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Research Paper

Effects of noise exposure on young adults with normal audiograms I: Electrophysiology

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ABSTRACT

Noise-induced cochlear synaptopathy has been demonstrated in numerous rodent studies. In these animal models, the disorder is characterized by a reduction in amplitude of wave I of the auditory brainstem response (ABR) to high-level stimuli, whereas the response at threshold is unaffected. The aim of the present study was to determine if this disorder is prevalent in young adult humans with normal audiometric hearing. One hundred and twenty six participants (75 females) aged 18–36 were tested. Participants had a wide range of lifetime noise exposures as estimated by a structured interview. Audiometric thresholds did not differ across noise exposures up to 8 kHz, although 16-kHz audiometric thresholds were elevated with increasing noise exposure for females but not for males. ABRs were measured in response to high-pass (1.5 kHz) filtered clicks of 80 and 100 dB peSPL. Frequency-following responses (FFRs) were measured to 80 dB SPL pure tones from 240 to 285 Hz, and to 80 dB SPL 4 kHz pure tones amplitude modulated at frequencies from 240 to 285 Hz (transposed tones). The bandwidth of the ABR stimuli and the carrier frequency of the transposed tones were chosen to target the 3–6 kHz characteristic frequency region which is usually associated with noise damage in humans. The results indicate no relation between noise exposure and the amplitude of the ABR. In particular, wave I of the ABR did not decrease with increasing noise exposure as predicted. ABR wave V latency increased with increasing noise exposure for the 80 dB peSPL click. High carrier-frequency (envelope) FFR signal-to-noise ratios decreased as a function of noise exposure in males but not females. However, these correlations were not significant after the effects of age were controlled. The results suggest either that noise-induced cochlear synaptopathy is not a significant problem in young, audiometrically normal adults, or that the ABR and FFR are relatively insensitive to this disorder in young humans, although it is possible that the effects become more pronounced with age.

1. Introduction

The primary account of noise-induced hearing loss (NIHL) is that cochlear hair cells are damaged (Liberman and Dodds, 1984), causing a loss of sensitivity to quiet sounds. This loss of sensitivity can be detected by pure tone audiometry, and thus NIHL can be identified by comparing thresholds to age-matched normal audiograms. Recently, experiments conducted in rodent models have demonstrated another mechanism of NIHL, cochlear synaptopathy, which is characterized by a loss of the synapses between inner hair

Abbreviations: ABR, auditory brainstem response; FFR, frequency following response; NIHL, Noise-induced hearing loss; OHC, outer hair cell; IHC, inner hair cell; AN, auditory nerve; SR, spontaneous rate; TEOAE, transient-evoked otoacoustic emission

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cells (IHCs) and auditory nerve (AN) fibers. Using a mouse model, Kujawa and Liberman (2009) demonstrated that after 2 h of exposure to 100 dB SPL noise (8–16 kHz), up to 50% of the synapses between IHCs and AN fibers had been permanently destroyed in the affected frequency region. This permanent loss of AN synapses was seen despite a recovery in absolute sensitivity. Their results suggest that cochlear synaptopathy can be identified from a reduction in the amplitude of wave I of the auditory brainstem response (ABR), which reflects AN function. The reduction was only observed in response to moderate-to-high-intensity stimuli, not for stimuli presented near threshold.

Cochlear synaptopathy has been demonstrated in a number of other rodent models (e.g. guinea pig, Lin et al., 2011; chinchilla, Hickox et al., 2015) and has been shown to occur after exposure to more moderate sound levels over a longer duration (84 dB SPL for a week, Maison et al., 2013). Furthermore, noise-induced synaptic loss has been shown to preferentially affect the synapses with low spontaneous-rate (SR) AN fibers (Furman et al., 2013). Low-SR fibers have high thresholds and high saturation levels, and so are used to encode high-intensity sounds. Hence, noise-induced cochlear synaptopathy could result in coding of supra-threshold sounds being affected despite sensitivity near threshold remaining unaltered. The low-SR account of how synaptopathy manifests in rodents appears straightforward and well understood, however there are still unresolved issues. For example Song et al. (2016) demonstrated that, after noise exposure, synapses can remain present but are no longer functionally normal.

Currently, the most direct evidence for noise-induced synaptopathy occurring in humans is from a study demonstrating that the amplitude of wave I of the ABR in response to high-intensity clicks was negatively correlated with noise exposure across 30 participants, despite little effect of exposure on absolute threshold up to 8 kHz (Stamper and Johnson, 2015a). The measure of noise exposure quantified the amount of high-intensity sound encountered over the previous 12 months, rather than lifetime exposure. Hence, some listeners may have been classified as low noise exposed, when in fact earlier noise exposure may have already caused synaptopathy. Furthermore there was a confound due to the distribution of sexes across the cohort: Male participants formed the majority of the highly noise exposed listeners, and males tend to show weaker ABRs than females due to factors such as head size. This was subsequently addressed with separate analyses for males and females (Stamper and Johnson, 2015b), though this information was presented only for the highest sound level tested (90 dB nHL), and the authors did not confirm that there was no relation between hearing threshold and noise exposure separately for the two sexes. This re-analysis found a significant decrease in ABR wave I amplitude as a function of noise exposure for females, but not for males.

A more recent study by Liberman et al. (2016) found no significant decrease in wave I amplitude ("action potential") measured from the ear canal in a group of listeners with normal audiometric thresholds identified as high-risk for noise-induced synaptopathy compared to a low-risk group. The authors do report a significant increase in the ratio of the summating potential (reflecting hair cell activity) to the action potential in the high-risk group, consistent with synaptopathy. However this increase in ratio was driven mainly by an increase in the summating potential in the high-risk group rather than by a decrease in the action potential in the high-risk group. Based on the studies of synaptopathy in rodents it was predicted that the summating potential would remain equivalent between the two groups. Hence, interpretation of this finding is not straightforward.

Attenuated wave I amplitudes have been observed in audiometrically normal human listeners with tinnitus compared to controls when hearing thresholds were matched between the groups (Schaette and McAlpine, 2011). Gu et al. (2012) also showed attenuated wave I amplitudes in tinnitus listeners compared to non-tinnitus controls, however the groups also differed in audiometric threshold above 8 kHz. Cochlear synaptopathy has been suggested as a possible cause of tinnitus in listeners with normal audiograms, with the percept arising from the auditory system trying to compensate for reduced AN input by increasing central neural gain. However, to the authors' knowledge, no published study has measured noise exposure and electrophysiological responses in the same human listeners with tinnitus and so it remains unclear the extent to which tinnitus is a symptomatic manifestation of noise-induced synaptopathy.

Wave I of the ABR is the most direct non-invasive measure of AN fidelity in humans, and in the rodent model has been shown to be a correlate of underlying cochlear synaptopathy, at least at the group level. However, one of the obstacles for the use of the ABR to identify synaptopathy in humans is that wave I amplitude is highly variable across individuals. Another objective measure that has been proposed as an indicator of synaptopathy is the frequency-following response (FFR). The FFR is a sustained evoked potential, reflecting neural phase locking to the fine structure or envelope of sounds. For frequencies from about 80 to 1000 Hz, the latency of the FFR is consistent with a generator in the rostral brainstem (Krishnan, 2006). Shaheen et al. (2015) demonstrated that the FFR may be a more robust indicator than the ABR of noise-induced synaptopathy in mice. Furthermore the FFR has been shown to relate reliably to behavioral performance on temporal discrimination tasks, which provides further evidence of the suitability of the FFR to detect noise-induced changes in neural processing (Bharadwaj et al., 2015).

The evidence for noise-induced synaptopathy in a range of rodent models is compelling. However, to date, evidence for noise-induced synaptopathy in humans is limited and it is unclear whether the same mechanism is involved in both males and females. Many of the rodent studies use male animals and sex has not been studied as a factor. Therefore, it remains unknown the extent to which the two sexes are equally susceptible to noise induced synaptopathy. If the pathology does occur in humans, we hypothesize that noise exposure will reduce the number of functioning low-SR AN fibers in the affected frequency region, leading to a reduction in the ABR response at high levels (specifically for wave I), and a reduction in the FFR at high carrier frequencies. The choice of stimuli for this study was informed by previous work in both rodents and humans and the approach assumes that synaptopathy will preferentially affect low-SR fibers and that the effects will be most readily observed in the 3 to 6 kHz characteristic frequency region where noise damage in humans is usually manifest (Toynbee, 1860; McBride and Williams, 2001).

In the present study, these measurements were compared to lifetime noise exposure. For both the ABR and the FFR two stimuli were used, the response to one of which was predicted to be more affected by noise-induced synaptopathy than the other. The ABR assumed to be most affected was that to a high-intensity click. This was compared to the ABR to a lower-intensity click that should have produced less activation of low-SR fibers. The bandwidth of the ABR stimuli was chosen to target the 3 to 6 kHz characteristic frequency region where NIHL is usually observed in humans (Toynbee, 1860; McBride and Williams, 2001). The FFR assumed to be most affected was that to the envelope of a 4-kHz carrier frequency. This was compared to an FFR for a low frequency pure tone (see Barker et al., 2014 for a preliminary use of this approach). The purpose of using such differential measures is to isolate the effects of