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Molecularly and structurally distinct synapses mediate reliable encoding and processing of auditory information

Carolin Wichmann

Molecular Architecture of Synapses Group, Institute for Auditory Neuroscience & InnerEarLab, University Medical Center, Göttingen, Germany

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ABSTRACT

Hearing impairment is the most common human sensory deficit. Considering the sophisticated anatomy and physiology of the auditory system, disease-related failures frequently occur. To meet the demands of the neuronal circuits responsible for processing auditory information, the synapses of the lower auditory pathway are anatomically and functionally specialized to process acoustic information indefatigably with utmost temporal precision. Despite sharing some functional properties, the afferent synapses of the cochlea and of auditory brainstem differ greatly in their morphology and employ distinct molecular mechanisms for regulating synaptic vesicle release. Calyceal synapses of the endbulb of Held and the calyx of Held profit from a large number of release sites that project onto one principal cell. Cochlear inner hair cell ribbon synapses exhibit a unique one-to-one relation of the presynaptic active zone to the postsynaptic cell and use hair-cell-specific proteins such as otoferlin for vesicle release. The understanding of the molecular physiology of the hair cell ribbon synapse has been advanced by human genetics studies of sensorineural hearing impairment, revealing human auditory synaptopathy as a new nosological entity.

1. Introduction

Sound encoding involves several processing stations along the auditory pathway and relies on synapses with distinct morphology and also function. The synapses of the auditory pathway are tuned for high-frequency stimulation at high rates though their morphology strikingly differs. In this review, I will highlight differences as well as similarities between the ribbon synapses of sensory inner hair cells (IHCs), that are the first synapses in the auditory system, and the calyceal synapses in the auditory brainstem: the endbulb of Held as well as the calyx of Held (Fig. 1).

When sound invades the ear, it causes vibrations of the basilar and tectorial membranes of the cochlea thereby stimulating the sensory hair cells located in the organ of Corti. Here two types of hair cells are found, (i) the outer hair cells (OHCs) function as acoustic amplifiers due to their ability to contract upon depolarization (for review see e.g. Oghalai, 2004) and (ii) the IHCs, which act as the sensory receptors and translate acoustical information into neuronal signals. Deflection of the apical stereocilia causes a depolarization of the IHC due to the opening of mechano-transduction channels (Fettiplace and Kim, 2014). This process produces graded receptor potentials that open presynaptic voltage-gated $Ca_v1.3$ Ca^{2+} channels (Platzer et al., 2000; Brandt et al., 2003) and the ensuing Ca^{2+} influx triggers exocytosis (Moser and Beutner, 2000) of glutamate from the ribbon-type active zones in the base of the IHC (Glowatzki and Fuchs, 2002). In general, ribbon synapses are commonly found in many vertebrate sensory systems such as vision, hearing, balance and also in electro-receptors (overview: Matthews and Fuchs (2010)). Ribbon synapses are highly specialized entities, characterized by a large electron-dense structure, the synaptic ribbon that tethers synaptic vesicles. Though the overall

Abbreviations: AMPA, Alpha amino-3-hydroxy-5-methyl-4-isoxazole propionate; ATD, Action potential transmission delay; AVCN, Anteroventral cochlear nucleus; CAPS, Ca^{2+}-dependent activator of protein secretion; CAST, (CAZ)-associated structural protein; CAZ, Cytomatrix at the active zone; ELKS, Glutamine, leucine, lysine, and serine-rich protein; EPSC, Excitatory postsynaptic currents; IHC, Inner hair cell; IID, Interaural intensity differences; ITD, Interaural time difference; LSO, Lateral superior olive; MNTB, Medial nucleus of the trapezoid body; mRNA, Messenger ribonucleic acid; MSO, Medial superior olive; Munc, Mammalian uncoordinated; OHC, Outer hair cell; PDZ, Postsynaptic density protein (PSD95), *Drosophila* disc large tumor suppressor (Dlg1), and zonula occludens-1 protein (zo-1); RIM, Rab3-interacting molecule; RRP, Readily-releasable pool; SDS, Sodium dodecyl sulfate; SGN, Spiral ganglion neurons; SNAP-25, Synaptosomal-associated protein 25; SNARE, Soluble N-ethylmaleimide-sensitive factor attachment protein receptor; VGAT, Vesicular GABA (γ-aminobutyric acid) transporter; VGLUT, Vesicular glutamate transporter

E-mail address: cwichma@gwdg.de.

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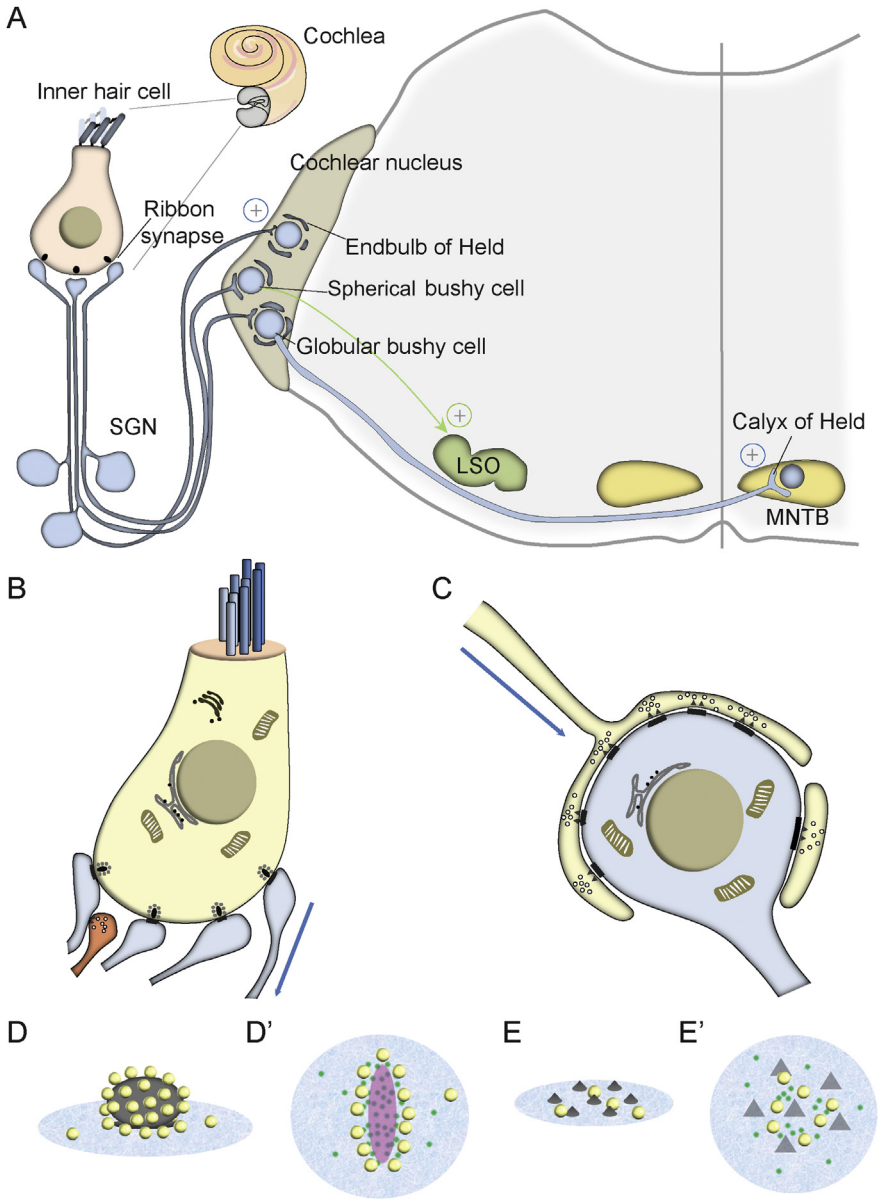

Fig. 1. Different synapses in the auditory pathway. (A) Circuit of the excitatory auditory pathway. Inner hair cells (IHC) are innervated by afferent fibers of the spiral ganglion neurons (SGN) that project onto bushy cells in the anteroventral cochlear nucleus (AVCN) forming the endbulbs of Held. Spherical bushy cells project onto principal cells in the lateral superior olive (LSO), whereas globular bushy cells project to the contralateral medial nucleus of the trapezoid body (MNTB), where they form the excitatory calyx of Held. Modified, courtesy of Linda Hsu, InnerEarLab, Göttingen, Germany). **(B)** Schematic drawing of an IHC with several afferent innervations (one fiber to one active zone relation) in light blue and in orange an efferent terminal. **(C)** Schematic drawing of a calyceal terminal forming many active zones on a single principal cell. **(D)** Scheme of a ribbon synapse with a large pool of ribbon-associated synaptic vesicles. **(D′)** Putative distribution of Ca^{2+} channels in correlation to the position of vesicles. **(E)** Schematic drawing of a calyceal synapse harboring small electron-dense specializations. **(E′)** Putative Ca^{2+} channel distribution at calyceal synapses. Ca^{2+} channels are reported to form clusters at active zones of the calyx of Held. The distribution of vesicles as well as their number is not clear to date. D-E': blue, active zone membrane; yellow: synaptic vesicles, gray: electron-dense specializations, green: Ca^{2+} channels. All schematic drawings are not drawn to scale.

morphology of ribbon synapses is conserved, they still vary considerably in size, shape and also molecular composition depending on the sensory system. Synaptic ribbons in the mature, hearing IHCs are oval or droplet-shaped when viewed in cross-section under the electron microscope. In the longitudinal direction, the mature ribbon is elongated (Sobkowicz et al., 1982; Wong et al., 2014). Vesicles are found clustered to the ribbon but also lined up at the active zone membrane (Frank et al., 2010; Wong et al., 2014; scheme in Fig. 1D, D′). For sound encoding at the IHC ribbon synapse, one particular feature is of great importance: every active zone is innervated via a single afferent spiral ganglion neuron (SGN) (Liberman, 1978) (Figs. 1B and 2A). Depending on the tonotopic position that determines the frequency sensitivity of the IHC, between 5 and 20 ribbon synapses are found within one cell (Meyer et al., 2009). Apart from distinct frequencies, IHC synapses also encode sound pressure levels. In this context, it has been suggested that functional and structural heterogeneity of synapses and SGN fibers in correlation to their position within one individual IHC account for this property (Liberman, 1982a, 1982b; Merchan-Perez and Liberman, 1996).

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