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Advances in the neurobiology of hearing disorders: Recent developments regarding the basis of tinnitus and hyperacusis☆

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ABSTRACT

The prevalence of hearing problems in the Western world has, due to aging of the population, doubled over the past 30 years. Thereby, noise-induced hearing loss is an important factor that worsens over time in addition to age-related hearing loss. Hearing loss is usually measured as an elevation of a person's hearing thresholds, expressed in decibel (dB). However, recent animal studies have unraveled a type of permanent cochlear damage, without an elevation of hearing thresholds. This subtle damage is linked to a permanent and progressive degeneration of auditory fibers that occurs in association with damage of the inner hair cell synapse. Afferent neuronal degeneration has been suggested to be involved in hyperacusis (over sensitivity to sound) and tinnitus (a phantom sound percept). Hyperacusis and tinnitus are potentially devastating conditions that are still incurable. The main risk factors to develop tinnitus or hyperacusis are hearing loss, social stress and age. Both tinnitus and hyperacusis have been discussed in the context of a pathological increased response gain in subcortical brain regions as a reaction to deprivation of sensory input. Novel studies confirm the involvement of peripheral deafferentation for tinnitus and hyperacusis, but suggest that the disorder results from different brain responses to different degrees of deafferentation: while tinnitus may arise as a failure of the brain to adapt to deprived peripheral input, hyperacusis may result from an 'over-adaptive' increase in response gain. Moreover, moderate and high stress levels at the time of acoustic trauma have been suggested to play a pivotal role in the vulnerability of the cochlea to acoustic damage and therefore for the development of tinnitus and hyperacusis.

Contents

Abbreviations: ABR, auditory brainstem response; AC, auditory cortex; AN, auditory nerve; Arc/Arg3.1, activity-regulated cytoskeleton-associated protein/activity-regulated gene 3.1; BLA, basolateral amygdala; CN, cochlear nucleus; DCN, dorsal cochlear nucleus; DPOAE, distortion product otoacoustic emission; fMRI, functional magnetic resonance imaging; HPA axis, hypothalamic-pituitary-adrenal axis; IC, inferior colliculus; IHC, inner hair cell; MGB, medial geniculate body; MNTB, medial nucleus of the trapezoid body; NIHL, noise-induced hearing loss; OHC, outer hair cell; SOC, superior olivary complex; SR, spontaneous (discharge) rate; VCN, ventral cochlear nucleus.

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1. Advances in the neurobiology of hearing disorders

1.1. Permanent elevation of hearing threshold after cochlear damage

Hearing impairment is a considerable disease burden. It has been estimated that adult-onset hearing impairment is the third leading cause of disability (WHO, 2008). Forty-two previous reports published between 1973 and 2010 in 29 countries have revealed increased hearing loss with age; developing countries report higher rates of moderate and moderately-severe hearing impairment due to higher rates of pre- and postnatal childhood infections such as rubella, measles and meningitis, and from the use of ototoxic drugs (Stevens et al., 2013). However, in industrialized countries, noise-induced hearing loss (NIHL) is a common cause of hearing impairments (Lu et al., 2005), with a prevalence that is second to presbycusis (Stanbury et al., 2008). Unfortunately, opportunities for sound overexposure abound and the sounds that damage hearing are not necessarily painful or even annoying. Thus, damage may occur in situations that are not easily recognized as potentially harmful. NIHL can also be caused by a one-time exposure to excessive sound pressure, such as explosions, gunfire, a large drum forcefully hit, or fire crackers. However, NIHL is more often caused by repeated exposures to medium- and high-intensity sounds (Flamme et al., 2009; Phillips and Mace, 2008). Exposure to high sound levels does not lead to NIHL in everyone. Apparently, the susceptibility to NIHL varies among individuals (Henderson et al., 1993). The variable susceptibility may have a genetic cause, as confirmed by several studies (Konings et al., 2007; Sliwinska-Kowalska et al., 2008; Sliwinska-Kowalska and Pawelczyk, 2013; Van Laer et al., 2006; Yang et al., 2006).

NIHL has been, in a previous view, typically defined by a permanent loss of hearing thresholds. Normal thresholds rely on the proper function of outer hair cells (OHCs) (Dallos and Harris, 1978). Per inner ear, there are approximately 11,000 OHCs, which are, in the human cochlea, typically arranged in 3 rows (Fig. 1, OHC). OHC function is to nonlinearly amplify basilar membrane vibration in response to soft sounds near the place of characteristic frequency within the cochlea (Ashmore, 2008). OHCs are therefore crucial for the high sensitivity of the hearing organ, its frequency selectivity, and understanding speech in noise (Ashmore, 2008; Dallos, 2008).

After mild acoustic overexposure, hearing function can recover within 2–3 weeks (Miller et al., 1963). This corresponds to a temporary threshold shift due to reversible damage to the mechanosensory hair bundles of hair cells (Fig. 1, stereocilia) (Liberman and Dodds, 1984a,b; Schneider et al., 2002). After intense or repeated acoustic overstimulation, however, hearing function stabilizes at an elevated value, leading to permanent threshold shift that mostly occurs due to destruction of OHCs (Spoendlin, 1985).

In the daily clinical routine, permanent hearing loss is typically detected through the increase of hearing thresholds as tested by tone-audiometry. More detailed clinical diagnostic testing may also include auditory brainstem response (ABR) testing or recording distortion product otoacoustic emissions (DPOAEs). ABR responses represent the summed activity of neurons in the ascending auditory pathways (see Section 1.3). ABRs can either be evoked by short click or noise sounds, or frequency-specific tone bursts. The specific function of intact OHCs can be measured by amplitudes of DPOAEs. DPOAEs are acoustic signals that arise from distortions in the OHCs' mechanoelectrical response to two continuous tones. These distortion products, which are at frequencies not present in the input stimulus, are generated by the OHCs' biological motors and can be detected with a microphone in the ear canal. DPOAEs responses thus reflect the electromotile properties of OHCs (Fitzgerald et al., 1993; Huang et al., 2005). DPOAE responses can be intact while ABRs dramatically decline, due to dysfunction of inner hair cell (IHC) synapses in, for example, DFNB9 patients during auditory neuropathy (Denoyelle and Petit, 2002; Smith et al., 1993). DFNB9 patients are suffering from non-syndromic autosomal recessive deafness due to dysfunction of otoferlin, a multi-C2 domain protein that acts as a calcium sensor in cochlear inner hair cells (Roux et al., 2006). Also, when DPOAEs are maximally reduced, ABRs nevertheless exist to a distinct degree, as OHC loss presumably contributes a maximum of ~40 dB to total threshold loss.

We can conclude that loss of hearing thresholds after noise exposure is mostly linked to OHC loss, which specifically can be measured by DPOAEs. Through DPOAE and ABR measurements, in combination, a differential damage of OHCs and IHCs can be detected.

1.2. Permanent cochlear damage without elevation of hearing threshold

Regarding more recent findings on NIHL, it is most important to remember that OHC loss can be accompanied by IHC (Fig. 1, IHC) damage (Liberman and Dodds, 1984a,b).

The IHCs are the primary sensory hair cells of the cochlea that transmit sound information over an intensity range spanning 12 orders of magnitude (120 dB) and 3 orders of magnitude of frequency (20 Hz to 20 kHz) (Robles and Ruggero, 2001). This powerful capacity of IHC synapses is achieved through their numerous specialized afferent contacts. Each IHC is innervated by 8 (human) or up to 20 (rodents) (Glowatzki and Fuchs, 2002) unbranched spiral ganglion neurons, which represent about 90–95% of all afferent fibers (AF) in the auditory nerve (AN) (Fig. 1, AN; Figs. 1 and 2, AF type I). Each IHC contains electron-dense presynaptic subcellular structures, so-called ribbons (Figs. 1 and 2, red) that tether >100 synaptic vesicles (Glowatzki and Fuchs, 2002). This specialized presynaptic machinery thereby maintains a large releasable pool of neurotransmitter, allowing afferent