

Research paper

Consequences of unilateral hearing loss: Time dependent regulation of protein synthesis in auditory brainstem nuclei

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Abstract

Conductive hearing impairment results in marked changes in neuronal activity in the central auditory system, particularly in young animals [Tucci, D.L., Cant, N.B., Durham, D., 1999. Conductive hearing loss results in a decrease in central auditory system activity in the young gerbil. *Laryngoscope* 109, 1359–1371]. To better understand the effects of conductive hearing loss (CHL) on cellular metabolism, incorporation of ³H-leucine was used as a measure of protein synthesis in immature postnatal day 21 gerbils subjected to either unilateral CHL by malleus removal or profound sensorineural hearing loss by cochlear ablation. ³H-leucine uptake was measured after survival times of 6 or 48 h. Protein synthesis values were standardized to measurements from the abducens nucleus and compared with measurements from sham animals at similar age/survival times. Protein synthesis in the medial superior olive (MSO) was found to be significantly down-regulated (bilaterally) after CHL in animals surviving 48 h. However, 6 h after CHL manipulation, protein synthesis is up-regulated in MSO (bilaterally) and in the ipsilateral medial nucleus of the trapezoid body.

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1. Introduction

Conductive hearing loss (CHL) changes the way sound is processed in the central auditory system. Using 2-deoxyglucose (2-DG) as a measure of neuronal activity, unilateral CHL has been shown to produce changes in glucose uptake, with significantly reduced uptake in the major afferent projection originating from the affected ear (Tucci et al., 1999). Effects are most marked in young, developing animals. In these animals, CHL results in a decrease that is statistically similar to that observed following cochlear

ablation (CA), despite the more substantial (profound) hearing loss observed after the latter manipulation.

Cochlear destruction causes transneuronal degeneration in central auditory pathways (e.g., Jean-Baptiste and Morest, 1975; Pasic et al., 1994; Morest and Bohne, 1997; Potashner et al., 1997; Tierney et al., 1997). Furthermore, studies of CA-induced plasticity within these pathways have shown that CA affects the internal metabolism of central auditory system neurons. For example, the regulation of glutamate and glycine release by protein kinase is altered by CA (Zhang et al., 2002, 2003a,b, 2004), as are signal transduction pathways (Suneja and Postashner, 2003) and cyclic AMP levels (Mo et al., 2006). CA also can induce the re-emergence of GAP-43 expression in adult animals (Illing et al., 1997; Michler and Illing, 2002; Kraus and Illing, 2004). Each of these findings suggests that CA may have an affect on central auditory system neurons at the gene level (Holt et al., 2005).

Abbreviations: AVCN, anteroventral cochlear nucleus; CA, cochlear ablation; CHL, conductive hearing loss; contra, contralateral; ipsi, ipsilateral; LSO, lateral superior olive; LSOL, lateral limb of the lateral superior olive; LSOM, medial limb of the lateral superior olive; MSO, medial superior olive; MTB, medial nucleus of the trapezoid body; SH, sham

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Cellular changes following CHL are less dramatic (Webster and Webster, 1979; Webster, 1983a–c; Coleman and O'Connor, 1979; Blatchley et al., 1983; Trune and Morgan, 1988a,b; Doyle and Webster, 1991; Walsh and Webster, 1994; Tucci and Rubel, 1985; Tucci et al., 1987; Moore et al., 1989), but there is evidence that the auditory deprivation produced by CHL, particularly if unilateral, alters the way that sound is processed, at least in lower brainstem nuclei. Some authors suggest that the symmetry of input may be important in establishing and maintaining neural projections, and that unilateral CHL may alter the anatomical structure of bilaterally innervated nuclei (Killackey and Ryugo, 1977). Moore et al. (1989) found that, despite the lack of change in neuron area in ipsilateral CN following unilateral CHL, there was a significant change in the projection from the CN opposite the affected ear to the ipsilateral IC, reflecting a possible compensatory increase in input to the IC from the normal ear (uncrossed pathway). In the barn owl, Knudsen (1999) found evidence for altered localization cues and reorganization of binaurally innervated central auditory nuclei following unilateral CHL produced by occlusive earplug placement during a critical period in development.

2-DG uptake is decreased in the ipsilateral cochlear nucleus after unilateral CHL, and there is information from several studies indicating there may be up-regulation of the contralateral cochlear nucleus (Tucci et al., 1999). Following unilateral CHL in young adult (6 week old) gerbils, there is a slight but significant increase in 2-DG uptake in the contralateral cochlear nucleus that is not seen following cochlear ablation (Tucci et al., 1999). A similar pattern of change, although less marked, is observed in cytochrome oxidase (CO) activity following unilateral CHL (Tucci et al., 2001). In this experiment, for adult animals, a significant decrease in CO activity is observed in the ipsilateral and a significant increase is observed in the contralateral anteroventral cochlear nucleus (AVCN). Morphological changes have also been observed in the contralateral AVCN after unilateral hearing loss, where a slight increase in the size of spherical cells has been reported (e.g., Coleman and O'Connor, 1979; Dodson et al., 1994).

Possible compensatory changes were also observed in the contralateral AVCN following CHL in adult guinea pigs (Sumner et al., 2005). In that study of binaural properties of AVCN neurons following unilateral conductive impairment, the investigators found a dramatic increase in the proportion of units in the ipsilateral AVCN that responded with excitation to broad band noise stimulation of the contralateral (intact) ear.

One consequence of severe end organ damage on cellular metabolism is a decrease in protein synthesis in the ipsilateral cochlear nucleus (Steward and Rubel, 1985; Born and Rubel, 1988; Hyson and Rubel, 1989; Sie and Rubel, 1992). A similar decrease in protein synthesis has also been observed in the ipsilateral cochlear nucleus following unilateral CHL (Trune and Kiessling, 1988). However, little is known about how unilateral hearing loss affects protein

synthesis in other auditory brainstem structures. In order to better understand some of the cellular events associated with changes in central auditory system activity subsequent to CHL, we initiated the current study to investigate protein synthesis in central auditory system nuclei in immature gerbils.

2. Materials and methods

2.1. Subjects

Thirty-three Mongolian gerbils (*Meriones unguiculatus*) obtained from a commercial supplier (Charles River) were used in the present study. All anesthetic, operative, and postoperative procedures and care were approved by the Institutional Animal Care and Use Committee and followed NIH guidelines. All animals entered the experimental paradigm at postnatal day 21 (P21).

Protein synthesis was examined in animals subsequent to a sham (SH), CHL, or CA procedure, with survival times of 6 h (SH = 5, CHL = 6, CA = 6) or 48 h (SH = 5, CHL = 7, CA = 4). Our nomenclature is a P21 animal that survived 6 h falls in the category of P21(21) meaning manipulation and assessment both on postnatal day 21; or P21(23) meaning manipulated on P21 and uptake assessed 48 h later on P23.

Our choice of age was guided by past studies and by our interest in the effects of hearing loss in young animals beyond the age of hearing onset. Gerbils first respond to sound at approximately P12 (Finck et al., 1972; Woolf and Ryan, 1984; Ryan and Woolf, 1993). At P16, gerbils possess sufficient sensorimotor integration to accurately approach the source of a sound in space (Kelly and Potash, 1986). By P18 gerbils have mature middle and inner ears, and both the auditory nerve and ventral cochlear nucleus show adult-like physiological response characteristics (Woolf and Ryan, 1985). However, central auditory system development continues until at least P30 (Woolf and Ryan, 1985) and perhaps even longer (Poulsen et al., 2007). Thus gerbils at P21 have acoustic experience and a mature peripheral apparatus, yet central auditory system structures are continuing to develop.

2.2. Surgical procedures

Animals were anesthetized with an IP injection of a mixture of ketamine (75 mg/kg) and xylazine (5 mg/kg). All surgical procedures were performed unilaterally on the left ear. Animals in the SH condition served as our anesthesia only control group. For CHL and CA animals, the fur was shaved behind the left ear, a postauricular incision was made and tissue surrounding external ear canal was dissected away, with care taken to preserve the exiting facial nerve. A small opening was made in the cartilaginous portion of the ear canal, and the tympanic membrane visualized. Using fine forceps, the tympanic membrane was punctured and the malleus gently removed. The stapes

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