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Review Article

Cochlear Synaptopathy in Humans. Review of the Evidence and Future Directions

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Abstract

Cochlear synapthopathy, is a condition where the damage is located at the level of the synapses between IHCs and type-I afferent auditory nerve fibres. The disrupted function of these synapses, either can or can't be re-established, thus resulting in various signal coding deficits and hearing impairment. Cochlear synaptopathy can be widely present in ears with intact hair cell populations and relatively 'normal' audiograms, representing the major cause of "hidden" hearing loss. The present study reviews the major mechanisms involved in hidden hearing loss, emphasizing on future directions regarding appropriate diagnosis of cochlear synaptopathy in humans.

Keywords: Cochlear synaptopathy; Noise induced hearing loss; Speech in noise difficulty; Hidden hearing loss

Introduction

Sensorineural hearing loss is considered among the most common chronic impairments nowadays. Two major categories of such type of hearing deficits, noise induced hearing loss and age related hearing loss, often coexist in the same ear [1]. Noise induced threshold shift is the main cause of preventable hearing loss worldwide. It now accounts for more than a third of all cases of hearing loss in developed countries. Although historically sensorineural hearing loss was attributed to loss of hair cells and spiral ganglion neurones (SGNs) [1], recent evidence suggests that synaptic loss between inner hair cells (IHCs) and SGNs is the primary pathology even with only temporary threshold shifts (TTS), and this synaptic loss is independent of both IHC and SGN loss [2]. Therefore, the synaptic connection between IHCs and SGNs may be the most vulnerable cochlear structure to ageing or noise-induced damages, a key pathology for sensorineural hearing loss.

Underlying Anatomy, Physiology and Pathophysiology

Each cochlear nerve fibre has the cell body located inside the spiral ganglion, a peripheral axon in the osseous spiral lamina and an unmyelinated terminal dendrite in the organ of Corti. IHCs communicate with the unmyelinated terminal dendrites (afferent neurones) via connections known as chemical synapses [1]. This means that the electrical signals generated by hair cells' activation, further trigger channel proteins that allow calcium ions to flow in. This in turn activates membrane-bound packages called vesicles inside the hair cell to fuse with its surface membrane and release their contents to the outside [1,3]. The contents, which are chemicals and called neurotransmitters, then travel across the space between the IHC and SGN transmitting the signal to the nerve cell itself.

Two types of SGN afferent fibres exist, that carry auditory information from cochlear hair cells centrally: type I and II SGNs. The type II SGNs account for 5% of total SGNs and make synapses with outer hair cells (OHCs) in the cochlea. The type I SGNs, (95% of total SGNs) make synapses with IHCs and can be further subdivided into three functional groups based on their spontaneous discharge rates (SR) and dynamic range. High-SR SGNs, making up to 60% of all type I SGNs, have low thresholds and wide dynamic ranges. Low-SR SGNs have high thresholds and wide dynamic ranges, and

medium-SR SGNs have both thresholds and dynamic ranges values intermediate to the previous ones [1].

The depolarisation of the IHCs causes L-type voltage-sensitive calcium channels located near the regions of afferent synapses to open. Each active region in characterized by the presence of an electron-dense structure called a synaptic ribbon [4]. This is because they have a ribbon-like structure that appears to binds together a number of vesicles close to the active zone where neurotransmitters are released. The exact role of this synaptic ribbon still remains unknown despite decades of study [3]. This synaptic ribbon is anchored to the plasma membrane and surrounded by synaptic vesicles, which contain glutamate, the actual IHC neurotransmitter. There is one ribbon per active region and ten to twenty active regions per IHC [4]. Each active region synapses with a dendrite from a single fibre from the auditory nerve. This means that 10 to 20 type I SGNs connect to a unique IHC.

Hair cell synapses, as stated before, are equipped with an organelle of highly functional selectivity: the synaptic ribbon. The latter is surrounded by a layer of synaptic vesicles and is anchored to the membrane by the protein "Bassoon" [4]. The protein "RIBEYE" is the major component of synaptic ribbons [3,4]. Recent studies show that mutant mice that lack this protein do not have any ribbons at their "ribbon synapses" [3]. Hair cells without synaptic ribbons are less able to reliably send signals to the nerve cells in the temporal domain, most likely because they cannot replace the vesicles at the synapse quickly enough [3]. Further analysis showed that the synaptic ribbon also helps to regulate the calcium channels at the synapse [3], which is important for linking the polarisation related electrical signals in the hair cell to the final release of the neurotransmitters.

Furthermore, there is a vesicular transporter called 'VGLUT3' that ensures that the synaptic vesicles are filled with glutamate. Otoferlin finally, is the gene-encoded protein responsible for the calcium detector used for exocytosis [4]. In responses to a sound stimulus, amplified by the outer hair cells' motility, the stretch-sensitive channels open. Then, influx of endolymphatic potassium occurs that subsequently depolarises the IHCs. Voltage-sensitive calcium channels open in response to the depolarisation, which causes an influx of calcium close to the ribbons. Fixation of calcium on the Otoferlin domains causes the synaptic vesicles to fuse with the plasma membrane, causing the release of glutamate into the synaptic cleft itself. Glutamate activates the AMPA glutamate receptors in the afferent nerve fibres permitting thus the nerve signal to be further transported by the afferent neurone to the cochlear nucleus [4].

Evidence suggests that hair cells without ribbons have the ability to reorganize their synapses to form multiple active zones that could permit the transfer of the neurotransmitter to the SGNs [3]. This could compensate, at least up to a certain extent, for the actual loss of the ribbons. The bottom line nevertheless is that efficient encoding and processing of sensory information in the ear strictly relies on healthy/active ribbon synapses [3].

Cochlear Synaptopathy

Synapthopathy in general, refers to a neurodegenerative condition that affects and disrupts the synaptic structure itself, which is a major histopathologic finding of several neurodegenerative brain diseases. With respect to cochlear synapthopathy, it is a condition where the damage is located at the level of the synapses between IHCs and type-I afferent auditory nerve fibres. The disrupted function of these synapses, either can or can't be re-established, thus resulting in various signal coding deficits and hearing impairment [5]. It is believed that such an interrupted synaptic communication between IHCs and subsets of cochlear nerve fibres regulates the affected neurones downwards either pausing or terminating their function. This temporary or permanent silencing of the affected neurones alters auditory information processing in a 'bottom-up' direction. Subsequently, it can be either accompanied by threshold elevations or not and is a potential contributor to a variety of perceptual abnormalities, including speech in noise difficulties, central auditory processing deficits, tinnitus and hyperacusis [5].

Noise Induced Synaptopathy, Pure Tone Audiometry and Hidden Hearing Loss

For many years it was thought that the main cause of hearing loss and the related difficulties understanding speech in noise was due to the death of hair cells and SGNs. Although behavioural pure tone audiogram (PTA) is still a key evaluation metric of this hearing impairment, audiometric thresholds do not necessarily reflect reported or even demonstrated auditory perceptual difficulties. PTA nevertheless, does provide documentation of the magnitude of the audibility loss, its pattern as a function of frequency, and to some extent potential anatomical site of lesion (e.g., middle versus inner ear); but obtained thresholds and underlying pathology are not always in agreement [5]. New evidence supports synapse loss as the key contributor. Specifically, recent studies [1] suggest that the synapses between IHCs and SGNs with low SR and high thresholds represent the most vulnerable link of the key chain, with respect to noise-induced deficits.

Morphologic support for the preferential loss of low-SR neurones comes from numerous studies suggesting preferential vulnerability of these neurones and their synapses after noise [5]. Low- and high-SR fibres have different synaptic positions on the IHC and magnitudes of synaptic ribbons and associated AMPA-receptor patches. Low-threshold, high-SR fibres tend to synapse on the pillar side of the IHC, whereas the high-threshold, low-SR fibres tend to synapse on the modiolar side. Normally, the density of synapses tends to be greater on the modiolar side of the IHC where greater loss of synapses takes place after noise exposure. This observation is consistent with the present evidence of selective loss of low-SR fibres in this noise damage model [5]. Low-SR fibres also

have fewer mitochondria which, in the central nervous system, are well documented to be of fundamental importance to mechanisms related to the control and endurance of excitotoxicity.

After noise exposure, synaptic positions along the IHC's basolateral membrane appear to partially redistribute, particularly where the greatest damage of synapses have occurred, recovering by up to one week afterwards. Thus, interpreting synaptic position after noise is further complicated and confounded by dynamic changes that occur in the acute post-exposure period [5]. Such cochlear synaptopathy is considered as "hidden" because this synaptic loss and reallocation can occur without permanent PTA threshold shifts. Recent evidence based on animal models reveals three important facts [5] in the noise-exposed ear;

1. Cochlear neurones are considered as a primary target.

2. Their peripheral synaptic connections are the most vulnerable part of the key chain.

3. Cochlear nerve synapses can be destroyed even when hair cells manage to survive.

Although PTA threshold shift is a relatively sensitive measure of an underlying hair cell damage, it is comparatively insensitive to this diffuse loss of IHC synapses or of the correspondent cochlear nerve fibres they are linked to. Since more than 60 years it has been documented that PTA thresholds are considerably stable until neural loss exceeds about 80-90% [5]. Thus, cochlear synaptopathy can be widely present in ears with intact hair cell populations and relatively 'normal' audiograms, representing the major cause of "hidden" hearing loss [5].

Glutamate Excitotoxicity

As mentioned before, IHC's synapse includes a presynaptic ribbon surrounded by a halo of neurotransmitter-containing vesicles within the IHC and a postsynaptic active zone on the afferent nerve terminal, with glutamate (AMPA-type) receptors for the released neurotransmitter [1]. Collectively, these synapses can pass on information about intensity and temporal characteristics of the stimulus over a wide dynamic range. Moreover, all the mechanisms supporting the differences and wide variety of afferent firing seem to be included within this complex, determining not only the intrinsic excitability of the neural elements, but also the chemically induced modulation of this excitability itself [1,6].

There is evidence that cochlear afferents are directly targeted by noise, through excess sound-induced release of glutamate [1]. This neurotransmitter released from the IHC must be maintained at levels low enough in order to ensure high S/N ratio and to prevent excitotoxic damage to afferent neurones. Rapid clearance of synaptic glutamate is further accomplished by the uptake system of glutamate transporters whose function seems less intense on the low-SR side of the IHC [5].

Moreover, the time course of the initial events after noise exposure also suggests such a potential excitotoxic process, as local application of glutamate receptor agonists can produce dose-dependent swelling of type I SGNs' terminals. This dendritic swelling can be prevented by prior intracochlear administration of glutamate antagonists and is observed under IHCs, but not OHCs [1]. Morphological studies have documented similar swelling of type I cochlear nerve terminals in the region of their synaptic contact with IHCs after exposures that produce either PTS or TTS. Surprisingly enough, recent evidence implies that IHC synaptopathy may also result from impulse noise exposure [7]. Although it is easy to imagine high amplitude impulsive stimuli damaging by direct mechanical effects, it is not clear how a stimulus lasting only for several microseconds should lead to over-release of neurotransmitter. More research necessitates to further understand whether all these elicitors of synaptopathy act via the same, or yet unknown mechanisms.

Neurophysiological and Functional Effects of Synaptopathy

As stated before, both synaptic and neural loss observed in noise-exposed ears does not elevate PTA thresholds. However, if DPOAE responses are still present or re-established after TTS, the supra threshold amplitude of ABR wave I seems to be highly predictive of the magnitude of synaptopathy [5] as affected neurones are silenced after the loss of their synaptic connection to the IHCs. The underlying theory is that each fiber contributes a tiny amount to the whole magnitude of evoked potential and the fractional decrease in ABR wave I amplitude scales linearly with the fractional loss of the synapses [8]. Furthermore, such permanent evoked amplitude declines are not seen after noise exposures that fail to produce synapses loss. Such correspondence is only straightforward when hair cell damage is absent as disruption of mechanoelectric transduction can also reduce the ABR amplitudes.

Interestingly, the combination of a reduction in wave I and an increase in wave V/I ratio is considered evidence of increased central gain, a potential mechanism for the generation of tinnitus in such cases [9]. It is clear that normal hearing thresholds do not guarantee normal hearing functions, especially in cases of noise exposure. Functionally, reduction in wave I amplitude suggests deficits in intensity coding, due to the decrease of operational afferents, following loss of their synapses. Moreover, temporal coding deficits in phase-locking responses have also been proposed based on the substratum loss of low- SR units and the functional features of this group of fibres [9]. All this reduced cochlear output due to either loss or incomplete repair of unhealthy synapses may further lead to central coding deficits, particularly listening difficulties in unfavourable listening environments. This relies on the fact that low-SR units are considered critical for hearing in noisy environments due to their ability to follow the quick change of the amplitude of acoustic signals. By contrast, high-SR units, being

responsible for the sensitivity to quiet sounds, are easily saturated by high-level background noise [9].

The Role of Neurotrophins

It has been hypothesised that glutamate excitotoxicity is a primary initial event in the degenerative series of events observed after noise exposure. After hours and days immediately post exposure, some unmyelinated terminal dendrites of SGCs degenerate back to the habenula as a direct effect of this excitotoxicity associated dendritic swelling and possible rupture of the terminal apparatus. Consequently, the loss of these peripheral terminals interrupts the neurotrophin signalling required for normal development and maintenance of the cochlear innervation as it removes the intimate connection between cochlear cells (including supporting and hair cells) and the neuronal receptors for the neurotrophins. This interruption of neurotrophin signalling compromises the long-term survival of those afferents, essentially determining their fate at an early stage of the process although the subsequent cell apoptosis may take several months to complete [1].

A key evidence of the hypothesised role of neurotrophins in the neurodegeneration that follows synaptic and terminal loss after noise exposure is provided by rescue experiments demonstrating not only synaptogenesis but also recovery of function [10]. Based on the fact that loss of SGNs and their central projections is very slow after such insults, and IHCs often survive, results suggest the exciting possibility of viable IHC and SGN reconnection over a long therapeutic window in human application. Evidence suggests that either neurotrophin over-expression or neurotrophin delivery to the round window can regenerate lost synapses by re-establishing functional recovery of ABR wave I [10].

Recent Evidence and Future Directions

Latest study [11] failed to diagnose synaptopathy related neural degeneration on a case-by-case basis by incorporating modified speech in noise tests along with middle ear function analyses. On the other hand, recent evidence [12] regarding hidden hearing loss suggests that disruption of the myelin layer of the cochlear nerve can cause a different type of synaptopathy-myelopathy that induces distinctive deficits in comparison to those observed by the loss of synapses. The disruption of the myelin layer desynchronizes sound induced neuron spiking, by decreasing the amplitude and increasing the latency of the compound action potential [12]. Moreover, elongation of the initial axon segment may cause spike generation failure leading to reduced spiking likelihood [12]. In contrast, the effect of synapse loss is found only to diminish the probability of firing, thus reducing the compound action potential amplitude without disturbing its latency [12].

The bottom line is that up to now, there is no proven method for adequately diagnosing synaptopathy in humans. Three possible reasons have been proposed for this inconsistency [13]:

1. Synaptopathy may be rare in young people.
2. Synaptopathy may be dominant only for low-intensity stimuli, and tests exercising higher-intensity stimuli may not expose pathologies
3. The present arsenal of tests is insensitive to synaptopathy [13].

The most promising method for diagnosing cochlear synaptopathy is related to selective loss of low-SR ANFs The subcortical steady state responses (SSSR) using off-frequency maskers and a shallow modulation depth may be able to successfully detect low-SR unit loss in humans [9]. This finding may help in the future in earlier assessment and intervention of noise related changes previously undetected by OAEs and audiometric threshold shifts.

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Conflict of Interest

No Conflict of Interest.

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