REVIEW ARTICLE

Journal of Otorhinolaryngology and Facial Plastic Surgery. 2019;5(2):1-6.

https://doi.org/10.22037/ORLFPS.v5i2.27999

Ribbon Synapse Reformation: A Key Role for the Hearing Restoration; A Review

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Article Info

Article Note:
Received: October, 2019
Accepted: October, 2019
Publish Online: December, 2019

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Keywords:
Ribbon Synapse;
Inner Hair Cells;
Spiral Ganglion Neurons;
Hearing Restoration

Abstract

Background: Auditory sensory epithelium of mammals has two types of mechanosensory cells including the inner hair cells (IHC) and outer hair cells (OHC). IHC in the mammalian inner ear is an important component for the sound perception. Information about the frequency, intensity, and timing of acoustic signals is transmitted rapidly and precisely via ribbon synapses of the IHCs to the type 1 spiral ganglion neurons (SGNs). Even in the absence of stimulation, these synapses drive spontaneous spiking into the afferent neuron. Evidence has shown that cochlear neuropathy leading to hearing loss may be a result of the damage to ribbon synapses

Aim: Here, we review how these synapses promote the rapid neurotransmitter release and sustained signal transmission. We also discuss the mechanisms involved in ribbon synapse reformation for hearing restoration.

Conclusion: Although cochlear ribbon synapses fail to regenerate spontaneously when injured, recent studies have provided evidence for cochlear synaptogenesis that will be relevant to regenerative methods for cochlear neural loss. A better understanding of mechanisms underlying synaptic reformation would be helpful in achieving reversal of sensorineural hearing loss.

Conflicts of Interest: The authors declare no conflicts of interest.
Please cite this article as: Niknazar S, Peyvandi AA, Abbaszadeh HA, Khoshsirat S. Review of Ribbon Synapse Reformation: A Key Role for the Hearing Restoration. J Otorhinolaryngol Facial Plast Surg. 2019;5(2):1-6. https://doi.org/10.22037/ORLFPS.v5i2.27999

Introduction

Mammalian cochlear hair cells (HCs) are located in the basal membrane of the auditory sensory epithelium or organ of Corti (1). The main function of HCs is conversion of vibration produced by sound waves into electrochemical impulses which reach spiral ganglion neurons (SGNs). Information about the acoustic environment is conveyed from inner hair cells (IHCs) into to the peripheral processes of SGNs through a specialized connection known as the ribbon synapse (2), while, outer hair cells (OHCs) intensify the mechanical amplification of sound-induced vibrations (3). Indeed, the sense of hearing is dependent on the function of the ribbon synapses between IHCs and SGN. IHCs within the cochlea are innervated by type I SGNs fibers (4). The cochlear ganglion contains bipolar neurons with peripheral processes that transmit complex acoustic information from HCs to target neurons in the central nervous system (CNS) through the eighth cranial nerve. The synapse between the IHCs and the type I SGN are usually of ribbon synapse type (5). The presynaptic ribbons in the basolateral membrane of the inner ear are

Journal of Otorhinolaryngology and Facial Plastic Surgery. 2019;5(2):1-6.
https://doi.org/10.22037/ORLFPS.v5i2.27999

localized at the opposite side of the postsynaptic glutamate receptors on the dendrite.

The synaptic transmission by the sensory receptors of the auditory systems is determined through tonic and graded neurotransmitter release which requires sustained and rapid rates of exocytosis (6). The importance of this type of synapse lies in the fast transduction of the neurotransmitter to the active zone. They start and synchronize firing in response to a stimulus to the active zones at the base of the hair cell. In response to acoustic stimulus, presynaptic ribbons vesicles are released quickly and synchronously with a high temporal resolution (7-9).

Excitatory neurotransmission is created by glutamate receptors such as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) in the postsynaptic dendrite of afferent fibers (10). Several factors and signaling pathways such as brain-derived neurotrophic factor (BDNF) and neurotrophin-3 play roles in the establishment of IHC ribbon synapses during cochlear development (11, 12). Studies have revealed that cochlear neuropathy leading to hearing loss may be a result of the injury to ribbon synapses. This review will provide an overview of the mechanism involved in ribbon synapse reformation for hearing restoration.

Hair cell ribbon synapse formation

Synaptic 'ribbons' differ significantly from conventional CNS synapses in terms of their structure, physiology, and molecular composition. Hair cell ribbons have different morphologies such as planar, spherical, or oblong in shape and variable in size with 20–400 vesicles (13). In mammalian cochlea, ribbon synaptic vesicles have about 100 to 200 voltage-gated calcium channels (14, 15). These vesicles may contain the neurotransmitter glutamate. Ribbon electron dense synaptic bodies are attached to the membrane of a postsynaptic neuron. It is still not clear how the cochlear ribbon synapse formation occurs. SGNs enable production of action potential at E14(16). Also, changes in the membrane capacitance induced by evoked exocytosis can be detected in IHCs at E16.5 (17). In rat pups, spontaneous spiking activity in immature IHCs can initiate action potentials in apical SGNs (18). Another study showed that afferent synaptogenesis in the cochlea occurs predominantly during the postnatal period (19). Studies have shown that presynaptic development appears to initiate autonomously in the hair cells organ of Corti in the developing mouse and culture. This development is associated with the ribbon synapse formation in the absence of SGN terminals (20). Following the growth of SGN neurites, the pre-formed ribbons are organized into the basolateral membrane of IHC (21). The basolateral membrane of each hair cell contains multiple presynaptic active zones, where the chemical neurotransmitter is released (22).

Hair cells ribbon synapse degeneration

Two major types of sensorineural hearing loss are noise-induced and age-related hearing loss which are associated with genetic disorders, chronic ear infections, and chronic diseases (23, 24). Although damage to hair cells and SGNs are the main cause of hearing impairment (25, 26), recent evidence suggests that ribbon synapse degeneration might be an underlying cause implicated in hearing disorders (27-29). Noise exposure can induce several pathological processes such as metabolic fatigue and exhaustion of the hair cells and cochlear tissues (30), blood flow disturbance in the cochlea (31), reactive oxygen species production in cochlear tissues (32) and structural abnormalities in the organ of Corti (33). SGN terminals at IHC ribbon synapses swell in response to acute noise overexposure (34), due to noise-induced glutamate excitotoxicity (35). However, OHC ribbon synapses, which release glutamate at a far lower average rate (36), are not injured by acute acoustic overexposure (37).

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It has been documented that age-related hearing loss is associated with progressive degeneration of cochlear hair cells and SGN (38,39). However, other studies in aged human and rodent cochleae have revealed that primary ribbon synapses synaptic degeneration is associated with minimal or no loss of hair cells and SGN (40-42). In addition, the decline in the amplitudes of auditory responses is a function of the alterations in ribbon synapses density (42). Similar to the noise-induced hearing loss, enlargement of afferent terminals is also detected in the cochlea of aged mouse (43). Age- and noise- related ribbon synapse loss is followed by delayed neuronal degeneration of SGN (44, 42).

Reformation of ribbon synapse in regenerated hair cells

Several studies have reported that cochlear ribbon synapses have very limited intrinsic capacity for regeneration (11, 45-49). Incomplete recovery of ribbon synapses in the cochlea after injury or over time with the aging could result in hearing difficulty in noisy places and a late onset of hearing loss. Thus, ribbon synapse reformation has a key role for the hearing restoration in the noise-induced and age-dependent hearing loss. Researchers have been attempting to restore auditory function through regeneration of both pre-synaptic ribbons and postsynaptic densities. New neurons ideally require to extend the axon to contact with hair cells in the organ of Corti and transmit sensory information towards the neurons in the cochlear nucleus (50). Indeed, the way regenerated SGNs can innervate hair cells spontaneously is under investigation (45, 51).

A previous study showed that HCs spontaneously regenerate from the supporting cells following cochlear damage in neonatal mice, but these HCs were negative for vesicular glutamate transporter VGlut3 (synaptic transmission) marker (52). In addition, studies have shown that Neutrophin family including BDNF, Neurotrophin-3 (NT-3), and (NT-4/5) have essential roles for regeneration of functional synaptic connections between neurons (53) (54, 55). BDNF and NT-3 with their receptors are critical for initial establishment of neuronal projections to sensory epithelia cochlea (56). Other studies have revealed that glutamate have important implications in the regulation of synaptic activity. Glutamate is another important synaptotrophic factor. In a deafferented ear, the average number of new synaptic contacts at the dendrite of SGN diminished remarkably in mice with a genetic deletion of Vglut3 suggesting that glutamate transmitter release is important for the synaptic contact regeneration (12). A study has shown thee expression of synaptic markers including synapsin 1 and synaptophysin at the contact site between auditory afferent dendrites of type I and hair cells in early postnatal period in vitro (49, 57). Therefore, the expression of synapsin1 can be regarded as a marker of stem cell-derived auditory neurons capacity for regeneration or formation of functional synapses with hair cells (40). A study found that synaptic markers including synaptophysin and synaptotagmin 1 were detected in the base of newly generated HCs induced by the ectopic expression of Atoh1, but normal synaptic ribbons were not detected at the site of new HCs and neuron contacts (58). Previous research studies have shown that human embryonic stem cell has the potential to establish new synapses with hair cells in the auditory system (59, 60). Synaptogenesis was observed between the human neural progenitors and hair cells in cochlear explants (61). Studies have reported that in vitro neonatal cochlear explants can promote the ability of afferent fibers to re-innervate and reform synaptic contacts in vivo (57, 60, 62).

Conclusion

Despite recent advances in hair cell regeneration, more studies are required about reformation of ribbon synapses and reinnervation of regenerated HCs for restoring the hearing function. Although cochlear ribbon synapses fail to regenerate spontaneously when injured, recent studies have provided evidence for cochlear synaptogenesis that will be relevant to regenerative methods for cochlear neural loss. A better understanding of mechanisms underlying synaptic reformation would be helpful in achieving reversal of sensorineural hearing loss.

Acknowledgements

The authors would like to thank the Clinical Research Development Unit (CRDU) of Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran, for their cooperation and assistance throughout the period of study.

Conflicts of Interest

The authors declare no conflicts of interest.

Financial Support

Not declared.

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