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Review

Cochlear afferent innervation development

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ABSTRACT

Sound signal is detected by sensory hair cells located in the cochlear region of the inner ear, and transmitted to the central nervous system by the spiral ganglion neurons (SGNs). These bipolar neurons develop long peripheral processes to connect hair cells, forming ribbon synapses, specialised for the precision and speed required to process auditory information. The establishment of a complex innervation pattern relies on specific signals, intrinsic to SGNs or provided by neighbouring cells, which are tightly controlled in time and space. In this paper, we review recent advances about stepwise development of afferent auditory neuronal circuitries, from neuron specification within the early otic vesicle to definitive synaptic connections with target cells. We especially focus on the cellular and molecular developmental changes involved in fibre outgrowth and extension to the sensory epithelium, specific afferent targeting to hair cells, and synaptic pruning.

1. Introduction

Hearing involves a sensory epithelium, known as the organ of Corti (OC) in mammals, which is located within the spiralled cochlea in the ventral region of the inner ear (Fig. 1A–B). The acoustic signal is detected by mechanosensory hair cells (HCs) which receive two different types of innervation: afferent innervation from spiral ganglion neurons (SGNs) (Kiang et al., 1982) and efferent innervation from the superior olivary complex (Liberman and Brown, 1986; Strutz, 1981). The primary afferent innervation includes two functionally distinct neuronal populations, which convey sound information from the cochlea to the central nervous system. In the mature OC, inner hair cells (IHCs) represent the principal encoder of the auditory signal, and each IHC is connected by multiple type I SGNs (about 90–95% of the neuronal population, see Fig. 1C–D). At mature stages an IHC forms synapses with 10–20 type I SGNs, depending on its particular position along the longitudinal axis of the cochlea (Meyer et al., 2009). By contrast, although the outer hair cells (OHCs) considerably outnumber the IHCs, their afferent innervation is much more limited. Type II SGNs, which represent approximately 5–10% of the total neuronal population, form “en passant” contacts with OHCs (Fig. 1C–E). Their fibres extend past the single row of IHC and turn towards the base of the cochlea upon reaching the OHCs. Type II SGNs form spiral bundles progressing towards the base of the cochlea (Fig. 1D), and each of them will innervate 3–10 target cells (Berglund and Ryugo, 1987). These type II connections are thought to modulate cochlear sensitivity (Jagger and Housley, 2003; Thiers et al., 2008) and have been recently demonstrated to drive the olivocochlear efferent reflex, which is responsible for a dynamic adjustment of hearing sensitivity and frequency selectivity (Froud et al., 2015). Additionally, type II SGNs have been suggested to play a nociceptive role upon noise-induced tissue damage (Flores et al., 2015). While peripheral projections of SGNs contact HCs, central axons - forming the VIIIth cranial nerve – project into the brainstem. The auditory system is extremely adept at discriminating acoustic signals according to sound frequency. Indeed, the cochlea houses IHCs and SGNs that are topographically organised along its longitudinal axis. The cells located in the basal portion of the cochlea respond to high frequency sounds while those residing at the apex are responsive to low frequencies. This tonotopic organisation is present at every level of auditory processing, from the cochlea to the auditory cortex.

Hearing impairments predominantly arise from a loss or defective function of HCs or SGNs in the cochlea. Currently,

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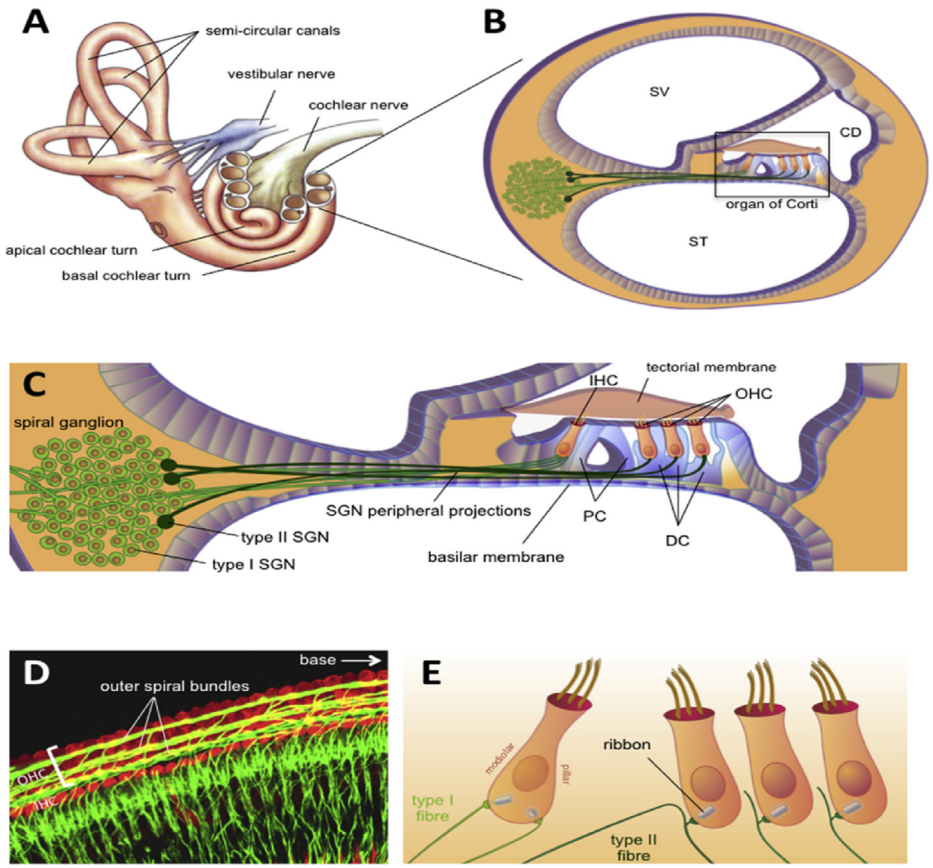

Fig. 1. The mature inner ear. (A) Schematic representation of the mature inner ear. The dorsal part contains the vestibule, which is the organ of balance and acceleration, and the ventral part contains the coiled cochlea responsible for the sense of hearing. Both regions are innervated by neurons that send their central projections, forming the VIIIth cranial nerve, to the brainstem. (B) Cross section through the cochlea showing the three fluid-filled chambers, scala tympanni (ST), scala vestibuli (SV) and cochlear duct (CD) where the organ of Corti (OC) is located. (C) The OC is composed of one row of inner hair cells (IHCs) and three rows of outer hair cells (OHCs), all of which bear an apical mechano-sensitive hair bundle. The extremity of the bundle is engulfed in the tectorial membrane. The surrounding supporting cells consist of, among others, Deiters' cells (DC) and Pillar cells (PC). Type I (light green) and type II (dark green) SGNs are gathered in the spiral ganglion on the modiolar side of the OC, and their peripheral projections travel long distances through the otic mesenchyme to connect IHCs and OHCs, respectively. (D) Optical confocal image of a whole-mounted cochlea. The HCs are labelled in red with specific Myosin VI antibody and SGNs are labelled in green with tubulin-βIII antibody. The majority of the fibres connect to IHCs and represent 90% of total SGNs (type I). The remaining 10% are type II SGNs and they pass through the IHCs row to project to OHCs. Once in the OHC area, type II projections shift toward the base of the cochlea and extend tangentially to form “en passant” contacts with 3–10 adjacent OHCs within the same row. Multiple fibres thus gather beneath the rows of OHCs to form the outer spiral bundles. (E) IHCs form ribbon synapses with 10–20 type I SGN fibres. Synapses located on the modiolar side (towards the spiral ganglion) display large ribbons that are associated with high-threshold fibres, characterised by a low-spontaneous discharge rate (LSR). Conversely, fibres that contact the pillar side (towards PCs and OHCs) are characterised by having low sensitivity thresholds and high spontaneous firing rates (HSR).

deafness resulting from HC loss can be treated with cochlear implants that directly stimulate the SGNs, shortcutting the need for sound detection by the HCs. The efficacy of this treatment is dependent on a reliable cochlear innervation pattern. Therefore it is crucial to understand exactly how the precisely ordered auditory circuitry is established.

The development of complex wired connections in the cochlea broadly involves the same succession of events that govern the formation of the peripheral and central nervous system (Nakamura and O'Leary, 1989; Walsh and Lichtman, 2003). After neuronal cell specification, neurites grow towards their target cells under the influence of survival and guidance cues (see section 2) and form initial synaptic contacts that will subsequently be remodelled to refine their functional connections (section 3). In this review we collate the most recent findings concerning the cellular and molecular mechanisms involved in SGNs development, from the initial formation to the subsequent maturation stages required for an accurate transmission of sound-induced vibrations.

2. Embryonic development of afferent innervation

2.1. Development of spiral ganglion neurons

The inner ear develops from a thickened portion of surface ectoderm located around the rostral neural plate, called the otic placode, which invaginates very early during embryogenesis (E8.5 in mice, see Fig. 2). The forming otic vesicle is instructed by extrinsic signals from surrounding tissues to give rise to progenitors of all of the neural, sensory and non-sensory cells that comprise the inner ear. The cells fated to develop as neurons, i.e. neuroblasts, delaminate from the anterior-ventral region of the otocyst and coalesce to form the cochlear-vestibular ganglion (CVG), which subsequently segregates to create the spiral and the vestibular ganglions. After successive rounds of proliferation, neuroblasts undergo terminal mitosis and SGNs begin to differentiate between E9.5 and E13.5 in a basal-to-apical progression along the length of the cochlea (Koundakjian et al., 2007; Matei et al., 2005). Fate-mapping experiments, as well as gene expression

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