ from ipsilateral targets (Cant and Benson, 2003), a distinction important in sound localization. For example, the chick nucleus magnocellularis (NM) projects to its target, nucleus laminaris (NL), bilaterally. The auditory brainstem circuitry of chicks is shown schematically in Fig. 1A. The ipsilateral branch of NM axons contacts the dorsal dendrites and cell bodies of NL, while the contralateral branch contacts ventral dendrites of NL and cell bodies. This arrangement aids in the computation of interaural phase differences (Young and Rubel, 1983; Carr and Konishi, 1990; Overholt et al., 1992). In an analogous pathway in the mammalian brainstem (Fig. 1B), neurons in the anteroventral cochlear nucleus (AVCN) project to the medial superior olive (MSO) on both sides of the brain, with ipsilateral

Abbreviations: AVCN, anteroventral cochlear nucleus; GPI, glycosyl-phosphatidylinositol; LSO, lateral superior olive; MGB, medial geniculate body; MNTB, medial nucleus of the trapezoid body; MSO, medial superior olive; NL, nucleus laminaris; NM, nucleus magnocellularis

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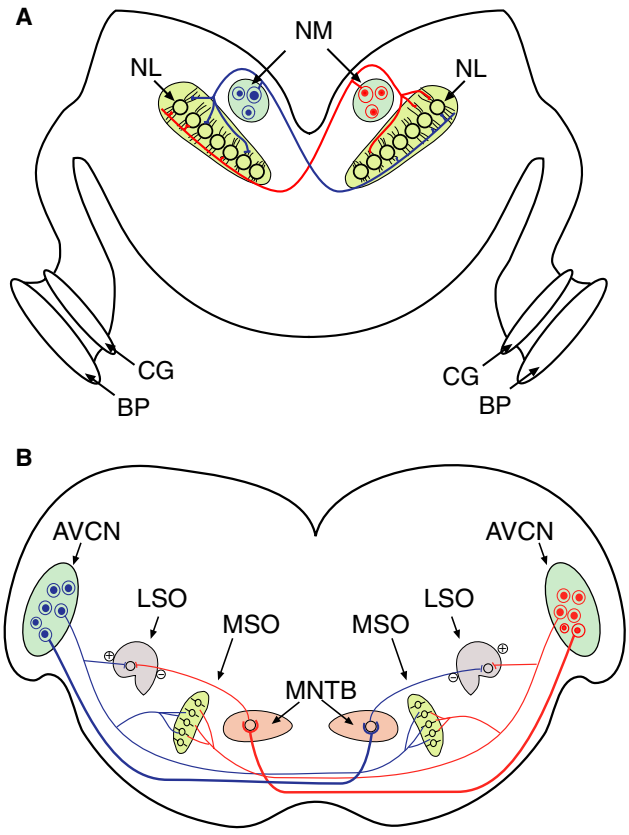

Fig. 1. Schematic illustrations of some auditory pathways in avian and mammalian brainstems. (A) Chick auditory brainstem connections. The basilar papilla (BP) and NM both receive tonotopic input from cochlear ganglion (CG) neurons. NM in turn projects tonotopically to NL. Each NL neuron receives segregated inputs from the ipsilateral and contralateral NM. This circuit computes interaural phase differences, used to localize sound sources in the low frequency ranges. (B) Mammalian auditory brainstem connections. The anteroventral cochlear nucleus (AVCN) is homologous to NM. Spherical bushy cells in AVCN project to ipsilateral and contralateral MSO, which is analogous to NL. This pathway computes interaural phase differences. This computation in MSO also relies on inhibitory inputs (not shown), which arise from MNTB and LNTB. In addition, globular bushy cells in AVCN make strictly contralateral projections to MNTB, which sends inhibitory ipsilateral connections to LSO. LSO cells receive a tonotopically matched input from spherical bushy cells in ipsilateral AVCN. These inhibitory and excitatory projections to LSO neurons aid in the computation of interaural intensity differences, which are used to localize high frequency sounds.

axons contacting the lateral dendrites of MSO and contralateral axons contacting the medial dendrites (Cant, 1992; Cant and Benson, 2003). The mammalian MSO differs from NL in that inhibitory projections contribute significantly to the computation of interaural intensity differences (Brand et al., 2002; Grothe, 2003). These inhibitory projections arise from the lateral and medial nucleus of the trapezoid body (Cant and Hyson, 1992; Kuwabara and Zook, 1992; Grothe and Sanes, 1993; Smith et al., 2000). In another mammalian brainstem pathway, AVCN neurons project to MNTB on the contralateral side, but not on the ipsilateral side (Fig. 1B). MNTB neurons in turn make inhibitory projections to the lateral superior olive (LSO). LSO receives these tonotopic projections in register with excitatory ipsilateral inputs from AVCN spherical bushy cells (Glendenning et al., 1985). The balance between inhibitory and excitatory projections to LSO neurons contributes to the computation of interaural intensity differences, which are used to localize high frequency sounds.

An important challenge for auditory neuroscience is to understand how these circuits are assembled during embryonic and postnatal development. Patterns of connectivity are in essentially correct locations from their initial arrival at target regions, with some projections and synaptic weights refined by activity-dependent processes (Sanes and Rubel, 1988; Friauf and Lohmann, 1999; Leake et al., 2002; Rubel and Cramer, 2002). Moreover, tonotopic connections between the cochlea and spiral ganglion form even in the absence of differentiated hair cells (Xiang et al., 2003). It is thus likely that auditory circuits form largely through activity-independent processes. Several axon guidance molecules have recently been identified that have roles in many regions of the nervous system and are thus good candidates within the auditory region. How does the auditory system make use of developmental molecules during the formation of its specialized structures and connectivity? The roles of one class of molecules, the Eph family proteins, are discussed here, with special emphasis on the formation of the auditory regions of the nervous system and their connectivity in the periphery and brainstem.

2. Eph proteins

The Eph proteins consist of Eph receptor tyrosine kinases and their ligands, called ephrins. Eph receptors are the largest known family of receptor tyrosine kinases (for review, see Flanagan and Vanderhaeghen, 1998). Eph-ephrin binding mediates cell–cell interactions because ephrin ligands are membrane-associated. The ephrin-A ligands are associated with the membrane through a glycosyl-phosphatidylinositol (GPI) linkage, while the ephrin-B ligands have a transmembrane domain. Eph receptors are also classified into A and B classes. In general, ephrin-A ligands bind EphA receptors, while ephrin-B ligands bind EphB receptors. Two exceptions to this rule have been identified. EphA4 binds ephrin-B ligands (Gale et al., 1996), and EphB2 binds ephrin-A5 (Himanen et al., 2004). While interactions are often promiscuous within a class, there are differences in the affinity of a ligand for the different receptors.

The Eph family proteins are especially promising in the study of auditory circuitry because they have a well-established role in the formation of topographic maps