Hearing Research 311 (2014) 3–16

Contents lists available at ScienceDirect

Hearing Research

journal homepage: www.elsevier.com/locate/heares

Review

Morphological and physiological development of auditory synapses

Wei-Ming Yu, Lisa V. Goodrich*

Department of Neurobiology, Harvard Medical School, Boston, MA 02115, USA

ARTICLE INFO

Article history:
Received 5 October 2013
Received in revised form
13 January 2014
Accepted 20 January 2014
Available online 5 February 2014

ABSTRACT

Acoustic communication requires gathering, transforming, and interpreting diverse sound cues. To achieve this, all the spatial and temporal features of complex sound stimuli must be captured in the firing patterns of the primary sensory neurons and then accurately transmitted along auditory pathways for additional processing. The mammalian auditory system relies on several synapses with unique properties in order to meet this task: the auditory ribbon synapses, the endbulb of Held, and the calyx of Held. Each of these synapses develops morphological and electrophysiological characteristics that enable the remarkably precise signal transmission necessary for conveying the miniscule differences in timing that underly sound localization. In this article, we review the current knowledge of how these synapses develop and mature to acquire the specialized features necessary for the sense of hearing.

This article is part of a Special Issue entitled <Annual Reviews 2014>.

1. Preface

The sense of hearing provides critical information about the presence, location, and salience of diverse sounds encountered in the environment. We use sound information to communicate and interact with other people, to appreciate music, and to become alert to dangerous situations. Animals rely on sound signals for long distance communication and to locate prey or predators, both of which are essential for their survival. In order for the brain to distinguish among a wide range of complex sounds, the salient features of acoustic stimuli must be preserved as the signal is transferred along auditory pathways, from the initial detection of sound in the cochlea to perception in the brain. For instance, sound location is determined by networks of neurons in the brainstem that compare the differences in the level and timing of the sound when it arrives at each ear. Because these are microsecond differences, each signal must be received and transmitted faithfully with minimal loss of time and intensity information. To meet this demand, neurons in auditory circuits develop several unusual synapses – the ribbon synapse, the endbulb of Held, and the calyx of Held – that are capable of remarkably fast, sustained and reliable neural transmission. In this review, we summarize our current understanding of how these specialized synapses acquire the unique morphological and functional properties that underlie the sense of hearing.

2. Organization of neural circuits in the cochlea and auditory brainstem

Hearing begins with the detection of sound by hair cells in the cochlea of the inner ear. There are two types of hair cells in the sensory epithelium of the mammalian organ of Corti: a single row of inner hair cells (IHCs) and three to four rows of outer hair cells (OHCs). IHCs directly encode acoustic information (Nienhuys and Clark, 1978), whereas OHCs are responsible for mechanical amplification of sound-induced vibration (Ashmore and Kolston, 1994). Both types of HCs convert the mechanical stimuli that are generated by sound waves into electrochemical signals, which are passed on to spiral ganglion neurons (SGNs). As the sole neurosensory link from the cochlea to the brain, SGNs transmit all sound information from IHCs to target neurons in the central nervous system (CNS). SGNs are bipolar neurons, with peripheral processes that project toward HCs and central processes that extend through the eighth nerve into the auditory brainstem (Fig. 1). They are grouped into two classes depending on their pattern of peripheral innervation: Type I neurons, which innervate IHCs and constitute 90–95% of the total SGN population, and Type II neurons, which form *en passant* and terminal contacts with multiple OHCs and represent the remaining 5–10% of SGNs (Simmons and Liberman, 1988). HCs transmit frequency, intensity, and timing information to the SGNs via a specialized connection called the *ribbon synapse* (Fig. 1). The ribbon synapse contains a presynaptic ribbon, which is an electron-dense multi-protein structure tethering large clusters of synaptic vesicles (Khimich et al., 2005). It is suggested that the presynaptic ribbon supports a large pool of readily releasable vesicles, allows

* Corresponding author.
E-mail address: Lisa_Goodrich@hms.harvard.edu (L.V. Goodrich).

0378-5955/$ – see front matter © 2014 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.heares.2014.01.007

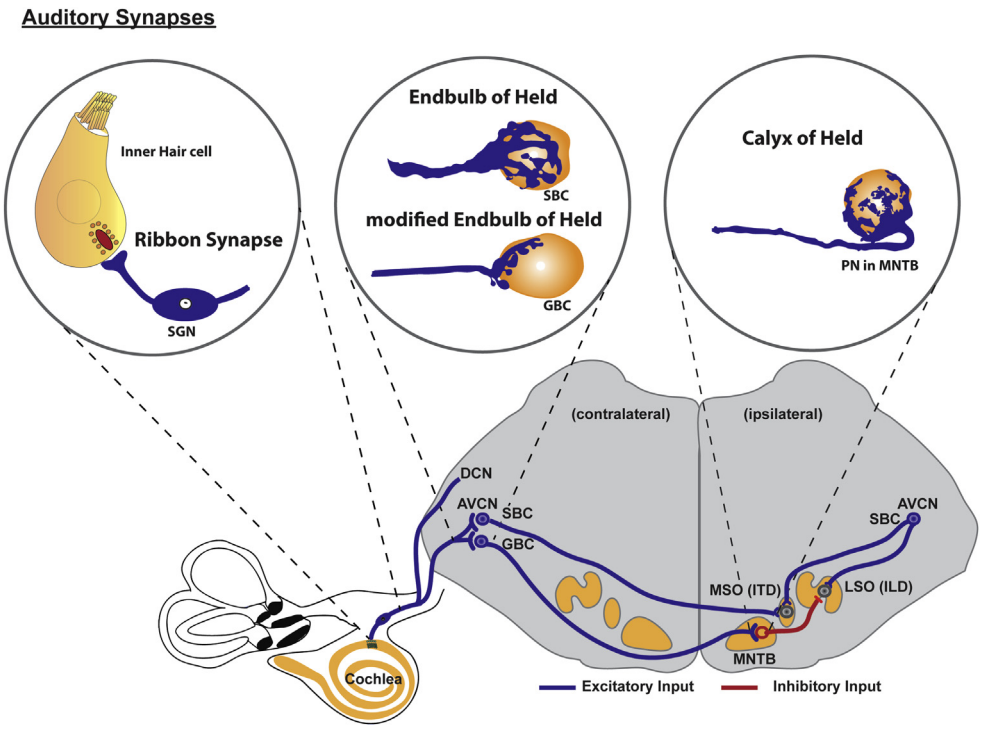

Fig. 1. Overview of the synapses that are specialized for transmission of signals along the auditory pathway. Peripheral processes of spiral ganglion neurons (SGN) receive input from inner hair cells in the cochlea via the ribbon synapse. Central projections of SGNs bifurcate upon entering the brainstem. The ascending branch extends toward the anteroventral cochlear nucleus (AVCN) and forms an endbulb of Held synaptic contact on spherical bushy cells (SBC) or smaller, modified endbulbs of Held on globular bushy cells (GBC). SBCs send bilateral projections to terminate on neurons of the contralateral and ipsilateral medial superior olive (MSO), which forms a pathway crucial for determining interaural time differences (ITD). Axons of GBCs project contralaterally to the medial nucleus of the trapezoid body (MNTB) and elaborate the calyx of Held synapse on principal neurons. The principal neurons of the MNTB provide glycinergic inhibitory inputs to neurons in the lateral superior olive (LSO), converging with excitatory inputs from SBCs of the ipsilateral AVCN. LSO neurons use contralateral inhibition from GBCs by way of the MNTB and ipsilateral excitation from SBCs to compute interaural level (intensity) differences (ILD). Computation of ITD and ILD permits binaural sound localization.

synchronous release of multiple vesicles, and promotes the replenishment of vesicles after exocytosis (Buran et al., 2010; Frank et al., 2010; Khimich et al., 2005). Therefore, the ribbon synapse is able to respond to graded changes in the HC membrane potential, and is capable of fast, sustained, and precise signaling (Buran et al., 2010; Khimich et al., 2005; Safieddine et al., 2012). These features allow us to sense sound over a dynamic range of several orders of magnitude in intensity with high temporal acuity.

SGNs relay sound information to neurons in the auditory brainstem through their central processes. Upon entering the brainstem, the central axon of each individual SGN bifurcates (Fekete et al., 1984). The descending process projects through the posteroventral cochlear nucleus (PVCN) into the dorsal cochlear nucleus (DCN), extending branches that make both *en passant* and standard bouton contacts with a variety of target neurons. The ascending process sends a major projection into the anteroventral cochlear nucleus (AVCN) and elaborates an extraordinarily large synaptic ending, known as the *endbulb of Held*, which envelops the cell body of the bushy cell neuron (Fig. 1) (Ryugo and Fekete, 1982). Additional branches off the ascending process generate boutons, smaller complex terminals and up to two additional endbulbs of Held. There are two major types of bushy cell neurons – spherical and globular (Wu and Oertel, 1984) – as defined by their appearance and location in the AVCN. Spherical bushy cells (SBCs) receive the largest endbulbs of Held, whereas globular bushy cells (GBCs) receive several smaller, modified endbulbs of Held (Rouiller et al., 1986). The large presynaptic terminal of the endbulb of Held harbors hundreds of release sites with a large number of synaptic vesicles (Nicol and Walmsley, 2002; Ryugo et al., 1996). These structural features of the endbulb of Held enable high frequency firing without depletion of the vesicle pool and facilitate rapid neurotransmission with high accuracy. These properties permit processing of the precise timing features necessary for interaural sound localization (Brenowitz and Trussell, 2001) and speech perception, such as voice onset/offset, temporal gap and syllabic stress (Blackburn and Sachs, 1990).

Within the auditory brainstem, GBCs and SBCs are responsible for passing auditory information from the AVCN to the superior olivary complex for additional processing largely related to sound localization. SBC axons form excitatory synapses ipsilaterally with neurons in the lateral superior olive (LSO) and bilaterally on neurons of the medial superior olive (MSO). MSO neurons help determine where each sound stimulus originates by detecting interaural time differences (ITD) between acoustic inputs from each ear (Fitzpatrick et al., 1997; Yin and Chan, 1990) (Fig. 1). In parallel, GBC axons cross the midline of the brainstem and terminate in the contralateral medial nucleus of the trapezoid body (MNTB), signaling via another giant synaptic ending, *the calyx of Held* (Fig. 1). With hundreds of active zones and a large readily releasable pool in the presynaptic ending (Taschenberger et al., 2002), the calyx of Held, similar to its smaller analogue, the endbulb of Held, allows signals to be relayed in the reliable and fast manner necessary for sound localization and speech recognition. The principal neurons in the MNTB are glycinergic and send inhibitory projections to the LSO. Therefore, the GBC-MNTB connection converts excitation originating from the contralateral cochlea into inhibition. The contralateral inhibitory input converges with the ipsilateral excitatory input from SBCs within the LSO, where post-synaptic neurons use these two inputs to compute interaural level differences (ILD)