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REVIEW

IS THERE A RELATIONSHIP BETWEEN BRAIN-DERIVED NEUROTROPHIC FACTOR FOR DRIVING NEURONAL AUDITORY CIRCUITS WITH ONSET OF AUDITORY FUNCTION AND THE CHANGES FOLLOWING COCHLEAR INJURY OR DURING AGING?

T. SCHIMMANG, [a]* **B. DURÁN ALONSO,** [a] **U. ZIMMERMANN** [b] **AND M. KNIPPER** [b]

[a] *Instituto de Biología y Genética Molecular, Universidad de Valladolid y Consejo Superior de Investigaciones Científicas, E-47003 Valladolid, Spain*

[b] *University of Tübingen, Department of Otolaryngology, Head and Neck Surgery, Tübingen Hearing Research Center (THRC), Molecular Physiology of Hearing, Elfriede-Aulhorn-Straße 5, 72076 Tübingen, Germany*

Abstract—Brain-derived neurotrophic factor, BDNF, is one of the most important neurotrophic factors acting in the peripheral and central nervous system. In the auditory system its function was initially defined by using constitutive knockout mouse mutants and shown to be essential for survival of neurons and afferent innervation of hair cells in the peripheral auditory system. Further examination of BDNF null mutants also revealed a more complex requirement during re-innervation processes involving the efferent system of the cochlea. Using adult mouse mutants defective in BDNF signaling, it could be shown that a tonotopical gradient of BDNF expression within cochlear neurons is required for maintenance of a specific spatial innervation pattern of outer hair cells and inner hair cells. Additionally, BDNF is required for maintenance of voltage-gated potassium channels (K_V) in cochlear neurons, which may form part of a maturation step within the ascending auditory pathway with onset of hearing and might be essential for cortical acuity of sound-processing and experience-dependent plasticity. A presumptive harmful role of BDNF during acoustic trauma and consequences of a loss of cochlear BDNF during aging are discussed in the context of a partial reversion of this maturation step. We compare the potentially beneficial and harmful roles of BDNF for the mature auditory system with those BDNF functions known in other sensory circuits, such as the vestibular, visual, olfactory, or somatosensory system.

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Key words: BDNF, sensory system, $K_V3.1$, injury, homeostatic adaptation.

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*Corresponding author. Address: Instituto de Biología y Genética Molecular, C/Sanz y Forés 3, E-47003 Valladolid, Spain. Tel: +34-983-184818; fax: +49-983-184800.

E-mail address: schimman@ibgm.uva.es (T. Schimmang).

Abbreviations: ABR, auditory brainstem response; AC, auditory cortex; AF, afferent fiber; AF type II, afferent type II fibers; AP, action potential; BDNF, brain-derived neurotrophic factor; DCN, dorsal cochlear nucleus; DPOAE, distortion product otoacoustic emission; DRG, dorsal root ganglia; EF, efferent fiber; HPA axis, hypothalamic–pituitary–adrenal axis; IC, inferior colliculus; IHC, inner hair cell; K_V, voltage-gated potassium channel; LOC, lateral olivocochlear (system); LSO, lateral superior olive; MeCP2, methyl-CpG-binding protein-2; MSO, medial superior olive; NG, nodose ganglia; NTS, nucleus tractus solitaries; OHC, outer hair cell; PG, petrosal ganglia; PGC, periglomerular cells; RTT, Rett Syndrome; SG, spiral ganglion; SGN, spiral ganglion neuron; Shc, Src homology and collagen homology; SK2, small-conductance Ca^{2+}-activated potassium channel; SOC, superior olivary complex; SR, spontaneous (discharge) rate; VCN, ventral cochlear nucleus; VHC, vestibular hair cells.

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INTRODUCTION

Brain-derived neurotrophic factor (BDNF) is an important signaling molecule in the mammalian central nervous system (CNS) that plays a crucial role in the proper development and function of the CNS (for reviews see (Tucker et al., 2001; Rauskolb et al., 2010)). In the adult CNS, BDNF displays crucial functions for maintaining synapses and dendritic networks (Nosrat et al., 1997; Rauskolb et al., 2010; Dieni et al., 2012). BDNF is released from neurons and regulates synaptic plasticity, which is thought to underlie learning and memory. More recent studies provide evidence for a role of BDNF for mature circuit formation, acting during the functional onset of sensory circuits as shown for the auditory, somatosensory, or visual system, when sensory activity appears to drive a BDNF-dependent increase of cortical inhibition (for a review, see (Singer et al., 2014)).

New roles of BDNF have been discovered through the analysis of conditional mouse mutants, in which tissue-specific deletion of BDNF bypasses the early postnatal lethality of constitutive BDNF mutants. The current review summarizes the different functions of BDNF in the mature auditory organ in the context of deficits known to occur during injury and during aging. Recent results indicate a crucial role of BDNF for changing activity patterns of neurons from the onset of hearing onward within the ascending pathway, e.g. through control of first-order inner hair cell (IHC) synapses and auditory fiber phenotypes that may drive central pathways. An injury- or age-dependent reversal of this process is discussed in the context of hearing disorders. Parallels to other sensory organs, such as the vestibular, visual, olfactory, and somatosensory system are highlighted.

ROLE OF BDNF FOR MATURATION OF THE AUDITORY CIRCUIT

Role of BDNF for maintaining mature neuronal innervation in the cochlea

Multiple reviews have described a crucial function of BDNF for survival of placode- and neural crest-derived neurons during neonatal development (Lindsay et al., 1985; Krimm, 2007; Harlow et al., 2011). We refer readers interested in the function of BDNF in the neonatal auditory organ to several excellent reviews (Davis, 2003; Fritzsch et al., 2004; Ramekers et al., 2012).

In the inner ear that comprises the vestibular and auditory system (Fig. 1A, C), BDNF alters its expression pattern with onset of sensory function. At birth, BDNF is expressed in IHCs and outer hair cells (OHCs), where it is down-regulated postnatally, but remains present in neighboring supporting cells, likely corresponding to phalangen cells (Sobkowicz et al., 2002) and in spiral ganglia neurons (SGNs) in basal cochlear turns of the mature auditory organ (Schimmang et al., 2003; Flores-Otero et al., 2007). The co-expression of BDNF and its receptor TrkB, found in adult SGNs in the basal part of the cochlea, suggested the existence of an autocrine mechanism, which maintains neuronal function during adulthood (Schimmang et al., 2003). These findings were also consistent with results demonstrating that exposure of postnatal apical SGNs to BDNF can trigger physiological characteristics of typical mature basal SGNs (Adamson et al., 2002a; Flores-Otero et al., 2007).

The role of BDNF during auditory development was initially analyzed in constitutive mouse mutants for BDNF and its corresponding receptor TrkB (Ernfors et al., 1995; Schimmang et al., 1995; Bianchi et al., 1996; Fritzsch et al., 1997). Examination of the cochlea revealed a reduction of afferent innervation on the OHCs (Fig. 1C) in the apical part of the cochlea and a concomitant loss of afferent type II fibers (AF type II) (Fig. 1C) (Ernfors et al., 1995; Schimmang et al., 1995; Fritzsch et al., 1997). Next to this requirement for afferent innervation on OHCs, a role of BDNF for the rearrangement of efferent innervation on OHCs and IHCs was described (Wiechers et al., 1999), which included an axosomatic switch of efferent fibers from the lateral olivocochlear nucleus (EF-LOC) to IHCs (Fig. 1C) and synapse formation of efferent fibers projecting from the medial olivocochlear nucleus (EF-MOC) to OHCs (Fig. 1C). The rearrangement of fibers precedes the maturation within the ascending auditory pathway, including the first target neurons of the SGNs in the cochlear nucleus (CN), followed by the superior olivary complex (SOC), the inferior colliculus (IC), the medial geniculate body (MGB), and the auditory cortex (AC) (Fig. 1D).

To obtain insight into the role of BDNF in adult sensory systems, TrkB mutants with a mutation in the docking domain for the Src homology and collagen homology (Shc) adaptor protein and therefore lacking part of the TrkB-mediated signaling pathway were used (Postigo et al., 2002). These mice were crossed with TrkB mutants lacking the tyrosine kinase receptor domain to create $TrkB^{shc/-}$ mutants and thus resulted in the creation of a mouse model with a severe loss of TrkB signaling (Postigo et al., 2002; Schimmang et al., 2003). $TrkB^{shc/-}$ mice were found to be viable and thus permitted analysis of the auditory system in adulthood. The mutant animals suffered from a hearing loss of 10–30 dB as measured through auditory brainstem responses (ABR) across all frequencies and severely reduced distortion product otoacoustic emissions (DPOAEs) at higher frequencies. ABR measurements are an often used methodology to monitor neurosensorial hearing loss (Burkard and Don, 2007), whereas via DPOAEs (Kemp, 2008) the functionality of OHCs can be monitored. Similar to BDNF mutants,