Hearing Research 261 (2010) 30–35

Contents lists available at ScienceDirect

Hearing Research

journal homepage: www.elsevier.com/locate/heares

Intermittent exposure with moderate-level sound impairs central auditory function of mature animals without concomitant hearing loss

Martin Pienkowski, Jos J. Eggermont *

Departments of Physiology and Pharmacology, and Psychology, University of Calgary, Calgary, Alberta, Canada

ARTICLE INFO

Article history:
Received 27 October 2009
Received in revised form 16 December 2009
Accepted 18 December 2009
Available online 29 December 2009

Keywords:
Auditory cortex
Plasticity
Passive sound exposure
Extracellular recording
Single-unit activity
Local field potential
Receptive field
Tonotopic map

ABSTRACT

Long-term, passive, continuous exposure of mature animals to moderate-level, band-limited sounds can profoundly decrease neural activity in primary auditory cortex (AI) to sounds in the exposure frequency range, and increase activity to sounds outside the exposure range. The resulting reorganization of the AI tonotopic map resembles that following a restricted lesion of the cochlear epithelium. Here we show qualitatively similar effects of passive exposure when it is limited to 12 h/day, simulating a noisy-work/quiet-living environment, albeit at substantially lower intensity levels (68 dB SPL) than are considered harmful to hearing. Compared to continuous exposure at the same SPL and over a similar duration (6–12 weeks), this intermittent exposure produced a smaller decrease in AI spike and LFP (local field potential) activity in response to sound frequencies in the exposure range, and an increase in activity only for frequencies above the exposure range. As expected at these exposure levels, cortical changes occurred in the absence of concomitant hearing loss (i.e., absolute threshold shifts). Our results have implications for occupational noise exposure standards, which presently may not prevent changes in central auditory function that cannot be detected on the standard behavioral audiogram.

1. Introduction

The normal development of the brain can be delayed or even irreversibly altered by sensory deprivation or other manipulations of natural sensory environments, giving rise to the notion of "critical periods" (e.g., Hubel and Wiesel, 1970; Knudsen, 1985; Stanton and Harrison, 1996; Chang and Merzenich, 2003; Hooks and Chen, 2007). However, the mature brain is also susceptible to large-scale reorganization following long-term changes in the patterns of sensory input. In adult mammals, partial lesion of the cochlea (Robertson and Irvine, 1989), retina (Kaas et al., 1990) or hand (Merzenich et al., 1984) ultimately leads to the re-activation of the corresponding region of primary sensory cortex by inputs originating from the nearest functioning areas of sensory epithelium. Exposure of adult mammals to various experimental acoustic environments had been shown to affect stimulus representations in primary auditory cortex (AI) (e.g., Recanzone et al., 1993; Weinberger et al., 1993; Bao et al., 2003; Engineer et al., 2004; Polley et al., 2006), but always in conjunction with behavioral training or stimulation of the basal forebrain system (which is implicated in associative learning). However, we recently demonstrated that long-term (6–20 wk) *passive exposure* of adult cats to moderate-level (68–80 dB SPL), band-limited (4–20 kHz) tone pip ensembles could profoundly decrease AI responsiveness to sounds in the exposure frequency range, and increase responsiveness to sounds outside that range (Noreña et al., 2006; Pienkowski and Eggermont, 2009). The resulting reorganization of the AI tonotopic map resembled that following partial lesion of the cochlea, although no absolute threshold shifts could be detected either in the auditory periphery or central pathways. Following the cessation of exposure, these changes were slow to reverse, and the tonotopic map remained abnormal after up to 3 months of recovery in a quiet environment (Pienkowski and Eggermont, 2009).

Here we show qualitatively similar albeit weaker effects of long-term (6–12 wk), moderate-level (68 dB SPL) passive exposure when it was limited to 12 h/day (followed by 12 h of quiet). Our intent was to simulate the alteration of noisy-work/quiet-living environments, albeit at substantially lower intensity levels than are considered harmful to hearing (90 dBA for 8 h/day; OSHA, Standard 1926.52). We find that such acoustic environments can profoundly alter the sound frequency representation in AI without affecting hearing sensitivity.

2. Methods

2.1. Exposure stimulus

The exposure stimulus was the same as used previously (Noreña et al., 2006; Pienkowski and Eggermont, 2009). Briefly, it was

* Corresponding author. Address: Department of Psychology, University of Calgary, 2500 University Drive NW, Calgary, AB, Canada, T2N 1N4. Tel.: +1 403 220 5214; fax: +1 403 282 8249.
E-mail address: eggermon@ucalgary.ca (J.J. Eggermont).

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doi:10.1016/j.heares.2009.12.025

constructed from a set of 50 ms-long gamma-shaped tone pips, with 38 frequencies logarithmically-spaced between 4 and 20 kHz. Each frequency was randomly and independently generated at a mean rate of 3 s^{-1}, so that the average aggregate pip presentation rate was 114 s^{-1}. The average A-weighted, linearly-integrated level, measured at various locations in the cat room ~10 cm off the floor, was ~68 dB SPL.

2.2. Animals

Animal use was approved (BI 2007–12) and reviewed on a yearly basis by the Life and Environmental Sciences Animal Care Committee of the University of Calgary, according to the guidelines set by the Canadian Council of Animal Care. Five cats were exposed to the stimulus described above for 12 h/day over 6–12 wk, beginning at ~3 months of age, when the AI tonotopic map is mature and any developmental critical periods have ended (Bonham et al., 2004; Pienkowski and Eggermont, 2009). Immediately following the cessation of exposure, cats were deeply anesthetized with 25 mg/kg of ketamine hydrochloride and 20 mg/kg of sodium pentobarbital, injected intramuscularly. Smaller doses of ketamine were administered as required, typically once per hour, to maintain a state of non reflexive anesthesia during neural recording (average across cats: ~10 mg/[kg h]). Surgery was performed to expose auditory cortex, as described previously (Pienkowski and Eggermont, 2009).

2.3. Sound stimulation and neural recording

Cats were secured on a vibration-isolation table in an anechoic, sound-proof booth. Sound stimuli were presented from a calibrated speaker system (Fostex RM765 in combination with a Realistic super-tweeter) that produced an approximately flat spectrum (± 5 dB up to 40 kHz, measured at the cat's head), and was placed ~30° from the midline into the contralateral field, ~50 cm from the cat's left ear. Stimuli were 50 ms-long gamma-shaped tone pips (Pienkowski and Eggermont, 2009), which exceeded half-peak power (i.e., were within 6 dB of the peak SPL) between ~3 and 17 ms.

Auditory brainstem responses (ABRs) were recorded with needle electrodes in the ipsi- and contralateral muscles covering the mastoids. Stimulus frequencies were 3, 4, 6, 8, 12, 16, 24 and 32 kHz, each presented at the rate of 10 s^{-1} for up to ~500 repetitions at a given SPL. Recorded potentials were amplified between 0.3 and 3 kHz (WPI, DAM 500) and averaged, using a custom algorithm for artifact rejection. The SPL was decreased in 10 dB steps for as long as the ABR was reproducible, with threshold defined as the lowest SPL minus 5 dB.

Cortical spikes and local field potentials (LFPs) were recorded extracellularly with a pair of 8 × 2-microelectrode arrays with 0.25 mm inter-electrode spacing within a row and 0.5 mm between rows, at depths of ~700–1200 μm (deep layer III or layer IV). Stimuli were two sets of gamma-pip ensembles, which both covered the frequency range of 0.3–40 kHz at high resolution. In the first ensemble, pips were presented individually, at 4 s^{-1}, and frequency response curves (FRCs) were obtained at (peak) pip levels of −5–65 dB SPL; in the second ensemble, each pip frequency was the realization of an independent Poisson process, with an average aggregate presentation rate of 28 s^{-1}, and spectrotemporal receptive fields (STRFs) were obtained at 65 dB SPL (for details see Pienkowski and Eggermont, 2009). Recorded potentials were amplified and processed by a multichannel data acquisition system (TDT, RX5). Spikes were identified online (using a trigger level set well outside of the noise floor) from a 0.3–3 kHz filtered signal, and LFPs were obtained from a 2–40 Hz filtered signal. Spikes were sorted offline using an automated procedure based on principal component analysis and *K*-means clustering (Eggermont, 1990). Up to a maximum of three well-sorted waveforms on an electrode were considered as single-unit (SU) recordings.

Great care was taken to separate responses recorded in AI from those recorded in the surrounding anterior (AAF), posterior (PAF) and ventral (AII) fields, as detailed previously (Pienkowski and Eggermont, 2009). AI was densely and homogenously sampled in all exposed cats, and in a group of 22 normal-hearing unexposed cats used as controls. Importantly, the proportion of electrode penetrations in each of three sub-regions of AI – those with units normally tuned to frequencies of <4 kHz, 4–20 kHz, and >20 kHz, respectively – was approximately equal for the exposed and control groups (Table 1). Thus, our findings can be attributed to the effects of exposure and not to any bias in sampling the AI population.

3. Results

3.1. Sound exposure did not cause hearing loss due to cochlear trauma

As expected, the intermittent, moderate-level (68 dB SPL) sound exposure did not cause hearing loss. In no exposed cat did ABR thresholds exceed mean control values at any sound frequency (Fig. 1a). Threshold was determined using cat ABR wave IV (equivalent to wave V in humans), which effectively measures evoked potentials at the level of the lateral lemniscus. Since there were no threshold changes at the level of the generator of wave IV, there could be none at more peripheral stations. Furthermore, despite the *average* decrease in AI responsiveness to frequencies in the exposure band (detailed below), *individual* SUs and LFPs in exposed cats could be as sensitive at those frequencies as the most sensitive recordings in controls, again arguing against cochlear trauma resulting from exposure. To illustrate, Fig. 1b gives the distribution of SU thresholds in AI as a function of the characteristic frequency (CF: best frequency at response threshold), in control (left) and exposed cats (right). With the exception of CFs > 22 kHz (i.e., above the exposure band), there are individual units in exposed cats with thresholds as low as those of the most sensitive units controls.

3.2. Sound exposure decreased AI responsiveness in the exposure frequency range

Fig. 2 shows SU- and LFP-derived FRCs and STRFs, from one electrode penetration in an exposed cat (a) and another in an unexposed control (b); both penetrations were made in a region of AI normally tuned to the middle of the exposure band. Such broadly-tuned recordings best illustrate the effects of exposure, although most SUs and LFPs in AI were more narrowly-tuned. In the exposed cat, there is a clear decrease of spike and LFP activity at frequencies near 10 kHz. Such FRCs and STRFs were far more common in exposed than in control cats. The effects of exposure on narrowly-tuned units were generally more subtle, but there typically appeared to be a drop in spike firing and LFP amplitude

Table 1
Number of electrode penetrations in each of three regions of AI; the percentage of the total number for each cat group is given in parentheses. The first region, located at <10% of the distance along the PES–AES (posterior to anterior ectosylvian sulcus) axis, typically corresponds with unit CFs of <4 kHz (i.e., below the exposure band) in control cats. The second region, located between 10 and 70% of the PES–AES distance, normally corresponds to CFs within the EAE range, and the third region, at >70% of the PES–AES distance, corresponds to CFs of >20 kHz (i.e., above the exposure band).

	Location of electrodes along the PES–AES axis		
	<10%	10–70%	>70%
Control	436 (19%)	1283 (56%)	573 (25%)
Exposed 12 h	145 (17%)	469 (55%)	238 (28%)