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Auditory Central Gain Compensates for Changes in Cochlear Output after Prolonged Low-Level Noise Exposure

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Abstract

Remarkably, the central auditory system can modify the strength of its sound-evoked neural response based on prior acoustic experiences, a phenomenon referred to as central gain. Gain changes are well documented following traumatic noise exposure, but much less is known about central gain dynamics following prolonged exposure to low-level noise, a common acoustic experience in many urban and work environments. We recently reported that the neural output of the cochlea is reduced, while gain was enhanced in the inferior colliculus (IC) following a 5-week exposure to 75 dB noise. To determine if similar effects were present at even lower intensities, we exposed rats to a 65 dB noise expecting to see little to no change in the cochlea or IC. The exposure had little effect on distortion product otoacoustic emissions and did not cause any hair cell loss. However, the amplitude of the CAP, which reflects the neural output of cochlea, was depressed by 50–75%. Surprisingly, neural responses from the IC were enhanced up to 70%, mainly at frequency within the noise exposure band. One-week post-exposure, CAP amplitudes returned to normal at frequencies within or above the exposure band, whereas responses evoked by frequencies below the exposure band were enhanced by more than 80%. In contrast, IC responses below the exposure frequency were depressed 10–20% whereas responses within the exposure frequency band were enhanced 10–20%. Thus, the central auditory system dynamically up- and down-regulates its gain to maintain supra-threshold neural responses within a narrow homeostatic range; a function that likely contributes to the prevention of sounds from being perceived as muffled or too loud.

Keywords

Central Gain; noise exposure; inferior colliculus; compound action potential; otoacoustic emissions

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Introduction

Human exposure to low and moderate level noise has steadily increased over the years, especially for urban dwellers [4, 10, 15, 22, 39]. Remarkably, the auditory system can acclimate to prolonged changes in the acoustic environment by adjusting its neural representation of loudness [11, 24]. Growing evidence suggests these adaptive changes emanate from a neural mechanism responsible for the control of central gain, whereby central auditory nuclei enhance or suppress gain to adjust for changes in the neural output from the cochlea [2, 9, 31]. While enhanced central gain following exposure to traumatic noise and ototoxic drugs is well established [2, 31], research is only beginning to explore central gain changes associated with prolonged exposure to continuous low-level sounds; a pervasive condition in modern societies.

Continuous exposure to low-level noise can have an unexpectedly large effect on both the peripheral and central auditory systems. In mice, exposure to a continuous moderately loud (84 dB SPL) octave band noise for one week damages synapses (synaptopathy) between inner hair cells (IHCs) and type I cochlear nerve fibers [19]. Synaptopathy and selective damage to auditory nerve fibers can lead to enhanced central gain in the auditory cortex [5, 20]. In contrast, reports using an exposure consisting of tone-pips (68–72 dB) to create an enriched acoustic environment depressed sound evoked responses in the auditory cortex without causing hearing loss [26]. Recently, we reported that a continuous low-level, octave band noise (10–20 kHz, 75 dB SPL), an intensity level similar to highway traffic, significantly reduced the amplitude of rat cochlear compound action potentials (CAPs), but elevated sound-evoked activity in the inferior colliculus (IC), indicating enhanced central gain [33]. Interestingly, at one-week post-exposure, CAP amplitudes were slightly enhanced, and sound-evoked IC responses partially recovered toward normal levels [33]. These observations suggest that continuous exposure to low-level noise may provoke a sequence of cochlear mediated central gain changes in response to prolonged changes in acoustic experience.

In light of our recent findings, we questioned if exposure to an even lower-level noise (65 dB SPL), comparable to levels in urban and work environments could produce similar potent effects on cochlear and IC physiology. To test this hypothesis, we exposed Sprague-Dawley rats to a continuous 65 dB noise for 5 weeks, an intensity level similar to an air conditioning window unit, then measured cochlear function with distortion product otoacoustic emissions (DPOAEs) and the cochlear compound action potentials (CAP) and also evaluated central auditory function by measuring sound-evoked local field potentials (LFPs) from the IC. Measurements were made immediately after the 5-week exposure to assess acute change and at one-week post-exposure to determine if changes were temporary or permanent.

Methods

Subjects:

Twenty-five Sprague-Dawley rats (3–4 months old, 300–400 g, Charles River) were used in the study. Cochlear CAPs and IC LFPs were obtained from 17 animals that were randomly assigned to one of three groups: 1) controls (n=6), 2) low-level noise (LLN, n=6), and 3)

one-week post noise exposure (1WPE, n=5). DPOAE measures were obtained from eight rats before the LLN exposure, after 5 weeks in LLN, and 1WPE. Animals were housed one per cage, provided free access to food and water, and kept on a 12/12 h light-dark cycle. All procedures were approved by the Institutional Animal Care and Use Committee (IACUC) at the University at Buffalo in accordance with NIH guidelines.

Noise Exposure:

Animals were exposed to a 10–20 kHz octave-band noise presented at a total integrated intensity level of 65 dB SPL. The noise was generated and presented in an identical manner to our previously published study [33]. Briefly, the noise was generated using a Tucker Davis Technology RP2 real-time processor, sent to a power amplifier, then routed to a loudspeaker suspended with wire mesh above the animals cage. The noise was calibrated from the center of the cage using a sound level meter (Larson Davis System 824). Neurophysiologic responses were obtained from the IC immediately after animals were removed from the noise, or 1-week post exposure, and CAP data were obtained within 8 hours of animals being removed from the noise, or 1-week post exposure.

Compound Action Potential (CAP):

Details of our methods for acquiring and analyzing the CAP can be found in previous publications [33, 34]. Briefly, animals were placed in a customized head-holder, the right bulla was exposed and a small fistula was made to access the cochlear round window. A silver ball electrode was placed on the round window and a reference electrode was inserted into the neck muscles. Tone bursts were generated using a Tucker Davis Technologies (TDT) real-time processor (RP2.1, System 3) and presented via an ACO ½" microphone driven in reverse. Stimulus intensity was decreased in 10 dB steps from 80 to 0 dB SPL using a TDT PA5 programmable attenuator. The cochlear response within a 20 ms time window was amplified (1000x) with a WPI DAM50 differential amplifier and filtered online (0.1 –10000 Hz). The voltage difference between N1 and P1 was measured and used to compute CAP amplitude. CAP amplitudes were tested for significance using a two-way ANOVA and Bonferroni post-hoc analysis.

Distortion Product Otoacoustic Emissions:

Our methods for collecting and analyzing DPOAEs have been described in detail in previous publication [34, 35]. Briefly, DPOAEs were measured with the Smart Distortion Product Otoacoustic Emission System (version 4.53, Intelligent Hearing System, Miami, FL), using two primary tones (f1 and f2) with an f2/f1 ratio of 1.2. The f1 intensity (L1) was presented at an intensity 10 dB higher than the intensity of f2 (L2). L1 was decreased from 80 to 25 dB SPL in 5-dB steps. The DPOAE signal-to-noise ratio (SNR) was plotted as function of L1 intensity and DPOAE input/output (I/O) functions were analyzed for significance using a two-way ANOVA and Bonferroni post-hoc analysis.

Cochleograms:

Our methods for assessing inner hair cell (IHC) and outer hair cell (OHC) loss are described in detail in previous publications [6, 33]. After decapitation, and cochleae removal, the oval

windows were opened and a small fistula was placed at the apex of the cochlea. Cochleae were perfused with succinate dehydrogenase (SDH) incubation solution (0.05 M sodium succinate, 0.05 M phosphate buffer and 0.05% tetranitroblue tetrazolium) then immersed in a SDH solution for 1 h (37 °C). Cochlea were then fixed in 10% formalin for 2 days then decalcified in 7% ethylenediamine tetracetic acid (EDTA) for 3 days. The organ of Corti was carefully microdissected out as a surface preparation, mounted in glycerin on glass slides and SDH-labeled hair cells examined along the entire length of the cochlea using a light microscope (400X). Percent hair cell loss was obtained by comparing the hair cell counts from animals in the LLN group to counts in the control group (Figure 1B).

IC Local Field Potentials:

Details of our electrophysiological techniques have been described in previous publications [7, 33]. Rats were anesthetized with ketamine (60 mg/kg, i.p.) and xylazine (6 mg/kg, i.p.) and secured in a stereotaxic apparatus. The dorsal surface of the skull was exposed and using stereotaxic coordinates [43], a craniotomy was made over the left IC. The dura was removed and a linear 16-channel silicon microelectrode (A-1×16–10 mm 100–177, NeuroNexus Technologies) was advanced into the IC using a hydraulic microdrive (FHC Inc., Bowdoin, ME). Several electrode penetrations were performed in order to obtain neural responses across the entire tonotopic area of the IC. Tone bursts were presented to the right ear at a rate of ~3/s through a loud speaker (FT28D, Fostex). LFPs were obtained with a resolution of 40.96 μ s using a TDT RA16PA preamplifier and RX5 base station controlled with a custom MATLAB software. LFPs were extracted by low-pass filtering (2–300 Hz) and responses were down-sampled online at 610 Hz. LFPs were averaged 100 times and the root mean square (RMS) voltage was measured over a 50 ms time window following stimulus onset.

Results

DPOAEs and Hair Cells:

DPOAEs, arising from the nonlinear electromotile response of OHCs, are a reliable measure of OHC function [41]. To determine if the 65 dB SPL LLN affected OHC function, we measured DPOAE I/O functions immediately after the LLN, and at 1WPE and compared the results to pre-exposure amplitudes. Figure 1A shows the DPOAE I/O functions for 4, 8, 16, and 24 kHz. DPOAE I/O functions immediately after the LLN exposure were nearly the same as baseline except for slight, yet significant reductions ($p < 0.05$) at several frequency/intensity combinations (8 kHz/35 dB, 16 kHz/35 dB and 24 kHz/35 dB). At 1WPE, DPOAE amplitudes were nearly the same as baseline except for slight, but significant ($p < 0.05$) changes at a few frequency/intensity combinations (8 kHz/40 dB, 16 kHz/30 & 35 dB and 24 kHz/35 dB). Notably, most of these significant changes occurred at SNRs below 0 dB, meaning the DPOAE was already below the noise floor. Therefore, the results suggest that OHC function was essentially unchanged after the LLN exposure. Figure 1B shows the mean cochleograms for the Control and LLN groups ($n=3$ /group). Neither group showed evidence of OHC or IHC loss consistent with the DPOAE data.

CAP:

CAP I/O functions from the LLN and 1WPE groups were compared to Controls to determine if the 65 dB SPL noise affected the neural output of the cochlea (Figure 1C). Compared to controls, CAP amplitudes in the LLN group were significantly reduced at moderate and high intensities at 8, 16 and 24 kHz. CAP amplitudes in the 1WPE group were similar to those in the Control group at 8, 16 and 24 kHz; however, amplitudes at 4 kHz were significantly larger than Controls at 70 and 80 dB SPL. Thus, the 65 dB noise significantly reduced the neural output of the cochlea, amplitudes recovered 1WPE and were even elevated significantly at 4 kHz.

IC LFPs:

To determine if the 65 dB LLN induced changes in the auditory midbrain, we measured tone-evoked LFPs in the IC. Figure 1D shows LFP amplitude I/O functions for four similar frequencies to those plotted in 1A and 1C. At frequencies below the noise exposure band (i.e., 4 & 8 kHz) the LLN caused significantly enhanced LFP amplitudes at supra-threshold levels. LFP enhancements largely recovered to control amplitudes at 1WPE. At frequencies within and above the noise exposure band (i.e., 18 & 27 kHz), LFP amplitudes were significantly enhanced after the LLN exposure, more so than those below the exposure band. LFPs mostly recovered to control amplitudes at frequencies above the noise band, and only partially at frequencies within the noise exposure band (see 18 kHz 60–80 dB).

Central Gain:

To illustrate the large dynamic changes in central gain, we plotted the percent difference in CAP and LFP amplitudes in the LLN and 1WPE groups relative to the control group (Figure 2). CAP amplitudes in LLN group declined 40–60% over a broad range of frequencies following the 65 dB SPL LLN (Figure 2A–C). Despite the large reductions in CAP amplitudes, LFP amplitudes in the LLN group were enhanced more than 50% at frequency near the 10–20 kHz noise; these increases were most pronounced at 60–70 dB and less so at 80 dB SPL. CAP amplitude reductions of 50% in the 10–20 kHz region were compensated by increases in LFP amplitudes of more than 50%.

Major changes also occurred when animals were removed from the LLN for one week prior to data collection. While CAP amplitudes were depressed more than 50% immediately after the exposure, by 1WPE CAP amplitudes were back to normal above 20 kHz, slightly elevated between 10–20 kHz and enhanced (>50%) below 10 kHz. In contrast, IC amplitudes, which were enhanced immediately after the LLN exposure, were now slightly depressed or normal below 10 kHz, slightly elevated from 10 to 20 kHz region, and normal above 20 kHz.

Discussion:**DPOAE and Hair Cells:**

We expected that prolonged exposure to 10–20 kHz noise at 65 dB SPL would have little effect on the cochlea. This prediction was partly substantiated by the fact that DPOAE were largely unaltered and OHCs remained intact following the LLN. In addition, there was also

no visually apparent disruption of IHCs. Despite the essentially unaffected function of OHCs, the neural output of the cochlea was grossly reduced.

Cochlear Output:

CAP amplitudes were reduced 40–60% over a broad range of frequencies immediately after the noise exposure (Figure 2A–C), indicating that LLN suppressed the flow of information between the IHC and type I auditory nerve fibers. The large reduction in CAP amplitudes and subsequent recovery could be due to presynaptic dysfunctions, reducing the release of synaptic vesicles from the IHC or interfering with other aspects of IHC function [16, 21, 23, 30, 36, 38]. Alternatively, the reduction and subsequent recovery of the CAP could involve post-synaptic changes that disrupt the afferent auditory nerve terminal and receptor expression [8, 16, 23, 27–29, 36]. Unexpectedly, at 1WPE CAP amplitudes became enhanced at frequencies below the 10–20 kHz exposure. Enhanced CAP responses similar to this have been observed in sound conditioning studies [18], in which the cochlea becomes more resistant to subsequent acoustic trauma, presumably by increasing the cochlea's anti-oxidant defenses [12, 17]. Alternatively, the CAP enhancement could involve various forms of pre- or post-synaptic rescaling that affect the probability of neurotransmitter release, quantal size and/or size of the releasable pool of neurotransmitter [23, 25, 42, 45].

Dynamic Gain:

Immediately after LLN exposure, the positive gain changes in the IC were unexpectedly large; despite reductions in CAP amplitude of 50–60% across a broad spectral region, LFP amplitudes were enhanced more than 50% at frequencies near the noise exposure band (Figure 2A–C, red arrow). However, it should be clearly noted that enhanced positive gain did not occur universally at all frequencies that demonstrated a reduced neural output from the cochlea. For instance, the LLN also caused diminished cochlear output at frequencies above and below the noise band, yet LFPs at these frequencies only showed positive gain enhancements of approximately 20–30%. One interpretation of these results is that LFP amplitudes outside the noise band exhibit a “healthy” amount of positive gain, correcting for diminished CAP amplitudes without exceeding typical activity levels. Whereas frequencies in the noise band exhibit unhealthy amounts of positive gain, which may contribute to hyperacusis percepts. The disparities in gain changes among frequencies inside versus outside the noise band could be the result of changes in central lateral inhibition or tonotopic reorganization [3]. Similarly, reductions in CAP amplitudes across a broad frequency range induced by high dosage of sodium salicylate has shown to shift central neuron characteristic frequencies towards the center of the 10–20 kHz region; changes which are thought to partially occur from an imbalance of lateral inhibition [32, 37].

At 1WPE, CAP and LFP amplitudes were both essentially normal above 10 kHz; suggesting that the gain changes in this region had reached homeostatic equilibrium. At frequencies below 10 kHz, LFP amplitudes also remained normal, but CAP amplitudes became enhanced. This observation suggests that somewhere between the auditory nerve and IC the neurological signal is suppressed (Figure 2D, blue arrow). One interpretation of these results is that the gain changes between the cochlea and IC are bidirectional; decreased output from the cochlea is countered by positive gain at the IC whereas increased output from the

cochlea is countered by negative gain in order re-establish homeostatic equilibrium. The positive and negative gain changes between the cochlea and IC likely involve homeostatic synaptic reorganization in the auditory brainstem [9, 40, 44]. Similar gain changes induced by a transient conductive hearing loss have suggested that the synaptic plasticity may originate from synaptic scaling at the level of the cochlear nucleus [9].

Clinical Implications:

Noise levels have steadily been increasing so that levels in many urban environments are 60–75 dBA or higher [4, 10, 22]. The Environmental Protection Agency (EPA) recommends a maximum noise dose of ~70 dBA for a 24 h period [1]; however, these limits are based primarily on audiometric threshold shifts, not changes occurring at supra-threshold levels. Our results indicate that prolonged exposure to 10–20 kHz noise at 65 dB SPL can cause significant changes in the neural output of the cochlea at supra-threshold levels that could provoke a cascade of central gain changes. While CAP amplitudes recover from this five-week exposure, it is conceivable that prolonged exposure for decades could lead to permanent changes at the IHC/auditory nerve synapse.

Hearing loss often gives rise to tinnitus and hyperacusis, debilitating conditions believed to be caused by excessive positive central gain [2]. While there are no effective drugs to treat tinnitus or hyperacusis, patients often report relief from sound therapies involving prolonged exposure to LLN [13, 14], which presumably reduces central gain and alleviates tinnitus and hyperacusis [11, 24]. Our findings indicate that continuous exposure to 10–20 kHz noise at 65 dB SPL for five weeks may temporarily worsen tinnitus or hyperacusis by increasing central gain. However, in preliminary studies we found that presenting the 10–20 kHz noise intermittently (12 h/d) reduces central gain (unpublished data) suggesting that intermittent sound therapies may be more useful than continuous sound therapy.

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Highlights

- Prolonged low-level noise is capable of evoking changes in auditory central gain
- Central gain compensates for changes in cochlear function to maintain homeostatic equilibrium
- Prolonged Low-level noise reduces cochlear compound action potentials without altering distortion product otoacoustic emissions

Figure 1:

Low-level noise-induced changes in cochlea and IC. (A) DPOAE I/O functions for controls (blue $\pm$ 95% confidence intervals), LLN exposure (red $\pm$ SEM), and at 1WPE (green $\pm$ SEM). DPOAE values in LLN or 1WPE groups that are significantly different from baseline are shown as open symbols (Two-way ANOVA, $p < 0.05$ Bonferroni post-hoc comparison). (B) Mean cochleogram for control group (n=3) and LLN group (n=3) showing percent missing IHC and OHC as function of percent distance from apex. Note absence of hair cell loss. (C) CAP I/O functions for controls (blue $\pm$ 95% confidence intervals), LLN exposure (red $\pm$ SEM) and at 1WPE (green $\pm$ SEM) groups. CAP values in LLN group or 1WPE group that are significantly different from controls are indicated by open symbols (Two-way ANOVA, $p < 0.05$ Bonferroni post-hoc comparison). (D) LFP I/O functions for controls (blue $\pm$ 95% confidence intervals), LLN exposure (red $\pm$ SEM) and at 1WPE (green $\pm$ SEM). Mean data shown for control group (n=432 channels), LLN group (n=480 channels) and 1WPE group (n=400 channels). Open symbols show data points that were significantly different from controls (Two-way ANOVA, $p < 0.05$ Bonferroni post-hoc comparison).

Figure 2:

Mean percent difference in CAP amplitude and IC LFP amplitude at 60, 70 and 80 dB SPL. (A-C) Immediately post LLN exposure, CAP amplitudes were depressed 40–60% over a broad frequency range while IC LFPs were enhanced by as much as 70%, mainly at frequencies near the noise band (gray area). Red up arrow indicates enhanced central gain over a broad frequency range. (D-F) At 1WPE, CAP amplitudes were nearly normal at high frequencies, but enhanced at near the lower edge of noise band and below. In contrast, LFP amplitudes were nearly normal or slightly enhanced near 10–20 kHz and normal or slightly depressed below 10 kHz. Down blue arrow indicates suppressed central gain (i.e. CAP amplitude enhanced, but IC amplitude normal) occurring at frequencies below the noise band.