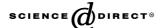
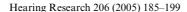


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# Reconnecting neuronal networks in the auditory brainstem following unilateral deafening

Robert-Benjamin Illing \*, K. Suzanne Kraus, Markus A. Meidinger

Neurobiological Research Laboratory, Department of Otorhinolaryngology, University of Freiburg, D-79106 Freiburg, Germany

Received 14 October 2004; accepted 10 January 2005 Available online 13 April 2005

#### **Abstract**

When we disturbed the auditory input of the adult rat by cochleotomy or noise trauma on one side, several substantial anatomical, cellular, and molecular changes took place in the auditory brainstem. We found that: (1) cochleotomy or severe noise trauma both lead to a considerable increase of immunoreactivity of the growth-associated protein GAP-43 in the ventral cochlear nucleus (VCN) of the affected side; (2) the expression of GAP-43 in VCN is restricted to presynaptic endings and short fiber segments; (3) axon collaterals of the cholinergic medial olivocochlear (MOC) neurons are the path along which GAP-43 reaches VCN; (4) partial cochlear lesions induce the emergence of GAP-43 positive presynaptic endings only in regions tonotopically corresponding to the extent of the lesion; (5) judging from the presence of immature fibers and growth cones in VCN on the deafened side, at least part of the GAP-43 positive presynaptic endings appear to be newly formed neuronal contacts following axonal sprouting while others may be modified pre-existing contacts; and (6) GAP-43 positive synapses are formed only on specific postsynaptic profiles, i.e., glutamatergic, glycinergic and calretinin containing cell bodies, but not GABAergic cell bodies. We conclude that unilateral deafening, be it partial or total, induces complex patterns of reconnecting neurons in the adult auditory brainstem, and we evaluate the possibility that the deafness-induced chain of events is optimized to remedy the loss of a bilaterally balanced activity in the auditory brainstem. © 2005 Elsevier B.V. All rights reserved.

Keywords: Superior olivary complex; Synaptic remodeling; Cochlear lesion; Plasticity; Adult CNS; Regeneration

## 1. Introduction

The capacity for regeneration of the mature mammalian central nervous system is limited. However, as this statement is often repeated, it is regularly ignored that the potential for reorganization is far from absent. As for other sensory systems, several reports pointed to a lack of neuronal growth processes following lesioned fiber tracts in the central auditory system under normal conditions (Ito et al., 1998; Hafidi et al., 1999). There is a growing body of literature, though, indicating that to molecular modifications and local axonal or synaptic growth induced by injury or other forms of altered experience (Buonomano and Merzenich, 1998; Illing, 2001).

The adult central auditory system has been subject to a considerable number of studies evaluating its plasticity

Abbreviations: ABC, avidin-biotin complex; ABR, auditory brainstem response; AVCN, anteroventral cochlear nucleus; ChAT, choline acetyltransferase; DCN, dorsal cochlear nucleus; DY, Diamidino Yellow; FB, Fast Blue; GABA, gamma-aminobutyric acid; GAP-43, growth associated protein-43; LOC system, lateral olivocochlear system; LSO, lateral superior olive; MOC system, medial olivocochlear system; Mt, mitochondria; n8, eighth cranial nerve; PB, phosphate buffer; PBS, phosphate-buffered saline; PVCN, posteroventral cochlear nucleus; SOC, superior olivary complex; SV, synaptic vesicles; vas, ventral acoustic stria; VCN, ventral cochlear nucleus; VNTB, ventral nucleus of the trapeziod body; VSO, ventral superior olivary region

<sup>\*</sup> Corresponding author. Tel.: +49 761 270 4273; fax: +49 761 270 4075. E-mail address: robert.illing@uniklinik-freiburg.de (R.-B. Illing).

using various approaches. Late-onset deprivation leads to a marked plasticity of binaural processing in humans (Florentine, 1976; Moore, 1993). Removal of the middle ear ossicles has been shown to induce plastic changes in cochlear nucleus transmitter metabolism in guinea pigs (Potashner et al., 1997; Suneja et al., 1998). Following induced deafness, a marked decrease of GABA was also seen in the rat inferior colliculus (IC, Bledsoe et al., 1995). Acoustic overstimulation of chinchillas has immediate effects on the response characteristics of cochlear nucleus neurons (Boettcher and Salvi, 1993) and entails loss of nerve fibers, even transsynaptically, over the days following the trauma (Kim et al., 1997). A cochlear lesion causes morphological changes of neurons in cochlear nucleus and the medial nucleus of the trapezoid body in the gerbil (Pasik et al., 1994). At the same time, a transient downregulation of several neurotransmitter receptors was observed on specific cell types of the cochlear nucleus (Sato et al., 2000), while the amplitude of excitatory postsynaptic currents increases and the inhibitory synaptic strength decreases in the IC (Vale and Sanes, 2002). Beyond transmitter metabolism, changes occur in molecular signaling pathways of cochlear nucleus neurons (Suneja and Potashner, 2003), some of which are apparently related to cell death (Mostafapour et al., 2000). Ultrastructural changes have been described after cochleotomy in the superior olive (Russell and Moore, 2002). Partial cochlear lesions even evoke changes in the cochleotopic organization of primary auditory cortex of the cat (Rajan et al., 1993). Specific acoustic and electrical intracochlear stimulation may induce expression of the immediate early gene c-fos (Friauf, 1995; Illing et al., 2002) and its mRNA (Saint Marie et al., 1999) essentially in all auditory brainstem nuclei.

Brain areas known for their adult plastic potential are characterized by the presence of a molecular marker, the growth- and plasticity-associated protein GAP-43, also known as B-50, F1, pp46, P-57, or neuromodulin (Benowitz et al., 1988; Benowitz and Routtenberg, 1997). This protein is a calmodulin-binding phosphoprotein and substrate for protein kinase C (Gispen et al., 1991; Schaechter and Benowitz, 1993). There are several lines of evidence relating this protein to axonal growth as well as to plasticity. It is produced at high levels in every nerve cell during neurite outgrowth and early stages of synaptogenesis (Skene and Willard, 1981; Mahalik et al., 1992) and represents a major constituent of the isolated growth cone (De Graan et al., 1985; Meiri et al., 1998). With maturation, its expression is downregulated by most neurons (Skene, 1989; Benowitz and Perrone-Bizzozero, 1991). When a sense construct of GAP-43 mRNA was transiently expressed in nonneuronal cultured cells, these cells grow filopodial like processes (Yankner et al., 1990; Verhaagen et al., 1994). If cells were transfected with a mutated construct of GAP-43 which prevented attachment of GAP-43 to the cell membrane, GAP-43 did not accumulate in pseudopods and no changes in cell morphology were induced (Widmer and Caroni, 1993). The attenuation of endogenous GAP-43 by an antibody that was raised against this protein and injected intracellularly has been found to reduce the degree of neurite outgrowth in a dose-dependent manner (Shea et al., 1991). The overexpression of GAP-43 in transgenic mice results in the formation of additional and aberrant neuronal connections spontaneously (Aigner et al., 1995). Conversely, null mutations of the GAP-43 gene are lethal shortly after birth, apparently by disturbances of axonal pathfinding (Strittmatter et al., 1995). In the adult brain, the distribution of the levels of GAP-43 and myelin is distinctly complementary (Schwab, 1996).

Ten years ago we discovered that the induction of unilateral deafness in the mature rat, induced by cochleotomy, invokes the expression of GAP-43 in the cochlear nucleus (Illing and Horváth, 1995). By that time we could only suspect that this induction hints to neuronal reorganization of the auditory brainstem as a consequence of a massively changed pattern of afferent activity. Over the years, details of this process have come to light that help us understand some of the rules that govern plasticity responses in the auditory brainstem of the adult mammal.

### 2. Materials and methods

# 2.1. Animals

For the studies presented here we used adult Wistar rats aged 6 weeks or older. Care and use of the animals were approved by Regierungspräsidium Freiburg, Germany, permission number 37/9185.81/1/267.2. For surgical procedures, 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).

#### 2.2. Experimental procedures

#### 2.2.1. Noise trauma

Unilateral traumatization was achieved by presenting a click-stimulus (frequency range 100–10,000 Hz, pulse duration 0.1 ms) at 20 Hz with 130 dB (SPL) for 30 min through a brass pipe equipped with a conical plastic tip inserted into the ear. To observe development and degree of hearing impairment, the auditory brainstem response (ABR) was continuously monitored. This treatment resulted in an instant and permanent increase of hearing threshold by 96 dB in the affected ear (Michler and Illing, 2002).

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