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Research Paper

Noise-induced cochlear synaptopathy in rhesus monkeys (*Macaca mulatta*)

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ABSTRACT

Cochlear synaptopathy can result from various insults, including acoustic trauma, aging, ototoxicity, or chronic conductive hearing loss. For example, moderate noise exposure in mice can destroy up to ~50% of synapses between auditory nerve fibers (ANFs) and inner hair cells (IHCs) without affecting outer hair cells (OHCs) or thresholds, because the synaptopathy occurs first in high-threshold ANFs. However, the fiber loss likely impairs temporal processing and hearing-in-noise, a classic complaint of those with sensorineural hearing loss. Non-human primates appear to be less vulnerable to noise-induced hair-cell loss than rodents, but their susceptibility to synaptopathy has not been studied. Because establishing a non-human primate model may be important in the development of diagnostics and therapeutics, we examined cochlear innervation and the damaging effects of acoustic overexposure in young adult rhesus macaques. Anesthetized animals were exposed bilaterally to narrow-band noise centered at 2 kHz at various sound-pressure levels for 4 h. Cochlear function was assayed for up to 8 weeks following exposure via auditory brainstem responses (ABRs) and otoacoustic emissions (OAEs). A moderate loss of synaptic connections (mean of 12–27% in the basal half of the cochlea) followed temporary threshold shifts (TTS), despite minimal hair-cell loss. A dramatic loss of synapses (mean of 50–75% in the basal half of the cochlea) was seen on IHCs surviving noise exposures that produced permanent threshold shifts (PTS) and widespread hair-cell loss. Higher noise levels were required to produce PTS in macaques compared to rodents, suggesting that primates are less vulnerable to hair-cell loss. However, the phenomenon of noise-induced cochlear synaptopathy in primates is similar to that seen in rodents.
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1. Introduction

Acoustic overexposure is a significant health concern in the industrialized world. Vulnerable populations include military personnel, professional musicians, miners, and construction workers (McBride, 2004; Humes et al., 2005; Gordon et al., 2016; Schink et al., 2014), but everyday noise-exposure from leisure activities may also threaten cochlear integrity (e.g., Portnuff et al., 2011; Flamme et al., 2012; Le Prell et al., 2012; Liberman et al., 2016). Noise-related damage to the cochlea scales with the intensity, duration, and number of acoustic overexposures (Harris, 1950; Eldredge et al., 1973; Hawkins et al., 1976; Bohne and Clark, 1982), and the perceptual consequences can range from degradations in temporal processing and speech perception (Plack et al., 2014; Bharadwaj et al., 2014, 2015) to significant impairments in sound detection.

An acoustic overexposure sufficiently intense to damage or destroy outer hair cells (OHCs) and/or their stereocilia will induce permanent threshold shifts (PTS) that are detectable by behavioral audiograms, auditory brainstem responses (ABRs), or distortion-product otoacoustic emissions (DPOAEs) (Wang et al., 2002; Liberman and Dodds, 1984). Exposures that were once thought to be benign, because hair cells were spared and threshold shifts were temporary, are now known to produce primary neuronal degeneration (Kujawa and Liberman, 2009). This degeneration begins immediately as an atrophy of the afferent cochlear synapses

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between IHCs and auditory nerve fiber (ANFs), and it is followed by a slow retraction of the myelinated distal axons of ANFs that finalizes after months or years with the death of the ANF cell bodies (the spiral ganglion cells) and their central axons projecting to the cochlear nucleus (Johnsson, 1974; Liberman and Kiang, 1978; Felix et al., 2002; Kujawa and Liberman, 2009; Lin et al., 2011). Cochlear synaptopathy may be a key contributor to the differences in speech-in-noise performance among listeners with similar threshold audiograms, a.k.a. hidden hearing loss (Liberman, 2015; Schaette and McAlpine, 2011).

Most of what we know about cochlear synaptopathy is based on studies in mice and guinea pigs (reviewed by Kujawa and Liberman, 2015), but several lines of evidence suggest that humans are less vulnerable to noise damage than smaller mammals (see Dobie and Humes, 2017). Nonetheless, emerging data in humans also suggest that, as in mice and guinea pigs, cochlear neurons are more vulnerable than hair cells. Because the inner ear cannot be biopsied, direct evaluation of cochlear synaptopathy in humans must rely on accrual of post-mortem specimens, and such material is slowly accumulating: normal-aging human ears show minimal hair-cell loss but a progressive primary neural degeneration, i.e. a steady age-related loss of spiral ganglion cells (Makary et al., 2011). Based on a small sample of cases, there appears to be a much more dramatic loss of cochlear synapses in the normal-aging human than can be seen in counts of ganglion cells (Viana et al., 2015), as has been more exhaustively documented in mice (Fernandez et al., 2015). No data are yet available on noise-induced cochlear synaptopathy in humans.

Here, we chose to study noise-induced cochlear synaptopathy in a non-human primate. Given that the physiological processes and biomarkers of human ailments are often closely mirrored in monkeys (e.g., Wendler and Wehling, 2010), these data may be useful in inferring the patterns of human synaptopathy, and a primate model of noise-induced synaptopathy could be key in assessing emerging therapies to reconnect surviving ANFs to IHCs (Wan et al., 2014; Suzuki et al., 2016). We show that rhesus ears are less vulnerable to hair-cell loss and permanent threshold shifts than other well-studied small mammals (cats, guinea pigs, mice, and chinchillas). However, as seen in rodent models (Kujawa and Liberman, 2009; Lin et al., 2011), primate cochlear synapses are more vulnerable than hair cells to acoustic trauma, and many of the IHCs remaining in acoustically traumatized ears are partially or largely deafferented.

2. Methods

2.1. Animals and groups

Ten rhesus monkeys (*Macaca mulatta*) 6.5–11 yrs of age were included in this study. Seven (5 male, 2 female) were housed at Vanderbilt University, and three (males) at Boston University. At both institutions, animals were on a 12 h light/dark cycle with access to food and water *ad libitum*, except for 12 h prior to physiological testing, noise-overexposure, and euthanasia. Four macaques (3 from Boston University, 1 from Vanderbilt) served as histological controls. The remaining six (from Vanderbilt) were subjected to acoustic overexposure. For all noise-exposed monkeys, cochlear function was measured before and immediately after the exposure, as well as 3–8 times during the 8–9 wks post exposure. All housing and procedural protocols were approved by the respective Institutional Animal Care and Use Committees and were in strict compliance with the guidelines established by the National Institutes of Health.

2.2. Acoustic overexposure

Monkeys were treated with atropine (0.04 mg/kg), anesthetized with a mixture of ketamine and dexmedetomidine (2–6 mg/kg and 5–15 μg/kg), intubated, and maintained on 1–1.5% isofluorane for the duration of each 4-hr exposure to a 50-Hz noise band centered at 2 kHz. Noise levels varied for different exposures, and some animals were exposed more than once (Table 1). Noise was presented binaurally via closed-field speakers (MF1 speakers, TDT Inc., Alachua, FL) coupled to the ears with foam inserts. The stability of the transducer output (±0.3 dB) was verified by replacing the monkey with a ¼″ microphone (Model 378C01, PCB piezotronics) during a 4-hr exposure session.

2.3. Cochlear function tests

Cochlear function tests were conducted in a double-walled sound-attenuating booth at Vanderbilt University (RE-246, Acoustic Systems) under ketamine/dexmedetomidine anesthesia (10–12 mg/kg/hr ketamine, periodic boluses of dexmedetomidine). DPOAEs were measured using a Bio-logic Scout OAE system (Natus) at 8 points per octave from $f_2 = 0.5–8$ kHz, with $f_2/f_1 = 1.22$ and $L_1/L_2 = 65/55$. For ABRs, tone bursts were generated and presented at a rate of 27.7 Hz by BioSigRZ software (TDT Inc.), amplified by an SLA2 amplifier (ART Pro Audio, Niagara Falls, NY), and delivered binaurally via SA1 speakers (Selah Audio). At each test frequency, tone-burst level was varied between 30 and 90 dB SPL in 5- or 10-dB steps. Responses were measured via subdermal needle electrodes, vertex-to-mastoid, with the ground at the shoulder. An RA4 preamplifier coupled with a RA4LI amplifier (TDT) amplified the signal (10,000X), and the waveform was digitally filtered between 10 Hz and 3 kHz. 1024 artifact-free waveforms were averaged to produce a final ABR trace, and two traces were collected at each stimulus level. Analysis was based on inspection of stacked waveforms. Threshold was defined as the lowest SPL to produce a repeatable waveform ≥120 nV at the appropriate latency.

2.4. Histological preparation

Monkeys from Vanderbilt (all noise-overexposed and one control) were euthanized via an overdose of sodium pentobarbital (130 mg/kg). The three histological control monkeys from B.U. were euthanized by transcardial perfusion with 4 °C Krebs buffer (pH 7.4) followed by 4% paraformaldehyde (pH 7.4), while deeply anesthetized with sodium pentobarbital (25 mg/kg to effect). Following euthanasia, the cochleas were exposed, the round and oval windows were punctured, and cochlear scalae were perfused with the same fixative. Cochleas were submersion-fixed for 2 h and then transferred to 0.12 M EDTA for decalcification. EDTA was refreshed weekly for 3–5 wks, and decalcified tissue was trimmed at each change. Decalcified cochleas were dissected into quarter- or half-turns, and the tissue was cryoprotected in 30% sucrose for 15 min and frozen on dry ice to permeabilize. The pieces were thawed, rinsed in phosphate-buffered saline (PBS; pH 7.3), and incubated in

Table 1
Noise-exposure history for each macaque with TTS and PTS.

Subject ID	108	120	140	146
M1	×	×	×	×
M2	×			×
M3			×	×
M4				×
M5	×			
M6	×			

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