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Research paper

Specific plasticity responses to unilaterally decreased or increased hearing intensity in the adult cochlear nucleus and beyond

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Abstract

Variations of sensory activation in strength and pattern are known to affect structure and function of the mammalian brain. Whereas such malleability is readily granted to forebrain structures at early developmental stages, acceptance of experience-dependent structural plasticity has been slow for the adult brainstem. Over the past years we have identified consequences of cochlear ablation, noise trauma, or electrical intracochlear stimulation on neurons and circuitry of the auditory brainstem of the adult rat. We found that loss of sensory activation as well as a substitution for it entail specific molecular, ultrastructural, and morphological changes to central auditory neurons. Here, we make a first attempt to compare these different patterns of central remodeling. We tentatively suggest that after hearing loss or intracochlear stimulation responses of the central neural network in the adult brainstem suit the concept of functional adaptation.

Keywords: Synaptic remodeling; Cochlear lesion; Cochlear implant; GAP-43; c-Fos

1. Introduction

Structure and function of the mammalian brain are characterized by both neuronal specificity and neuronal plasticity (Lund, 1978). Whereas the brains of individuals of a particular mammalian species show a high degree of structural similarity from gross anatomy over cellular morphology to molecular pattern, neuroscience has been forced to recognize that they are not identical and that their dissimilarity is functionally important. Part of this dissimilarity has its origin in the particular sensorimotor experiences for which no two individuals are identical. Meanwhile, much attention has been given to this dimension of plasticity that is found in the developing and mature mammalian brain in various kinds and to various degrees (Purves and Lichtman, 1985), serving mostly specific adaptation to the sensory environment but may not always be beneficial to the individual (Moller, 2001a).

While plasticity has been appreciated as a fundamental feature of the mammalian brain, much of it is still attributed to the forebrain, especially to the isocortex, particularly at its earlier developmental stages. Acceptance of the concept of subcortical plasticity has been slow, but even the adult brainstem, not long ago considered a distinctly rigid neuronal network, has finally been included into the 'learning' brain. In recent years, we have adopted two approaches to exploit our initial finding (Illing and Horváth, 1995) that there appears to be structural plasticity in the auditory brainstem of the adult rat. We made cochlear lesions (Illing et al., 1997, 1999; Förster and Illing, 1998) or induced a near-complete noise trauma (Michler and Illing, 2002, 2003) to investigate responses of the

Abbreviations: ABR, auditory brainstem response; DAB, diamino benzidine; DCN, dorsal cochlear nucleus; EIS, electrical intracochlear stimulation; GABA, γ-aminobutyric acid; GAP-43, growth-associated protein 43; IC, inferior colliculus; IEG, immediate early gene; LSO, lateral superior olive; LTD, long-term depression; LTP, long-term potentiation; PB, phosphate buffer; SOC, superior olivary complex; VCN, ventral cochlear nucleus; VSO, ventral superior olive

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system to unilateral loss of sensory excitation, and we performed electrical intracochlear stimulation (EIS) in one ear to trace responses of the affected neuronal networks to a sustained monotone activation (Illing and Michler, 2001; Illing et al., 2002). As indicators for the dynamics of the neuronal networks affected by deafening or stimulation we used molecular markers such as the growth and plasticity associated protein GAP-43 and the immediate early gene (IEG) product c-Fos, both known to be related to the morphological and functional plasticity of neurons (Robertson, 1992; Kaczmarek, 1993; Benowitz and Routtenberg, 1997). Their localization by immunocytochemistry or in situ hybridization was combined with axonal tracing and analyzed with light and electron microscopical methods (Illing et al., 2005).

Sensory deprivation and artificial activation each led to specific cellular and molecular changes of central auditory neurons. We here draw a first comparison of these changes and suggest that both interventions induce specific adaptive strategies of the neuronal network involved.

2. Methods

2.1. Animals

For the studies presented here we used adult Wistar rats aged 6–12 weeks. Care and use of the animals were approved by the appropriate agency (Regierungspräsidium Freiburg, Germany). For cochlear ablation, 52 rats were anesthetized with an intraperitoneal injection of a mixture of ketamine (50 mg/kg, Ketanest, Parke-Davis, Ann Arbor, MI) and xylazine (5 mg/kg, Rompun, Bayer-Leverkusen, Germany). For 24 rats experiencing EIS, anesthesia was achieved by urethane (1.5 g/kg i.p.). Before fixation of the brain by transcardial perfusion, rats were given a lethal dose of pentabarbital (0.6 ml/kg of Narcodorm-n, Alvetra GmbH, Neumünster, Germany, i.p.).

2.2. Cochleotomy

Unilateral cochleotomy was performed on the left side using a retroauricular approach as described before (Illing et al., 1997). The facial nerve was sectioned at its exit from the skull and the bulla tympani was opened to provide good visibility of the cochlea. A hole was drilled in the cochlea and the interior of the cochlea, including organ of Corti and spiral ganglion, was removed (Fig. 1A). Subsequently, cochlea and middle ear cavity were filled with Gelfoam and the wound was surgically closed. For the experiments presented in this study, post-operative survival time was one week.

2.3. Electrical intracochlear stimulation (EIS)

To reduce the level of hearing-dependent activity in the auditory system, the tympanic membrane was disrupted and the outer middle ear bone (malleus) was removed bilaterally two days before EIS. Judging from the auditory brainstem response (ABR), interruption of middle ear transmission led to an immediate and sustained conductive hearing loss of 50 dB (Illing and Michler, 2001). We applied EIS unilaterally (left side) with a cochlear implant (Moller, 2001b) in acute experiments for 2 h. The cochlea was exposed using a retroauricular surgical approach and a hole was made into the bony wall of the basal cochlea to insert the electrode carrier (Fig. 1B). We applied bipolar stimulation, using a cochlear implant (Cochlear AG, Basel, Switzerland, Model CI24M) run by the Nucleus Implant Communicator. The ABR was recorded and visualized using an averager (Multiliner E; Evolution 1.70c; Toennies, Würzburg, Germany), calculating mean amplitudes over 500 sweeps in a frequency band between 0.1 and 3 kHz. We aimed to obtain an ABR amplitude in the range of 5–10 μV, corresponding to acoustically evoked amplitudes of 30–60 dB.

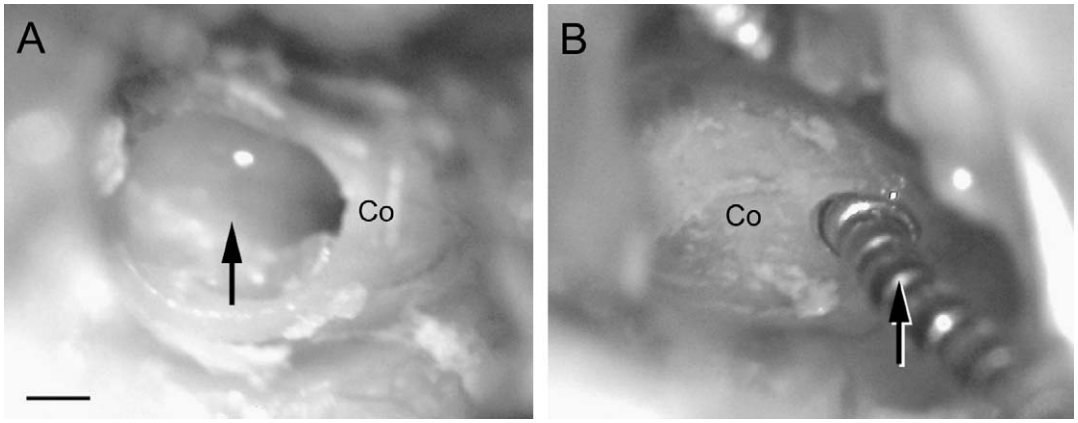

Fig. 1. Intraoperative views on the adult rat cochlea (Co), showing two experimental approaches to change activity in the 8th cranial nerve. (A) In the course of a cochleotomy, the interior of the cochlea, including the modiolus, the lamina ossea spiralis, the organ of Corti, and the spiral ganglion, has been completely removed (arrow), leading to a complete unilateral loss of sensory activation. (B) For EIS, an electrode carrier (arrow) is inserted into the basal turn of the cochlea to induce activation of part of the 8th cranial nerve. Rostral is to the left, dorsal is up. Scale bar: 0.5 mm.