Published in final edited form as:

Neuroscience. 2017 September 17; 359: 159–171. doi:10.1016/j.neuroscience.2017.07.005.

Prolonged Low Level Noise Induced Plasticity in the Peripheral and Central Auditory System of Rats

Adam M. Sheppard¹, Guang-Di Chen¹, Senthilvelan Manohar¹, Dalian Ding¹, Bo-Hua Hu¹, Wei Sun¹, Jiwei Zhao², and Richard Salvi¹

¹Center for Hearing and Deafness, State University of New York at Buffalo, 137 Cary Hall, 3435 Main Street, Buffalo, NY 14214, USA

²Department of Biostatistics, School of Public Health and Health Professions, State University of New York at Buffalo, Buffalo, NY 14214

Abstract

Prolonged low-level noise exposure alters loudness perception in humans, presumably by decreasing the gain of the central auditory system. Here we test the central gain hypothesis by measuring the acute and chronic physiologic changes at the level of the cochlea and inferior colliculus (IC) after a 75 dB SPL, 10–20 kHz noise exposure for 5 weeks. The compound action potential (CAP) and summing potential (SP) were used to assess the functional status of the cochlea and 16 channel electrodes were used to measure the local field potentials (LFP) and multi-unit spike discharge rates (SDR) from the IC immediately after and one-week post-exposure. Measurements obtained immediately post-exposure demonstrated a significant reduction in supra-threshold CAP amplitudes. In contrast to the periphery, sound-evoked activity in the IC was enhanced in a frequency-dependent manner consistent with models of enhanced central gain. Surprisingly, one-week post-exposure supra-threshold responses from the cochlea had not only recovered, but were significantly larger than normal, and thresholds were significantly better than controls. Moreover, sound-evoked hyperactivity in the IC was sustained within the noise exposure frequency band but suppressed at higher frequencies. When response amplitudes representing the neural output of the cochlea and IC activity at one-week post exposure were compared with control animal responses, a central attenuation phenomenon becomes evident, which may play a key role in understanding why low-level noise can sometimes ameliorate tinnitus and hyperacusis percepts.

Keywords

Cochlea; Inferior Colliculus; Low-Level Noise; Central Gain

Corresponding Author: Adam Sheppard, Center for Hearing and Deafness, 137 Cary Hall, Buffalo, NY 14214, phone: 315 719 8594, fax: 716 839 2980, asheppard315@gmail.com.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this article.

Introduction

, Henry, Schechter et al. 2006, Brotherton, Plack et al. 2015, Henry, Griest et al. 2015). Functional measures indicate that sound therapy can have a positive effect on tinnitus and hyperacusis patients; however, the mechanism which drives these improved outcomes is still poorly understood.

A number of studies have indicated that low-level sounds can alter the neural response properties of the auditory cortex (AC). A large portion of these studies have been performed in cats (Eggermont and Komiya 2000, Pienkowski and Eggermont 2009, Pienkowski and Eggermont 2009, Pienkowski and Eggermont 2010, Pienkowski and Eggermont 2010, Pienkowski, Munguia et al. 2011, Pienkowski and Eggermont 2012, Munguia, Pienkowski et al. 2013, Pienkowski, Munguia et al. 2013). Results from these studies indicate that sound-evoked local field potentials (LFPs), spike discharge rates (SDRs) and spontaneous firing rates in the primary auditory cortex (A1) become hypoactive to sound stimulation within the exposure frequency band (tone-pip ensembles, 68–72 dB SPL) and hyperactive to stimuli near the upper and lower edges of the exposure band (Pienkowski and Eggermont 2010, Pienkowski and Eggermont 2010, Munguia, Pienkowski et al. 2013). Neurons also shifted their characteristic frequencies away from the exposure band frequencies, thereby distorting the AC tonotopic map (Pienkowski and Eggermont 2010). Likewise, in rats, continuous exposure for one month to a broadband noise (4–45 kHz, 60–70 dB SPL) results in disrupted cortical tonotopy (Zheng 2012). In addition to altering neural response amplitudes and tonotopy, abnormal temporal processing has also been observed in the AC following a 2 month exposure to low-level noise bursts (Zhou and Merzenich 2012). Interestingly, these neuroplastic changes have all been reported in absence of peripheral hearing loss. Additional studies have indicated that similar neuroplasticity likely occurs at more peripheral auditory loci such as the medial geniculate body and inferior colliculus (IC) (Lau, Pienkowski et al. 2015, Lau, Zhang et al. 2015).

At the level of the peripheral auditory system, low-level noise has been shown to alter auditory function. In mice that exhibit early onset high-frequency hearing loss, conditioning animals with a 70 dB SPL broad band noise (12 h/night) significantly slowed the elevation of auditory brainstem response (ABR) thresholds. (Turner and Willott 1998, Willott and Turner 1999). Similarly, when normal-hearing guinea pigs were conditioned with a low-frequency, octave band noise (2–4 kHz) at 85 dB SPL for 6 h/day for 10 consecutive days, they demonstrated significantly enhanced distortion product otoacoustic emissions (DPOAEs) and compound action potential (CAP) amplitudes (Brown, Kujawa et al. 1998, Kujawa and Liberman 1999). These results suggest that conditioning the auditory system with low- or moderate-level noise can improve peripheral auditory function.

The neuroplastic changes occurring in the auditory pathway after prolonged exposure to low-level noise can increase loudness tolerance, presumably by decreasing central auditory gain (Formby, Sherlock et al. 2003, Henry, Schechter et al. 2006, Henry, Schechter et al. 2006, Norena and Chery-Croze 2007, Munro and Blount 2009, Zheng 2012, Auerbach, Rodrigues et al. 2014). However, exactly where these functional changes occur along the auditory pathway, and what neural mechanisms are involved in the process remains poorly

understood. To address this gap in knowledge, and further our understanding on the impact that low-level noise can have on the auditory system as a whole, we exposed rats for five weeks to 75 dB SPL octave band noise. Afterwards, we measured the neurophysiological changes at the level of the cochlea and IC immediately following exposure and at one week post-exposure to identify the acute and chronic changes respectively.

Experimental Procedures

Subjects

Sixteen male Sprague-Dawley rats (3–4 months old, 300–400 g, Charles River) were used in the study. Animals were housed one per cage, provided free access to food and water, and kept on a 12/12 h light-dark cycle. The rats were randomly assigned to one of three groups: Control group (n=6), Low-Level Noise (LLN) group (n=6), and 1-Week Post-Exposure (1WPE) group (n=4).

Noise Exposure

The exposure consisted of a 10–20 kHz octave band noise (OBN) presented at a total integrated intensity level of 75 dB SPL for 24 h/d for 5 weeks. The noise was generated with a TDT RP2 real time signal processor (Tucker-Davis Technologies) and sent to a power amplifier (Amp 300 AudioSource Inc. or Crown XLS202) connected to a loudspeaker (Fostex FT17H) suspended approximately 7.6 cm above the center of the animal's plastic cage (l = 45.7, w = 25.4 × h = 20.3 cm) with acoustically transparent wire mesh cover. The noise in each cage was calibrated using a sound level meter (Larson Davis System 824) equipped with a free-field ½" microphone (model 2540, Larson Davis); the microphone was located at the center of the animal's cage.

IC Electrophysiology

Electrophysiological measurements were obtained from rats in the LLN group 2–8 h post-exposure. Rats in the 1WPE group were removed from the noise and housed for 1 week in the same room as the control group prior to making electrophysiological measurements. The control group animals were age matched and housed for approximately the same time (5 weeks) prior to making the electrophysiological measurements. Details of our electrophysiological techniques are described in previous publications (Stolzberg, Chen et al. 2011, Chen, Manohar et al. 2012, Chen, Stolzberg et al. 2013). Rats were anesthetized with ketamine (60 mg/kg, i.p.) and xylazine (6 mg/kg, i.p.) and secured in a stereotaxic apparatus with blunt ear bars. Body temperature was maintained at 37 °C using a homoeothermic blanket (Harvard Apparatus, Holliston, MA). The dorsal surface of the skull was surgically exposed and a head bar firmly attached to the skull with a bone screw and dental cement. Then the right ear bar was removed to allow for sound stimulation to the right ear canal. Using stereotaxic coordinates (Watson and Paxinos 2004), a craniotomy was performed on the dorsal surface of the skull contralateral to the right ear to gain access to the 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 contralateral 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 (50 ms duration, 1 ms rise/fall time, cosine²-gated) were generated (TDT RX6-2, ~100 kHz sampling rate) and presented at a rate of ~3/s through a loud speaker (FT28D, Fostex) located 10 cm in front of the right ear. Stimuli were calibrated using the electrical output from a sound level meter (Larson Davis, ¼" microphone, model 2520) delivered to a custom sound calibration program. Neural responses from tone bursts were acquired at 10 frequencies (1.0, 1.5, 2.3, 3.5, 5.3, 8.0, 12.1, 18.3, 27.7, and 42.0 kHz) and 11 intensities (0–100 dB SPL, 10 dB steps, 50 repetitions per frequency-intensity combination).

LFPs and multi-unit SDRs were acquired simultaneously with a resolution of 40.96 µs using a TDT RA16PA preamplifier and RX5 base station (Tucker-Davis Technologies System-3, Alachua, FL) and custom MATLAB software (MATLAB R2007b, MathWorks). The LFP was extracted by low-pass filtering (2–300 Hz) and was down-sampled online at 610 Hz. LFPs were averaged 100 times over a 500 ms time window following stimulus onset, and the root mean square (RMS) was measured over a 50 ms time window. Neural discharges were high-pass filtered (300–3000 Hz) and spikes were detected by a manually set threshold. Multi-unit spike discharges were used to construct peristimulus time histograms (PSTH) in a time window of 200 ms with a bin width of 1 ms. PSTHs obtained from multiple recording sites from multiple animals in the same treatment group were averaged together to obtain a global overview of the IC population response.

CAP and Summating Potential (SP)

Immediately after acquiring the IC data, the CAP and SP were collected from the cochlea as described previously (Chen, Stolzberg et al. 2013, Sheppard, Chen et al. 2015). The animal was placed in a customized head-holder, the right bulla was exposed and a small fistula made to access the cochlear round window. Body temperature was maintained at 37 °C using a homoeothermic blanket (Harvard Apparatus, Holliston, MA). A Teflon-coated silver wire (76.2 µm in diameter, Cat#75810, A-M System Inc.) was used to make a ring-electrode which was placed on the cochlea's round window and a silver chloride electrode was inserted into the neck muscles as a reference. Tone bursts (2, 4, 6, 8, 12, 16, 20, 24, 30, 35 and 40 kHz, 10 ms duration, 1 ms rise/fall time) were generated using a Tucker Davis Technologies (TDT) real-time processor (RP2.1, System 3) and presented via a 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 (1000×) with a WPI DAM50 differential amplifier and filtered online (0.1 –10000 Hz) using a custom MATLAB program. The vertical distance between N1 and P1 was measured and used to compute CAP amplitude (Figure 1). The direct current shift from baseline to the positive quasi-steady state response was used to determine the SP amplitude (Figure 1). CAP threshold was defined as the stimulus intensity that elicited a 3 µV N1 amplitude. CAP and SP amplitude input/output (I/O) functions and CAP thresholds were tested for significance using the nonparametric Scheirer-Ray-Hare test in R (Dytham 2011).

IC Neuroanatomy

To verify the electrode recording site, electrode position was confirmed with a fluorescent dye (DiI, Cat no. 42364, Sigma-Aldrich) as described previously (Chen, Manohar et al.

2012). DiI was applied to the surface of the electrode and allowed to dry prior to insertion into the IC. After completing the electrophysiological recordings, the anesthetized rat was decapitated, the brain was carefully removed from skull and stored in 10% buffered formalin for 5–7 days, immersed in 30% sucrose solution for two days and then immersed in 15% sucrose solution for another two days. The brain was cryosectioned (50 μ m) in the coronal plane. Sections were blocked with normal horse serum and subsequently incubated in primary mouse anti-neuronal nuclei (NeuN) monoclonal antibody (1:1000, Chemicon, MAB377). Next, slices were washed three times with phosphate buffered saline (PBS) and incubated with a donkey anti-mouse secondary antibody conjugated with Alexa Fluor 488 (1:1000; Invitrogen, A21202). Finally, sections were washed in PBS, mounted on Fisher Superfrost polarized slides and coverslipped with Prolong Antifade mounting medium (Invitrogen). Sections were photographed and processed with a Zeiss Axio Imager Z1 Microscope equipped with a digital camera, Zeiss AxioVision software. Figure 2A shows a representative example of the DiI electrode track in the inferior colliculus.

Cochleograms

Immediately after decapitating the rat, the round and oval windows were opened and a small hole was made at the apex of the cochlea. The cochleae were perfused with succinate dehydrogenase (SDH) incubation solution (0.05 M sodium succinate, 0.05 M phosphate buffer and 0.05% tetranitroblue tetrazolium) and then immersed in SDH solution for 1 h (37 °C) with additional perfusions occurring approximately once every 15 minutes. The cochlea was then fixed in 10% formalin for at least 2 days. Afterwards, the cochleae were decalcified in 7% ethylenediamine tetracetic acid (EDTA) solution for three days. Then the entire organ of Corti was carefully microdissected out as flat surface preparation. All hair cells with detectable SDH staining (Figure 2B) were counted from base to apex under a light microscope. Percent hair cell loss was obtained by comparing the hair cell counts from animals in the LLN group to counts in the control group.

Results

CAP and SP Following LLN Exposure

To determine if our low-level noise exposure affected the summed neural output of the cochlea we measured the threshold and amplitude of the CAP. To test for changes in sensitivity, we compared the CAP thresholds in the control group with those in the LLN group. Mean ($\pm$ SEM, $n=6$) CAP thresholds in the control group were lowest (5–8 dB SPL) from 16–20 kHz and increased at higher and lower frequencies (Figure 3A). Mean ($\pm$ SEM, $n=6$) CAP thresholds in the LLN group were nearly identical to those of the control group at most frequencies above and below the 10–20 kHz exposure band, whereas thresholds in the 8–20 kHz region were typically 5–11 dB higher than in the controls. Statistical analysis using a nonparametric Scheirer-Ray-Hare test revealed no significant change in CAP thresholds between control and LLN groups ($p=0.194$).

To assess peripheral response amplitudes at supra-thresholds levels we measured CAP amplitudes at varying frequencies and intensities. CAP amplitudes at supra-threshold levels were substantially reduced over a broad frequency range in the LLN group. The greatest

amplitude reductions occurred at frequencies within and above the 10–20 kHz exposure as illustrated by the 20 kHz input/output (I/O) function (Figure 3B). At 20 kHz, the CAP amplitude at 80 dB SPL was reduced from roughly 180 μ V in the control group to 75 μ V (~60% reduction) in the LLN group and at 60 dB the amplitude was reduced from 75 μ V to 43 μ V (~43% reduction, Figure 3B). To quantify the reductions across all tested frequencies, we plotted supra-threshold CAP amplitudes measured at 80 dB SPL (Figure 3C). In the control group, CAP amplitudes ranged from ~70 μ V at 8 kHz to roughly 190 μ V at 20 and 40 kHz. CAP amplitudes in the LLN group ranged from ~70 μ V at low frequencies to ~95 μ V at high frequencies. CAP amplitudes in the LLN group were significantly lower than those in the control group (nonparametric Scheirer-Ray-Hare, $p < 0.0001$). To aid visualization, the percent difference in CAP amplitude in the LLN group relative to controls was plotted as a function of frequency at 80 dB SPL with 95% confidence intervals illustrated (Figure 3D). CAP amplitudes in the LLN group were normal at 2 kHz, but were reduced by ~50–60% at frequencies within and above the exposure frequency band. Nonparametric statistical analysis indicated that the percent difference in CAP amplitudes was significant for frequencies 12 kHz ($p = 0.0244$), 16 kHz ($p = 0.0432$), 20 kHz ($p = 0.0365$), and 24 kHz ($p = 0.0485$).

To gain further insights related to peripheral changes, we measured the SP, which largely reflects the stimulus-evoked DC response of inner hair cells (IHC) (Zheng, Ding et al. 1997, Durrant, Wang et al. 1998). Figure 3E presents the mean ($\pm$ SEM, $n = 6$ /group) SP amplitudes at 80 dB SPL as a function of frequency. At 6 kHz, below the exposure band, SP amplitudes in the LLN group were similar to the control group. However, SP amplitudes in the LLN group were significantly lower than in controls at frequencies within the 10–20 kHz exposure (nonparametric Scheirer-Ray-Hare, $p < .01$). To aid visualization, the mean percent difference between groups is plotted with 95% confidence intervals as a function of frequency at 80 dB SPL (Figure 3F). The percent difference in SP ranged from 60–80% for frequencies within and above the noise exposure whereas the reduction was roughly 17% at frequencies below the exposure band. Percent differences were found to be significant using a nonparametric statistical analysis at 12 kHz ($p = 0.0428$) and 20 kHz ($p = 0.0322$); these changes largely parallel those for the CAP.

Cochlear Hair Cells

To determine if the large CAP and SP amplitude reductions were due to hair cell loss, we counted the number of missing IHC and OHC in six rats in the LLN group and three rats in the control group. There was no evidence of hair cell loss in either the LLN group or the control group.

IC LFPs following LLN Exposure

To obtain a global perspective on how the LLN affected neural responses in the IC, we recorded LFPs over a range of frequencies and intensities. At 40 dB SPL (Figure 4A), LFP amplitudes were consistently larger in the LLN group than controls from 12–27.7 kHz, and smaller than controls at 1–4 kHz. To aid in the comparison, LFP amplitudes in the LLN group were normalized to controls and plotted as percent difference with 95% confidence intervals (Figure 4B). LFP amplitudes in the LLN group were ~30–40% larger than control

from 12–18.3 kHz and ~5–30% smaller than controls from 1–4 kHz. These differences were significant when analyzed with non-parametric test at frequencies 12 kHz ($p=0.047$), and 18.3 kHz ($p=0.0385$) for enhancement, and at 1 kHz ($p=0.0443$) for attenuation. At 60 dB SPL, LFP amplitudes in the LLN group were consistently larger than controls from 12–42 kHz, but smaller than controls from 1–4 kHz (Figure 4C). LFP amplitudes in the LLN group were 30–40% larger than controls from 12–41 kHz and roughly 5–20% smaller than controls at from 1–4 kHz (Figure 4D). A non-parametric analysis indicated significant enhancement of the LLN exposed group at 12 kHz ($p=0.0434$), and significant attenuation at 1 kHz ($p=0.0446$). At 80 dB SPL and at 100 dB SPL, LFP amplitudes in the LLN group and control group were nearly the same (Figure 4E, G) with no significant enhancement or attenuation as indicated with 95% confidence intervals (Fig. 4F, H). Collectively LFP amplitudes in the LLN group showed evidence of level- and frequency-dependent hyperactivity in the 40–60 dB range and from 12–18 kHz and hypoactivity at low frequencies.

IC Firing Patterns following LLN exposure

To further our global understanding of how LLN affected neural responses within the IC we measured multi-unit SDRs over a range of frequencies and intensities. Figure 5 illustrates the mean post-stimulus time histograms (PSTH) measured from the IC in control (448 multi-units) and LLN exposed (464 multi-units) animals from moderate to high intensities (40–100 dB SPL) at a low, mid, and high frequency. SDRs measured with low-frequency stimulation (2.3 kHz) were consistently enhanced at high intensity levels (80–100 dB SPL) but suppressed at moderate intensity levels (40–60 dB SPL) in LLN exposed rats (Fig. 5A). A two-way ANOVA of the first 60 ms of the PSTH revealed a significant enhancement of LLN SDRs at high intensity levels (100 dB $p<.0001$; 80 dB $p<.0001$) and a significant suppression of LLN SDRs at moderate intensity levels (60 dB $p<.0001$; 40 dB $p<.0001$). When stimulated with a mid-frequency tone (12.1 kHz), which was within the noise exposure frequency band (Figure 5B), or a high frequency tone (27.7 kHz, Figure 7C) SDRs were consistently enhanced at all intensity levels (40–100 dB SPL) within 60 ms post-stimulation. Subjective observations of the PSTHs suggests that the enhancement is greater when stimulated with a frequency within the noise exposures frequency band (Figure 5B vs. Figure 5C) and greater at higher intensity levels (100 dB vs. 40 dB). A two-way ANOVA performed on the first 60 ms of the PSTH revealed a significant enhancement of LLN SDRs for all intensities stimulated with a mid-frequency (100 dB $p<.0001$; 80 dB $p<.0001$; 60 dB $p<.0001$; 40 dB $p<.0001$), and at high frequencies (100 dB $p<.0001$; 80 dB $p<.0001$, 60 dB $p<.0001$; 40 dB $p<.0001$).

CAP and SP 1WPE

To determine if the changes associated with our LLN exposure were long lasting, CAP thresholds and amplitudes and SP amplitudes were measured in a group of animals allowed to recover from the LLN exposure for a period of one week. To test for changes in sensitivity, we compared the CAP thresholds in the control group with those in the 1WPE group (Figure 6A). Mean ($\pm$ SEM, $n=4$) CAP thresholds in the 1WPE group were nearly identical to those of the control group ($n=6$) at very high frequencies (35–40 kHz), whereas thresholds in the 2–30 kHz region were consistently 5–10 dB lower (improved) than

controls. A non-parametric analysis indicated that the 1WPE group had significantly better thresholds than controls (nonparametric Scheirer-Ray-Hare, $p < .05$).

CAP amplitudes at supra-threshold levels were substantially enhanced over a broad frequency range in the 1WPE group. At 16 kHz, the CAP amplitude at 80 dB SPL increased from approximately 132 μV in the control group to 235 μV in the 1WPE group (~60% enhancement) and at 60 dB the amplitude increased from approximately 75 μV to 115 μV (~53% enhancement) (Figure 6B). To quantify the enhancements across frequency, we plotted the supra-threshold CAP amplitudes at 80 dB SPL (Figure 6C). In the control group, CAP amplitudes ranged from ~70 μV at 8 kHz to roughly 190 μV at 20 and 40 kHz. CAP amplitudes in the 1WPE group ranged from ~150 μV at low frequencies to ~250 μV at mid frequencies and back down to ~200 μV at high frequencies. These enhancements were statistically significant when compared to controls (nonparametric Scheirer-Ray-Hare, $p < .01$). To aid in the visualization of this effect, the percent difference in CAP amplitude in the 1WPE group relative to controls was plotted with 95% confidence intervals as a function of frequency (Figure 6D). CAP amplitudes in the 1WPE group were enhanced approximately 200% at very low frequencies and ~30–50% enhancement at frequencies within and above the noise exposure frequency. Enhancements were found to be significant at lower frequencies using a nonparametric analysis (2 kHz $p = 0.0048$; 4 kHz $p = 0.0049$; 6 kHz $p = 0.0338$; 8 kHz $p = 0.017$).

To further understand how chronic LLN affects the cochlea we measured the SP response at 1WPE and compared the values to controls. At 1WPE SP amplitudes had recovered to control amplitude levels. Figure 6E presents mean ($\pm$ SEM, $n = 4$) SP amplitudes for the 1WPE and controls ($n = 6$) at 80 dB SPL. Mean SP amplitudes from 1WPE group were consistently larger than controls at all measured frequencies. To aid in visualizing this effect we plotted the percent difference in amplitudes with 95% confidence intervals as a function of frequency (Figure 6F). Enhancement was found to be significant with a nonparametric test at 8 kHz ($p < 0.001$).

IC LFPs 1WPE

To determine if changes in LFP response amplitudes were sustained or disappeared with time, we again measured LFPs at 1WPE over a range of frequencies and intensities. At 40 and 60 dB SPL (Figure 7A, C), LFP amplitudes were consistently larger in the LLN group compared to controls from 3.5–18.3 kHz, and nearly identical at 80 and 100 dB (Figure 7E, G). To aid in this comparison, LFP amplitudes were normalized to control amplitudes and plotted as percent differences with 95% confidence intervals (Figure 7B, D, F & H). At 40 and 60 dB SPL LFPs were ~15–30% larger than controls from 3.5–27.7 kHz (Figure 7B, D). At 80 dB SPL, LFPs were ~15–30% larger from 1–3 kHz and ~20% larger from 12.1–18.3 kHz (Figure 7F), and nearly identical at 100 dB SPL. Despite the relatively large percent differences at low and moderate intensities, only one frequency at 60 dB was significantly different from controls (12.1 kHz, $p = 0.0476$).

IC Firing Patterns 1WPE

To determine if neural response in the IC had recovered, we again analyzed the multi-unit SDRs over the same range of frequencies and intensities in the 1WPE group (320 multi-units). Figure 8 illustrates the post-stimulus time histograms (PSTH) measured from the IC in controls and 1WPE animals from moderate to high intensities at a low-, mid-, and high-frequency. SDRs measured with low-frequency stimulation (2.3 kHz) were significantly enhanced at all intensities (100 dB $p<0.0001$; 80 dB $p<0.0001$; 60 dB $p<0.0001$; 40 dB $p<0.0001$). When stimulated with a mid-frequency tone (12.1 kHz), the enhancement previously observed immediately after the LLN exposure was present for intensity levels 60–100 dB SPL (Figure 8B). This enhancement, although smaller than the enhancement observed immediately after the LLN exposure (Figure 7B), still reached statistical significance with a two-way ANOVA performed on the first 60 ms post-stimuli (100 dB $p<0.0001$; 80 dB $p<0.0001$; 60 dB $p<0.0001$). When stimulated with a high frequency tone (27.7 kHz) SDRs were significantly hypoactive compared to controls at intensity levels of 60–100 dB (two-way ANOVA, 100 dB $p<0.0001$; 80 dB $p<0.0001$; 60 dB $p<0.0001$).

Discussion

The central auditory system is extremely plastic, capable of altering sound-evoked response amplitudes at multiple nuclei along the auditory pathway following changes in the peripheral system (Salvi, Wang et al. 2000, Chen, Stolzberg et al. 2013, Auerbach, Rodrigues et al. 2014, Sheppard, Hayes et al. 2014). This homeostatic gain control within the auditory system can be beneficial for listeners, allowing for ease of communication in a variety of listening environments such as with background noise. However, if such gain becomes dysregulated, it is likely to result in perceptual consequences such as tinnitus and hyperacusis (Anari, Axelsson et al. 1999, Norena 2011, Schecklmann, Landgrebe et al. 2014). Management for such disorders often incorporates LLN for sound therapy techniques under the assumption that LLN induces neuroplastic changes which reduce dysregulated hyperactivity within the central auditory system (Henry, Schechter et al. 2006, Henry, Schechter et al. 2006, Brotherton, Plack et al. 2015). However, the neural mechanisms and location along the auditory pathway in which this occurs is poorly understood. To address these issues we exposed rats to a LLN for a period of five weeks and then collected sound-evoked physiological measures at the cochlea and IC immediately after the noise and at a one week post-exposure time point; these results were compared to control animal responses. Immediately after the LLN exposure, response from the cochlea were dramatically reduced in a frequency-dependent manner and IC LFPs and SDRs were enhanced at mid-high frequencies and reduced at lower frequencies in a level-dependent manner. At 1WPE, cochlear responses not only recovered but were larger than those from control animals. In the IC, hyperactivity in LFP and SDRs was sustained within the noise exposure frequency band and appeared to spread to lower frequencies; reduced LFPs and SDRs recovered in low frequency regions, and enhanced LFPs and SDRs in high frequency regions were significantly reduced at 1WPE.

Cochlear Responses and Hair Cells

Detailed measures were obtained from the cochlea to determine the acute and chronic influences of LLN on the peripheral auditory system. Immediately after the LLN exposure, rats displayed a dramatic reduction in supra-threshold CAP amplitudes within and above the noise exposure frequency band. There was a slight increase in CAP thresholds, but this did not reach statistical significance. These observations indicate that there is a significant reduction in the neural output of the peripheral auditory system following the LLN exposure, but this did not have a significant influence on thresholds. Surprisingly, at 1WPE CAP amplitudes had not only recovered, but exceeded control levels. This resulted in a significant improvement in CAP thresholds, suggesting enhanced hearing acuity at 1WPE. To gain further insights into the mechanism contributing to this fluctuation in neural output, we assessed test for hair cell loss and analyzed the SP response from the cochlea, which primarily represents the stimulus-evoked response from IHCs (Zheng, Ding et al. 1997, Durrant, Wang et al. 1998). There was no loss of IHCs or OHCs when compared to controls using a SDH stain. However, there was a significant reduction and enhancement in SP amplitudes which paralleled the CAP amplitude changes. These observations suggest that the changes in cochlear sensitivity does not stem from hair cell loss, but rather from changes in mechanisms that modulate the afferent signal strength. Some plausible mechanisms that may contribute to these cochlear changes are 1) activity induced synaptic re-scaling at the level of IHCs and type I afferents (Chen, Kujawa et al. 2007), 2) modulation of the afferent signal via the lateral and medial olivocochlear efferent pathway (LOC, MOC respectively) (Groff and Liberman 2003), or 3) changes in the amplification properties from OHCs (Eddins, Zuskov et al. 1999).

Pre-synaptic ribbons and post-synaptic AMPA receptors are responsible for mediating the glutamatergic transmission between IHCs and type I afferents (Parks 2000, Fuchs, Glowatzki et al. 2003). Post-synaptic AMPA receptors can be down-scaled following acoustic stimulation (Chen, Kujawa et al. 2007), and impaired signal efficiency at the synapse can reduce supra-threshold CAP amplitudes (Liberman, Suzuki et al. 2015). Therefore, down-scaling of the post synaptic receptor density may be partially responsible for the reduced CAP amplitudes immediately following LLN exposure. To our knowledge there have been no previous reports of post-synaptic up-scaling of AMPA receptors at the level of IHC and type I afferent synapse. However, previous studies have found significant up-scaling of AMPA receptors at the level of the cochlear nucleus following cochlear ablation (Rubio 2006). If this phenomenon were to occur at the level of IHC and type I afferent synapse, it would provide an explanation for the enhanced CAP amplitudes observed at 1WPE.

It is also possible for CAP amplitudes to be modulated through the cochlear efferent system (Groff and Liberman 2003). MOC efferent fibers primarily synapse on contralateral OHCs and inhibit their electromotile response, thereby suppressing the sensitivity of the peripheral auditory system and reducing CAP amplitudes (Bruce, Christensen et al. 2000, Groff and Liberman 2003). Whereas LOC efferents primarily synapse on ipsilateral type I afferent fibers below IHCs, and can either inhibit or enhance CAP amplitudes (Groff and Liberman 2003). Both MOC and LOC efferents can be indirectly stimulated via the IC (Groff and

Liberman 2003). In our study, we demonstrate hyperactivity in the IC after LLN exposure; this hyperactivity may indirectly activate LOC or MOC efferents, thereby suppressing or enhancing CAP amplitudes.

Lastly, fluctuations in OHC electromotive properties cannot be ruled out as a contributor to the suppressed or enhanced CAP amplitudes. DPOAE amplitudes can be reduced following exposure to LLN as low as 64 dB SPL in chinchillas (Eddins, Zuskov et al. 1999), but have also been reported as enhanced in guinea pigs following an intermittent (6 h/day) moderate intensity (85 dB SPL, 2–4 kHz) noise exposure for 10 consecutive days. (Kujawa and Liberman 1999). Enhanced DPOAEs were accompanied by enhanced CAP amplitudes, and DPOAEs showed the strongest enhancement in the low-frequency region (Kujawa and Liberman 1999). It should be noted that the strongest CAP amplitude enhancements in our study were also in low-frequency regions, suggesting the possible contribution of stronger OHC responses. Future DPOAE measurements after LLN may help to elucidate the mechanisms responsible for cochlear amplitude reductions and enhancements.

Adaptive Gain Control

Central auditory structures, such as the IC, enhance their response to sound when there is reduced neural output from the peripheral auditory system (Chen and Jastreboff 1995, Salvi, Wang et al. 2000, Munro and Blount 2009, Sun, Lu et al. 2009, Chen, Manohar et al. 2012, Sheppard, Hayes et al. 2014, Chen, Li et al. 2015, Chambers, Resnik et al. 2016, Chen, Sheppard et al. 2016); this is commonly known as enhanced central gain. The central gain mechanism is thought to function as a compensatory mechanism for hearing loss (Chambers, Resnik et al. 2016). However, if central gain becomes dysregulated it could result in enhanced central gain, which likely gives rise to tinnitus and hyperacusis (Salvi, Wang et al. 2000, Norena 2011, Auerbach, Rodrigues et al. 2014). Therefore, suppressing hyperactivity within the central auditory system is believed to suppress tinnitus and/or hyperacusis. Clinically, patients who suffer from tinnitus and hyperacusis often report symptom relief with the use of sound therapy (Henry, Schechter et al. 2006, Henry, Schechter et al. 2006, Norena and Chery-Croze 2007), which typically incorporates some form of LLN or sound amplification. Indeed, cats exposed to LLN alone or immediately following a traumatic noise exposure exhibit reduced SDRs and LFPs at the level of the AC (Eggermont and Komiya 2000, Pienkowski and Eggermont 2009, Pienkowski and Eggermont 2009, Pienkowski and Eggermont 2010, Pienkowski and Eggermont 2012, Lau, Zhang et al. 2015). Our data at the subcortical level of the IC demonstrate enhanced sound-evoked responses following prolonged exposure to LLN, which appear to conflict with previously published results. However, considering the complex interconnectivity and inhibitory capabilities of the cortex, it is theoretically possible to have varying levels of activity within sub-cortical auditory nuclei that do not coincide with cortical responses. For example, inhibitory neurons located within the AC can preferentially enhance bottom-up sensory information, without activating top-down feedback loops (Hamilton, Sohl-Dickstein et al. 2013). It is possible that the enhanced activity we observed at IC could further enhance local cortical or thalamocortical inhibitory networks. This theoretical framework has been proposed previously (Pienkowski and Eggermont 2012), but requires further investigation.

An alternative way of interpreting gain is to view response amplitude changes in relation to control animal activity. We have plotted the CAP and IC LFP amplitudes in the LLN exposure and 1WPE groups as a percent difference of control animal response amplitudes in order to visualize the degree of neural gain occurring between the cochlea and IC (Figure 9). Here we categorize the change in response amplitudes of the IC relative to the neural input provided by the CAP (i.e., r_{eCAP}). At low-frequencies (~2 kHz) there is little change in CAP or LFP amplitudes immediately after LLN at 60 and 80 dB SPL and a slight amount of gain present at 40 dB SPL (Figure 9A). At mid and high frequencies (12 & 40 kHz respectively), CAP amplitudes are drastically reduced ~50% whereas LFP are slightly enhanced, ~15% above control amplitudes immediately after LLN at all intensity levels (Figure 9B, C). These observations suggest the presence of enhanced central gain since amplitudes are normal or slightly enhanced at the level of the IC despite dramatically CAP amplitudes. At 1WPE, CAP amplitudes were enhanced approximately ~200% when evoked with 60–80 dB SPL low-frequency tones, but displayed no change in LFP response amplitudes at the level of the IC (Figure 9A). Low frequency stimulation at lower intensity levels (40 dB SPL) showed no gain change in CAP or IC LFPs compared to control levels. Mid and high frequency stimulation at 1WPE resulted in enhanced CAP amplitudes and either slightly enhanced, normal, or reduced IC LFP amplitudes when compared to control activity (Figure 9B,C). These observations are interpreted as central attenuation (r_{eCAP}) since peripheral responses were always greater than those observed at the level of the IC.

The mechanisms responsible for changes in central gain or attenuation are unclear. One well accepted theory is homeostatic plasticity, which describes central gain as a neural compensatory mechanism for hearing loss (Auerbach, Rodrigues et al. 2014). More recently, computational modeling has suggested that the central gain phenomena may result from stochastic resonance (Krauss, Tziridis et al. 2016), a phenomenon where signal intensity is enhanced with the introduction of noise to a system. This phenomenon has been shown to exist within the auditory system of humans (Zeng, Fu et al. 2000), and may play a primary role in the response changes observed in the present study.

Implications for Tinnitus and Hyperacusis Management

Sound therapy is commonly used to manage both tinnitus and hyperacusis (Henry, Schechter et al. 2006, Henry, Schechter et al. 2006, Norena and Chery-Croze 2007), and frequently incorporates low-level noise (Formby, Sherlock et al. 2003, Norena and Chery-Croze 2007). The physiological correlates responsible for improved outcomes with sound therapy in tinnitus and hyperacusis is poorly understood, but is thought to occur as a result of alterations in a central gain control mechanism (Munro and Blount 2009). Psychoacoustic studies suggest that the perception of loudness can be adaptively re-scaled following prolonged sound deprivation or stimulation (Formby, Sherlock et al. 2003, Norena and Chery-Croze 2007), and others have suggested that adaptive neural gain in the central auditory system stems from a homeostatic reaction that initiates at levels more peripheral than the auditory cortex (Pienkowski and Eggermont 2009). With our system level approach in the current study, we are able to observe gross changes in response amplitudes in both the peripheral and central auditory system. These changes in response amplitudes suggest a peripherally driven homeostatic gain control system. When peripheral responses are

reduced, IC responses were enhanced, and when peripheral responses were enhanced, IC LFPs were always smaller than the enhanced peripheral responses. Such a homeostatic gain control mechanism could explain earlier reports of psychoacoustic loudness rescaling (Formby, Sherlock et al. 2003, Norena and Chery-Croze 2007), and potentially provide an explanation for why noise therapy results in improved outcomes for hyperacusis and tinnitus patients (Henry, Schechter et al. 2006). More detailed studies assessing a variety of noise exposure paradigms and at multiple levels of the ascending auditory pathway is required to gain a full understanding of the neural gain mechanism, but could positively influence outcomes that noise therapy has with those who suffer from tinnitus and hyperacusis.

Conclusion

The auditory system has proven to be extremely plastic in both peripheral and central structures (Canlon and Fransson 1995, Kujawa and Liberman 1999, Salvi, Wang et al. 2000, Chen, Kujawa et al. 2007, Chen, Kermany et al. 2010, Auerbach, Rodrigues et al. 2014, Sheppard, Hayes et al. 2014). However, dysregulated gain could lead to auditory perceptual disorders such as hyperacusis and tinnitus, (Salvi, Wang et al. 2000, Norena and Chery-Croze 2007, Zeng 2013, Auerbach, Rodrigues et al. 2014, Chen, Li et al. 2015, Diehl and Schaette 2015). Low-level sound therapy can be an effective treatment for these disorders (Formby, Sherlock et al. 2003, Henry, Schechter et al. 2006, Henry, Schechter et al. 2006, Norena and Chery-Croze 2007). However, the physiological changes associated with these improved clinical outcomes are poorly understood. Our results suggest that prolonged exposure to LLN enables the auditory system to re-scale its response amplitudes in a homeostatic fashion and may explain earlier reports of loudness re-scaling, and subjective improvements in patients suffering from tinnitus and hyperacusis after the use of low-level sound therapy. Further research is required to determine the biological mechanism responsible for the physiologic changes, and to assess the most effective management technique for patients suffering from tinnitus and hyperacusis.

Acknowledgments

Research supported in part by grants from the National Institutes of Health to AS (F31DC015933) and RS (R01DC014693, R01DC014452) and from the American Academy of Audiology to AS. Special thanks to Xiaopeng Liu for development of the analysis software used in the presented study.

References

- Anari M, Axelsson A, Eliasson A, Magnusson L. Hypersensitivity to sound—questionnaire data, audiometry and classification. *Scand Audiol.* 1999; 28(4):219–230. [PubMed: 10572967]
- Auerbach BD, Rodrigues PV, Salvi RJ. Central gain control in tinnitus and hyperacusis. *Front Neurol.* 2014; 5:206. [PubMed: 25386157]
- Brotherton H, Plack CJ, Maslin M, Schaette R, Munro KJ. Pump up the volume: could excessive neural gain explain tinnitus and hyperacusis? *Audiol Neurotol.* 2015; 20(4):273–282. [PubMed: 26139435]
- Brown MC, Kujawa SG, Liberman MC. Single olivocochlear neurons in the guinea pig. II. Response plasticity due to noise conditioning. *J Neurophysiol.* 1998; 79(6):3088–3097. [PubMed: 9636110]
- Bruce LL, Christensen MA, Warr WB. Postnatal development of efferent synapses in the rat cochlea. *J Comp Neurol.* 2000; 423(3):532–548. [PubMed: 10870091]

- Canlon B, Fransson A. Morphological and functional preservation of the outer hair cells from noise trauma by sound conditioning. *Hear Res.* 1995; 84(1–2):112–124. [PubMed: 7642444]
- Chambers AR, Resnik J, Yuan Y, Whitton JP, Edge AS, Liberman MC, Polley DB. Central Gain Restores Auditory Processing following Near-Complete Cochlear Denervation. *Neuron.* 2016; 89(4):867–879. [PubMed: 26833137]
- Chen GD, Jastreboff PJ. Salicylate-induced abnormal activity in the inferior colliculus of rats. *Hear Res.* 1995; 82(2):158–178. [PubMed: 7775282]
- Chen GD, Kermany MH, D'Elia A, Ralli M, Tanaka C, Bielefeld EC, Ding D, Henderson D, Salvi R. Too much of a good thing: long-term treatment with salicylate strengthens outer hair cell function but impairs auditory neural activity. *Hear Res.* 2010; 265(1–2):63–69. [PubMed: 20214971]
- Chen GD, Manohar S, Salvi R. Amygdala hyperactivity and tonotopic shift after salicylate exposure. *Brain Res.* 2012; 1485:63–76. [PubMed: 22464181]
- Chen GD, Sheppard A, Salvi R. Noise trauma induced plastic changes in brain regions outside the classical auditory pathway. *Neuroscience.* 2016; 315:228–245. [PubMed: 26701290]
- Chen GD, Stolzberg D, Lobarinas E, Sun W, Ding D, Salvi R. Salicylate-induced cochlear impairments, cortical hyperactivity and re-tuning, and tinnitus. *Hear Res.* 2013; 295:100–113. [PubMed: 23201030]
- Chen YC, Li X, Liu L, Wang J, Lu CQ, Yang M, Jiao Y, Zang FC, Radziwon K, Chen GD, Sun W, Muthaiah VP Krishnan, Salvi R, Teng GJ. Tinnitus and hyperacusis involve hyperactivity and enhanced connectivity in auditory-limbic-arousal-cerebellar network. *Elife.* 2015; 4
- Chen Z, Kujawa SG, Sewell WF. Auditory sensitivity regulation via rapid changes in expression of surface AMPA receptors. *Nat Neurosci.* 2007; 10(10):1238–1240. [PubMed: 17828255]
- Diehl PU, Schaette R. Abnormal Auditory Gain in Hyperacusis: Investigation with a Computational Model. *Front Neurol.* 2015; 6:157. [PubMed: 26236277]
- Durrant JD, Wang J, Ding DL, Salvi RJ. Are inner or outer hair cells the source of summing potentials recorded from the round window? *J Acoust Soc Am.* 1998; 104(1):370–377. [PubMed: 9670530]
- Dytham, C. Choosing and using statistics: a biologist's guide. John Wiley & Sons; 2011.
- Eddins AC, Zuskov M, Salvi RJ. Changes in distortion product otoacoustic emissions during prolonged noise exposure. *Hear Res.* 1999; 127(1–2):119–128. [PubMed: 9925023]
- Eggermont JJ, Komiya H. Moderate noise trauma in juvenile cats results in profound cortical topographic map changes in adulthood. *Hear Res.* 2000; 142(1–2):89–101. [PubMed: 10748332]
- Formby C, Sherlock LP, Gold SL. Adaptive plasticity of loudness induced by chronic attenuation and enhancement of the acoustic background. *J Acoust Soc Am.* 2003; 114(1):55–58. [PubMed: 12880017]
- Fuchs PA, Glowatzki E, Moser T. The afferent synapse of cochlear hair cells. *Curr Opin Neurobiol.* 2003; 13(4):452–458. [PubMed: 12965293]
- Groff JA, Liberman MC. Modulation of cochlear afferent response by the lateral olivocochlear system: activation via electrical stimulation of the inferior colliculus. *J Neurophysiol.* 2003; 90(5):3178–3200. [PubMed: 14615429]
- Hamilton LS, Sohl-Dickstein J, Huth AG, Carels VM, Deisseroth K, Bao S. Optogenetic activation of an inhibitory network enhances feedforward functional connectivity in auditory cortex. *Neuron.* 2013; 80(4):1066–1076. [PubMed: 24267655]
- Henry JA, Griest S, Zaugg TL, Thielman E, Kaelin C, Galvez G, Carlson KF. Tinnitus and hearing survey: a screening tool to differentiate bothersome tinnitus from hearing difficulties. *Am J Audiol.* 2015; 24(1):66–77. [PubMed: 25551458]
- Henry JA, Schechter MA, Zaugg TL, Griest S, Jastreboff PJ, Vernon JA, Kaelin C, Meikle MB, Lyons KS, Stewart BJ. Clinical trial to compare tinnitus masking and tinnitus retraining therapy. *Acta Otolaryngol Suppl.* 2006; (556):64–69. [PubMed: 17114146]
- Henry JA, Schechter MA, Zaugg TL, Griest S, Jastreboff PJ, Vernon JA, Kaelin C, Meikle MB, Lyons KS, Stewart BJ. Outcomes of clinical trial: tinnitus masking versus tinnitus retraining therapy. *J Am Acad Audiol.* 2006; 17(2):104–132. [PubMed: 16640064]

- Krauss P, Tziridis K, Metzner C, Schilling A, Hoppe U, Schulze H. Stochastic Resonance Controlled Upregulation of Internal Noise after Hearing Loss as a Putative Cause of Tinnitus-Related Neuronal Hyperactivity. *Front Neurosci.* 2016; 10:597. [PubMed: 28082861]
- Kujawa SG, Liberman MC. Long-term sound conditioning enhances cochlear sensitivity. *J Neurophysiol.* 1999; 82(2):863–873. [PubMed: 10444683]
- Lau C, Pienkowski M, Zhang JW, McPherson B, Wu EX. Chronic exposure to broadband noise at moderate sound pressure levels spatially shifts tone-evoked responses in the rat auditory midbrain. *Neuroimage.* 2015; 122:44–51. [PubMed: 26232718]
- Lau C, Zhang JW, McPherson B, Pienkowski M, Wu EX. Long-term, passive exposure to non-traumatic acoustic noise induces neural adaptation in the adult rat medial geniculate body and auditory cortex. *Neuroimage.* 2015; 107:1–9. [PubMed: 25479019]
- Liberman LD, Suzuki J, Liberman MC. Dynamics of cochlear synaptopathy after acoustic overexposure. *J Assoc Res Otolaryngol.* 2015; 16(2):205–219. [PubMed: 25676132]
- Munguia R, Pienkowski M, Eggermont JJ. Spontaneous firing rate changes in cat primary auditory cortex following long-term exposure to non-traumatic noise: tinnitus without hearing loss? *Neurosci Lett.* 2013; 546:46–50. [PubMed: 23648387]
- Munro KJ, Blount J. Adaptive plasticity in brainstem of adult listeners following earplug-induced deprivation. *J Acoust Soc Am.* 2009; 126(2):568–571. [PubMed: 19640020]
- Norena AJ. An integrative model of tinnitus based on a central gain controlling neural sensitivity. *Neurosci Biobehav Rev.* 2011; 35(5):1089–1109. [PubMed: 21094182]
- Norena AJ, Chery-Croze S. Enriched acoustic environment rescales auditory sensitivity. *Neuroreport.* 2007; 18(12):1251–1255. [PubMed: 17632277]
- Parks TN. The AMPA receptors of auditory neurons. *Hear Res.* 2000; 147(1–2):77–91. [PubMed: 10962175]
- Pienkowski M, Eggermont JJ. Effects of adaptation on spectrotemporal receptive fields in primary auditory cortex. *Neuroreport.* 2009; 20(13):1198–1203. [PubMed: 19617858]
- Pienkowski M, Eggermont JJ. Long-term, partially-reversible reorganization of frequency tuning in mature cat primary auditory cortex can be induced by passive exposure to moderate-level sounds. *Hear Res.* 2009; 257(1–2):24–40. [PubMed: 19647789]
- Pienkowski M, Eggermont JJ. Intermittent exposure with moderate-level sound impairs central auditory function of mature animals without concomitant hearing loss. *Hear Res.* 2010; 261(1–2):30–35. [PubMed: 20036723]
- Pienkowski M, Eggermont JJ. Passive exposure of adult cats to moderate-level tone pip ensembles differentially decreases AI and AII responsiveness in the exposure frequency range. *Hear Res.* 2010; 268(1–2):151–162. [PubMed: 20630476]
- Pienkowski M, Eggermont JJ. Reversible long-term changes in auditory processing in mature auditory cortex in the absence of hearing loss induced by passive, moderate-level sound exposure. *Ear Hear.* 2012; 33(3):305–314. [PubMed: 22343545]
- Pienkowski M, Munguia R, Eggermont JJ. Passive exposure of adult cats to bandlimited tone pip ensembles or noise leads to long-term response suppression in auditory cortex. *Hear Res.* 2011; 277(1–2):117–126. [PubMed: 21316436]
- Pienkowski M, Munguia R, Eggermont JJ. Effects of passive, moderate-level sound exposure on the mature auditory cortex: spectral edges, spectrotemporal density, and real-world noise. *Hear Res.* 2013; 296:121–130. [PubMed: 23154196]
- Rubio ME. Redistribution of synaptic AMPA receptors at glutamatergic synapses in the dorsal cochlear nucleus as an early response to cochlear ablation in rats. *Hear Res.* 2006; 216–217:154–167.
- Salvi RJ, Wang J, Ding D. Auditory plasticity and hyperactivity following cochlear damage. *Hear Res.* 2000; 147(1–2):261–274. [PubMed: 10962190]
- Schecklmann M, Landgrebe M, Langguth B, T. R. I. D. S Group. Phenotypic characteristics of hyperacusis in tinnitus. *PLoS One.* 2014; 9(1):e86944. [PubMed: 24498000]
- Sheppard A, Hayes SH, Chen GD, Ralli M, Salvi R. Review of salicylate-induced hearing loss, neurotoxicity, tinnitus and neuropathophysiology. *Acta Otorhinolaryngol Ital.* 2014; 34(2):79–93. [PubMed: 24843217]

- Sheppard AM, Chen GD, Salvi R. Potassium ion channel openers, Maxipost and Retigabine, protect against peripheral salicylate ototoxicity in rats. *Hear Res.* 2015; 327:1–8. [PubMed: 25937133]
- Stolzberg D, Chen GD, Allman BL, Salvi RJ. Salicylate-induced peripheral auditory changes and tonotopic reorganization of auditory cortex. *Neuroscience.* 2011; 180:157–164. [PubMed: 21310217]
- Sun W, Lu J, Stolzberg D, Gray L, Deng A, Lobarinas E, Salvi RJ. Salicylate increases the gain of the central auditory system. *Neuroscience.* 2009; 159(1):325–334. [PubMed: 19154777]
- Turner JG, Willott JF. Exposure to an augmented acoustic environment alters auditory function in hearing-impaired DBA/2J mice. *Hear Res.* 1998; 118(1–2):101–113. [PubMed: 9606065]
- Watson, C., Paxinos, G. The rat brain in stereotaxic coordinates. 5th. Elsevier Academic Press; 2004.
- Willott JF, Turner JG. Prolonged exposure to an augmented acoustic environment ameliorates age-related auditory changes in C57BL/6J and DBA/2J mice. *Hear Res.* 1999; 135(1–2):78–88. [PubMed: 10491957]
- Zeng FG. An active loudness model suggesting tinnitus as increased central noise and hyperacusis as increased nonlinear gain. *Hear Res.* 2013; 295:172–179. [PubMed: 22641191]
- Zeng FG, Fu QJ, Morse R. Human hearing enhanced by noise. *Brain Res.* 2000; 869(1–2):251–255. [PubMed: 10865084]
- Zheng W. Auditory map reorganization and pitch discrimination in adult rats chronically exposed to low-level ambient noise. *Front Syst Neurosci.* 2012; 6:65. [PubMed: 22973201]
- Zheng XY, Ding DL, McFadden SL, Henderson D. Evidence that inner hair cells are the major source of cochlear summing potentials. *Hear Res.* 1997; 113(1–2):76–88. [PubMed: 9387987]
- Zhou XM, Merzenich MM. Environmental noise exposure degrades normal listening processes. *Nat Commun.* 2012; 3

Highlights

- Low-level noise exposure can induce changes in a neural gain mechanism
- Noise induced plasticity can occur at subcortical levels
- Prolonged low-Level noise exposure changes peripheral sensitivity

Figure 1.
CAP and SP analysis. Average CAP and SP responses to a 12 kHz tone burst with the low pass filter set at 11 kHz. Red lines illustrate measurements used to determine CAP and SP amplitude.

Figure 2. Electrode track in IC and SDH-labeled cochlear surface preparation. (A) Section from NeuN (green)-labeled IC showing the DiI labeling of electrode track (yellow, overlap of red/green). (B) SDH-labeled cochlear surface preparation from rat following 5-week exposure to 75 dB SPL, 10–20 kHz noise. Note strong SDH labeling in three rows of outer hair cells (OHC) and single row of inner hair cells (IHC).

Figure 3.

Noise-induced changes in CAP and SP. (A) Mean ($n=6$, $\pm$ SEM) CAP thresholds. (B) Mean ($n=6$, $\pm$ SEM) 16 kHz CAP I/O function. (C) Mean ($n=6$, $\pm$ SEM) CAP amplitudes as a function of frequency measured at 80 dB SPL. (D) Percent difference (95% CI) between control and LLN induced CAP amplitudes. (E) Mean SP amplitudes ($n=6$, $\pm$ SEM) as a function of frequency measured at 80 dB SPL. (F) Percent difference (95% CI) in SP amplitudes between control and LLN induced SP amplitudes. The LLN exposure resulted in a frequency-specific reduction in CAP and SP responses measured from the peripheral system.

Figure 4.

Noise-induced changes in IC LFPs. (A) Mean LFPs obtained at 40 dB SPL plotted as a function of frequency. (B) Percentage difference (95% CI) in LFPs obtained at 40 dB SPL. (C) Mean LFPs obtained at 60 dB SPL plotted as a function of frequency. (D) Percentage difference (95% CI) in LFPs obtained at 60 dB SPL. (E) Mean LFPs obtained at 80 dB SPL plotted as a function of frequency. (F) Percentage difference (95% CI) in LFPs obtained at 80 dB SPL. (G) Mean LFPs obtained at 100 dB SPL plotted as a function of frequency. (H) Percentage difference (95% CI) in LFPs obtained at 100 dB SPL. IC LFPs showed frequency-specific enhanced response amplitudes at moderate intensities within the noise exposure frequency band and suppressed response amplitudes when stimulated with low-frequencies.

Figure 5.

Noise-induced changes in IC multi-unit SDRs. (A) Mean post-stimulus time histograms obtained at a low-frequency (2.3 kHz) and at moderate to high intensities (40–100 dB SPL) plotted as a function of time. SDRs were significantly enhanced at high intensity levels (80–100 dB SPL), but significantly reduced at moderate intensity levels (40–60 dB SPL) in the Low-Level Noise group (red arrows). (B) Mean post-stimulus time histograms obtained at a mid-frequency (12.1 kHz) and moderate to high intensities (40–100 dB SPL) plotted as a function of time. The LLN group SDRs were significantly enhanced at all intensity levels at mid-frequencies (red arrows). (C) Mean post-stimulus time histograms obtained at a high-frequency (27.7 kHz) and moderate to high intensities (40–100 dB SPL) plotted as a function of time. The LLN group SDRs were significantly enhanced at all intensity levels at high-frequencies (red arrows).

Figure 6.

Noise-induced changes in CAP and SP at one week post-exposure. (A) Mean CAP thresholds in control group (n=6, $\pm$ SEM) and Mean 1WPE (n=4, $\pm$ SEM). (B) Mean 16 kHz CAP input/output function in control group and 1WPE. (C) Mean CAP amplitudes as a function of frequency measured at 80 dB SPL in the control group and 1WPE. Mean amplitudes were significantly higher in the 1WPE group than the control group. (D) Percentage difference (95% CI) CAP amplitudes in 1WPE group plotted as a function of frequency. (E) Mean SP amplitudes as a function of frequency measured at 80 dB SPL. Mean amplitudes were significantly higher in the 1WPE group than the control group. (F) Percentage difference (95% CI) in SP amplitudes in 1WPE group plotted as a function of frequency.

Figure 7.

Changes in IC LFPs at 1WPE. (A) Mean LFPs obtained at 40 dB SPL plotted as a function of frequency. (B) Percentage difference (95% CI) in LFPs obtained at 40 dB SPL. (C) Mean LFPs obtained at 60 dB SPL plotted as a function of frequency. (D) Percentage difference (95% CI) in LFPs obtained at 60 dB SPL. (E) Mean LFPs obtained at 80 dB SPL plotted as a function of frequency. (F) Percentage difference (95% CI) in LFPs obtained at 80 dB SPL. (G) Mean LFPs obtained at 100 dB SPL plotted as a function of frequency. (H) Percentage difference (95% CI) in LFPs obtained at 100 dB SPL.

Figure 8.

Changes in IC multi-unit SDRs at 1WPE. (A) Mean post-stimulus time histograms obtained at a low-frequency (2.3 kHz) and at moderate to high intensities (40–100 dB SPL) plotted as a function of time. The 1WPE group SDRs were significantly enhanced from 40–100 dB SPL (green arrows). (B) Mean post-stimulus time histograms obtained at a mid-frequency (12.1 kHz) and moderate to high intensities (40–100 dB SPL) plotted as a function of time. The 1WPE group SDRs were significantly enhanced from 60–100 dB SPL, but not at 40 dB SPL (green arrows). (C) Mean post-stimulus time histograms obtained at a high-frequency (27.7 kHz) and moderate to high intensities (40–100 dB SPL) plotted as a function of time. The 1WPE group SDRs were significantly enhanced from 60–100 dB SPL but not at 40 dB SPL (green arrows).

Figure 9.

Central Gain/Attenuation Plots – Percent of control CAP and LFP amplitudes immediately after LLN exposure and at 1WPE compared to controls. (A) Central gain/attenuation changes at ~2 kHz. CAP and LFPs are essentially equal to controls at 60 and 80 dB SPL and 40 dB SPL shows reduction in both CAP and LFPs immediately after LLN. At 1WPE CAP amplitudes are enhanced at 60 and 80 dB SPL while LFP are essentially equal to controls while at 40 dB SPL CAP amplitudes are normal while LFP are slightly enhanced. (B) Central gain/attenuation changes at ~12 kHz in CAP and LFPs. At all intensity levels CAP shows large reductions (~50%) and LFP show enhancement (~50%) immediately after LLN, suggestive of central gain. At 1WPE CAPs are largely enhanced (~70–150%) and LFPs are either enhanced (~50%) or normal, suggestive of central attenuation. (C) Central gain/attenuation changes at ~40 kHz. At all intensity levels CAPs show large reductions (~50%) and LFP show enhancement (~50%) or normal responses, suggestive of central gain. At 1WPE CAPs show enhancement (~50–150%) and LFP are normal or slightly enhanced or suppressed, suggesting a central attenuation of the signal.