Published in final edited form as:

Neuroscience. 2011 January 13; 172: 453–459. doi:10.1016/j.neuroscience.2010.10.056.

Impact of Sound Exposure and Aging on Brain-Derived Neurotrophic Factor and TrkB Receptors Levels in Dorsal Cochlear Nucleus 80 Days Following Sound Exposure

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Abstract

Recent studies suggested that acute sound exposure resulting in a temporary threshold shift in young adult animals within a series of maladaptive plasticity changes in central auditory structures. Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, is involved in post-trauma peripheral hair cell and spiral ganglion cell survival and has been shown to modulate synaptic strength in cochlear nucleus following sound exposure. The present study evaluated levels of BDNF and its receptor (tyrosine kinase B, [TrkB]) in the dorsal cochlear nucleus (DCN) following a unilateral moderate sound exposure in young (7–8 months) and aged (28–29 months) Fischer Brown Norway (FBN) rats. Eighty days post-exposure, ABR thresholds for young exposed rats approached control values while aged exposed rats showed residual permanent threshold shifts relative to aged controls. BDNF protein levels were significantly up-regulated by 9% in young exposed fusiform cells ipsilateral to the exposure. BDNF levels in aged sound-exposed fusiform cells increased 31% ipsilateral to the exposure. Protein levels of the BDNF receptor, TrkB, were also significantly increased in aged but not in young sound-exposed DCN fusiform cells. The present findings suggest a relationship between the up-regulation of BDNF/TrkB and the increase in spontaneous and driven activity previously observed for aged and sound-exposed fusiform cells. This might be due to a selective maladaptive compensatory down-regulation of glycinergic inhibition in DCN fusiform cells.

Keywords

sound exposure; BDNF; TrkB; ABR; hearing loss; glutamatergic synapses

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Introduction

In young adult animals, moderate unilateral sound exposure results in a limited partial deafferentation ipsilateral to the exposure (Syka, 2002 for review; Kujawa and Liberman, 2008; Wang et al., 2009b). The outcome of this insult reduces auditory afferent flow to the cochlear nucleus which triggers maladaptive compensatory inhibitory plastic changes in central auditory structures (Suneja et al., 1995; 1998a, b; Zhang and Kaltenbach, 1998; Kaltenbach et al., 2000a, b; Potashner et al., 2000; Brozoski et al., 2002; Fritschy et al., 2008; Wang et al., 2009b). The ventral and dorsal cochlear nucleus (DCN) comprises the first central target of acoustic nerve fibers to the primary ascending auditory pathway. The principal output neurons of the DCN, fusiform cells, receive direct excitatory input from ascending acoustic nerve fibers and form the primary output projection to the contralateral inferior colliculus (IC) via the dorsal acoustic stria (Fernandez and Karapas, 1967; Beyerl, 1978; Cant and Benson, 2003). Previous aging and sound exposure studies suggest that partial peripheral deafferentation initiates a selective down-regulation of glycinergic inhibitory neurotransmission onto fusiform cells in the DCN (Willott et al., 1997; Banay-Schwartz et al., 1989; Caspary et al., 2005; Milbrandt and Caspary, 1995; Wang et al., 2009a, b). Collectively, these studies suggest that DCN output neurons may be selectively vulnerable to partial deafferentation by sound exposure and/or aging. Brain-derived neurotrophic factor (BDNF), one of the neurotrophin families of growth factors, plays an important role in scaling the strength of inhibitory synapses in response to long-term alterations in neuronal activity (Lindholm et al., 1994; McAllister et al., 1999; Thoenen, 2000; Carter et al., 2002; Swanwick et al., 2006; Mattson, 2008 for review). Previous studies on the auditory periphery indicated that exogenous delivery of BDNF not only enhanced spiral ganglion neuron (SGN) survival but partially restored hearing levels in chemical-deafened animals (Shinohara et al., 2002; Miller et al., 2007; Tan et al., 2007; Agterberg et al., 2009). Tyrosine kinase B receptors (TrkB), high affinity receptors for BDNF, are presented in cochlear nucleus (CN) neurons and may also contribute to neuronal plasticity seen after cochlear ablation (Suneja and Potashner, 2002). The aim of the present study was to examine the role of endogenous BDNF in regulating inhibitory glycinergic plasticity in the partially deafferented DCN following sound exposure in young and aged Fischer Brown Norway (FBN) rats.

Methods

Subjects

Subjects were adult male Fischer Brown Norway (FBN) rats (Harlan Sprague-Dawley Inc., Maryland, MD, USA) and were divided into young (5–6 months old at the beginning of experiments) and aged (28–29 months old at the beginning of experiments) groups. Rats were generally housed at Southern Illinois University (SIU) and used under protocols approved by the SIU Laboratory Animal Care and Use Committee. All experiments were performed according to the National Institutes of Health Guide for the ethical use of animals.

Acoustic exposure

Forty-two (young: 21; aged: 21) rats were sound-exposed while anesthetized with a ketamine HCl (50 mg/kg, Aveco, Fort Dodge, IA, USA)/xylazine (9 mg/kg, Lloyd Laboratories, Shennandoah, IA, USA) mixture and placed in a modified stereotaxic head frame. At the time of the sound exposure, young rats were 5–6 months of age while aged rats were 28–29 months. Sound-exposed rats were exposed unilaterally using 116 dB SPL octave-band noise, centered at 17 kHz peak intensity for 1 hour (Fig. 1) (Bauer et al.,

1999; Bauer and Brozoski, 2001; Brozoski and Bauer, 2005). Thirty-eight control subjects (young: 21; aged: 17) were not exposed to the sound stimulus.

Auditory brainstem responses

Threshold shifts were measured using auditory brainstem responses (ABRs) of ipsi- and contralateral ears from young and aged control and sound-exposed rats as described in Wang et al. (2009a, b) for the same set of animals. Data were obtained prior to, immediately following and 80 days post sound-exposure for clicks and 5 msec tone bursts (4, 10, 16, 20, 24 and 32 kHz) presented at 50/sec. Evoked potentials were averaged over 1024 sweeps, amplification was 200,000 and waveforms were filtered at 0.1–3 kHz.

Immunocytochemistry

The procedure used for quantitative immunocytochemistry was based on those published by Ling et al. (2005) and Abbott et al. (1999). Eighty days post-exposure, 4 control rats and 4 exposed rats from both groups (young 6–9 mos; aged 30–32 mos) were anesthetized and transcardially perfused with 500 ml of fixative containing 4% paraformaldehyde in 0.1M K-Na phosphate buffer (PBS, pH 7.4). Brains were removed, placed in 20% sucrose and stored at -80°C . Cryostat frozen sections (16 μm in thickness) were cut and blocked in 0.1M PBS with 1.5% normal goat serum for 30 min, and transferred to purified primary antibodies (polyclonal rabbit anti-BDNF, 1:500; polyclonal rabbit anti-TrkB, 1:2000, Millipore, Temecula, CA, USA). Sections were incubated for 1.5 hrs at room temperature and then at 4°C overnight with agitation. ABC kits (Vector Laboratories, Burlingame, CA, USA) with secondary biotinylated antibodies were used. Sections were visualized by exposure to 3, 3'-diaminobenzidine tetrahydrochloride in PBS for 1–3 min. Positive immunostaining was expressed as brown staining in the fusiform cytoplasm and/or cell membrane. Processing and analysis were carried out in groups containing one young/aged control and one young/aged trauma processed at the same time to reduce variability. Slides were blinded to ensure unbiased measurement. Images were captured using a CoolSnap camera (10X) interfaced with a Leitz Diaplan microscope coupled to an ImagePro Plus imaging system. Fusiform cells were identified based upon their size, shape and location in DCN (middle layer of DCN). Relative optical density (ROD) for each immunolabeled DCN fusiform cell was measured using Scion Image (Scion Corporation, Frederick, MD, USA). All values were corrected by subtracting background obtained from the measurements of unstained strial fibers deep to the DCN.

Results

Auditory brainstem responses

Immediately following sound exposure, young sound-exposed, ipsilateral ears, showed significantly elevated thresholds for all tones as well as clicks when compared to the young control ($p < 0.02$, Fig. 1A). The largest threshold shifts for the aged group occurred between 16 and 32 kHz immediately following sound exposure ($p < 0.05$, Fig. 1B). There were non-significant threshold shifts contralateral to the sound exposure for both young and aged ears (Fig. 1A&B). Eighty days post-exposure, young exposed rats showed no significant threshold shifts for any stimuli conditions, suggesting that the 1-hour sound-exposure produced a measurable temporary threshold shift (TTS). Young control rats showed no threshold shifts at any frequency tested in both ears after 80 days (Fig. 1A). In contrast, aged exposed rats did not completely recover from the same sound exposure. Aged exposed ears showed threshold improvements 80 days following sound exposure at 16 and 20 kHz (Fig. 1B). However, thresholds of the aged exposed group remained elevated relative to aged control animals. This suggests a permanent threshold shift (PTS) following sound exposure in aged rats. In addition to the sound exposure induced PTS, when compared to pre-

exposure ABRs, there was an age-related shift due to the nearly 3 month passage of time in these aged animals (Fig. 1B).

Sound exposure-related BDNF and TrkB protein levels in the DCN

BDNF positive cells were evenly distributed throughout the fusiform cell layer of DCN 80 days following sound exposure (Fig. 2). There were significant exposure-related increases in relative optical density (ROD) of BDNF positive fusiform cells in the DCN of both young and aged exposed rats ($p < 0.05$, Table. 1 and Fig. 2). The TrkB levels were significantly increased in the DCN of aged exposed rats while no significant change was observed in young exposed rats (Table 1). Sound exposure had a greater impact on up-regulation of BDNF level in aged rat DCN relative to young-adult rat DCN.

Discussion

Interactions between sound exposure and age in animal models

The present study finds that one hour of moderate sound exposure under controlled experimental conditions results in TTS in young rats, which is consistent with previous studies in chinchillas (McFadden et al., 1998; Brozoski et al., 2002), Long Evans rats (Bauer and Brozoski, 2001) and Wistar rats (Fraenkel et al., 2003). The same sound exposure in aged FBN rats results in PTS. These findings suggest that the impact of the exposure depends, not only, on the intensity and duration of the sound exposure but also on the age of animals. The relationship between age and susceptibility to sound exposure has been a source of ongoing debate. Studies by Miller et al. (1997) in mouse, suggest that aging increased the sensitivity of the ear to sound exposure as measured by ABR. In contrast to these findings, young and aged Wistar rats were found to be equally susceptible to sound exposure, a conclusion also supported using ABR measurements from Long-Evans rats (Fraenkel et al., 2003; Campo et al., 2003). In the present study, young FBN rats demonstrated a significantly greater capacity for threshold recovery than did aged FBN rats, which suggests the sound-exposure-induced minimal functional damage as measured using ABR thresholds. However, as noted below, ABR threshold measurements do not reveal the entire picture.

Limited hair cell data collected from the present set of animals, suggested that young exposed rats had near normal inner hair cell counts throughout the extent of their cochleae and only slight outer hair cell losses. These preliminary findings showed that aged exposed rats had great variability in the magnitude of inner and outer hair cell loss, frequently showing significant losses across wide frequency regions (Caspari, unpublished data from 13 ears). The relationship between outer hair cell loss and the magnitude of the ABR threshold shift following sound exposure is complex (Kujawa and Liberman, 2008; Bauer et al., 2007). Both Kujawa and Liberman (2008) and Bauer and colleagues (2007) found poor correlation between ABR thresholds, hair cell damage and impact on spiral ganglion cells. Older studies suggest a more straight forward relationship between hair cell loss and PTS (Nordman et al., 2000; Hamernik and Qiu, 2000; Vicente-Torres and Schacht, 2006). The noticeable 80-day post-exposure PTS in aged sound-exposed rats likely reflected the synergy of aging and sound exposure, which could result from significant hair cell loss, loss of acoustic nerve fibers (spiral ganglion cells) and other possible periphery degenerative changes including strial damage.

Relationship between threshold shift and BDNF protein levels

BDNF protein levels in DCN were significantly increased in both young and aged sound-exposed groups. Significantly greater up-regulation of BDNF was found in DCN fusiform cells ipsilateral to the sound exposure in aged rats. Previous studies showed that intra-

cochlear infusion of BDNF could prevent the degeneration of SGNs in *in vivo* deafness models while BDNF knockout mice showed a near complete loss of hair cells as well as SGNs (Staecker et al., 1996; Miller et al., 1997; Fritzsche et al., 1997a, b, 1999; Gillespie et al., 2003, 2004; Yamagata et al., 2004). Furthermore, intervention with BDNF significantly enhanced the functional responsiveness of the central auditory system as measured using electrically evoked ABRs (Shinohara et al., 2002). In the present study, the elevated BDNF protein level 80 days following the present PTS induced by sound exposure was similar to that observed in a DCN unilateral cochlear ablation model (Suneja et al., 2005). They showed a significant up-regulation of BDNF protein in DCN 60 days following an ipsilateral cochlear ablation (Suneja et al., 2005). Increased synaptic activity onto fusiform cells is consistent with the suggestion that BDNF plays an important role in modulating synaptic strength at both excitatory and inhibitory synapses (Elmariah et al., 2004; Matsumoto et al., 2006; Flores-Otero et al., 2007). In our study, in response to the previously shown decrease in glycinergic inhibition in aged and sound exposed DCN (Brozoski et al., 2002; Caspary et al., 2005, 2008 for review; Schatteman et al., 2008; Wang et al., 2009a, b), BDNF could enhance glutamate release at glutamatergic synapses (Carvalho et al., 2007; Mattson, 2008 for review) and directly cause neuronal hyperactivity in a short term following sound exposure.

BDNF and TrkB protein expression following sound exposure

In the present study, BDNF and TrkB protein levels were significantly increased in aged DCN following sound exposure while only the BDNF level was increased in young exposed DCN. These findings are similar to a previous study (Suneja and Potashner, 2002) which showed that there was no significant change of TrkB protein level in the ipsilateral DCN of young guinea pigs during the first week following UCA. These observations might suggest that because of dual deafferentation of aging and sound exposure, the total auditory input into aged DCN is less than that into young DCN. The attempt to compensate for this greater deficit may require the aged DCN to produce greater, more measurable increases in TrkB levels. Increased TrkB protein level may be a reflection of age- and sound-exposure-related increased fusiform cell spontaneous activity (Kaltenbach, 2007 for review; Brozoski et al., 2002; Caspary et al., 2005; Wang et al., 2009a, b). Tinnitus-related hyperactivity in DCN could stimulate BDNF secretion from local glia and subsequent binding to TrkB receptors leading to a chronic hypersensitivity similar to that observed in chronic pain (Coull et al., 2005).

The evidence from a hippocampal *in vitro* study showed that activation of postsynaptic TrkB receptors by BDNF led to increased GABA_A receptor clustering in an activity-dependent manner. TrkB signaling is necessary for maintaining GABA_A receptor clustering at synapses (Elmariah et al., 2004). By analogy, elevated BDNF level may have altered BDNF/TrkB signaling to initiate events that are involved in modulating excitatory and/or inhibitory synaptic plasticity changes at the level of the IC. Observations from this study suggest that up-regulated BDNF level in DCN fusiform cells may have long-term physiological and functional implications to the IC and throughout the auditory neuraxis possibly by altering synaptic transmission months following sound exposure.

Clinical implications

About 50 million people in the USA have experienced tinnitus with about 15% to 35% of the United States population experiencing chronic tinnitus and 10% of tinnitus patients subjected to chronic, persistent tinnitus that affects their quality of life (Hoffman and Reed, 2004; American Tinnitus Association). In addition, the aging population shows widely different levels of hearing loss (Toh et al., 2002; Gopinath, 2010). Recent studies suggest that sound exposure and aging result in increased neuronal activity in the auditory brainstem

and auditory cortex (Hughes et al., 2010; Schmidt et al., 2010; Syka, 2002 for review; Caspary et al., 2008 for review). This up-regulation of neural activity with hearing loss in young individuals and in the elderly likely results from a partial deafferentation-induced compensatory down-regulation of inhibitory neurotransmitter function (Suneja et al., 1998a, b; Syka, 2002 for review; Wang et al., 2009a). Up-regulated signaling from BDNF and TrkB after cochlear ablation or sound exposure might link to SGN loss/survival and the regulation of synaptic plasticity in peripheral as well as central auditory structures (Miller et al., 1997; Suneja and Potashner, 2002; Gillespie et al., 2003, 2004). Recently, Panford-Walsh et al. (2008) showed an elevated BDNF message level in SGNs following salicylate application in tinnitus animals. These results suggest that increased levels of BDNF and TrkB in fusiform cells likely result from increased fusiform cell activity and may also reflect BDNF signaling which alters inhibitory receptor composition and function. Tan et al. (2007) observed an increase in BDNF protein in the IC 6 days following sound exposure in rats with behavioral evidence of tinnitus. These findings are consistent with the present findings. Future studies should investigate the role of BDNF and TrkB receptors in the context of the compensatory activity-dependant down-regulation of inhibitory neurotransmitter function following sound exposure and in aging at higher levels of the auditory neuraxis.

Abbreviations

ABR	auditory brainstem response
ANOVA	analysis of variance
BBN	broadband noise
BDNF	brain-derived neurotrophic factor
CF	characteristic frequency
CN	cochlear nucleus
DAB	3,3'-diaminobenzidine tetrahydrachloride
DCN	dorsal cochlear nucleus
FBN	Fischer Brown Norway
GlyR	glycine receptor
HF	high frequency
LF	low frequency
MF	middle frequency
PBS	phosphate buffered saline
PKC	protein kinase C
ROD	relative optical density
SGNs	spiral ganglion neurons
TrkB	tyrosine kinase B
SPL	sound pressure level
PTS	permanent threshold shift
TTS	temporary threshold shift
UCA	unilateral cochlear ablation
VCN	ventral cochlear nucleus

Acknowledgments

This study is supported by NIH grant DC008532 and American Tinnitus Association to DMC.

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Figure 2.

BDNF immunolabeled fusiform cells from transverse sections through the high frequency region of the left rat dorsal cochlear nucleus. Sections are representative of the four experimental conditions (young control, young exposed, aged control, and aged exposed). Sound exposure increased BDNF labeling over both young and aged fusiform cells. The aged control panel (lower left) displays the faint labeling of fusiform cells described in the quantitative results for BDNF protein (Table 1) in aged control DCN.

Exposure-related BDNF and TrkB protein changes (relative optical density [ROD]) over fusiform cells in young and aged DCN.

Table 1

	Young Control ± SE	Young Sound- exposed ± SE	%change ± SE	Aged Control ± SE	Aged Sound- exposed ± SE	%change
BDNF (ROD)	25.4±0.64	27.8±0.61*	9%	21.9±0.76	28.7±0.52*	31%
TrkB (ROD)	54.8±0.78	52.0±1.46	5%	54.3±0.83	67.5±1.46*	24%

* Indicates significant, $p < 0.05$, changes relative to unexposed control rats.