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NON-PLASTIC REORGANIZATION OF FREQUENCY CODING IN THE INFERIOR COLLICULUS OF THE RAT FOLLOWING NOISE-INDUCED HEARING LOSS

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Abstract—It is well established that restricted mechanical lesions of the cochlea result in reorganization of the tonotopic map in the auditory thalamus and cortex, but it is unclear whether acoustic trauma produces similar effects at earlier stages of the auditory pathways. To test whether the tonotopic map is reorganized after acoustic trauma at the midbrain level, i.e. the inferior colliculus (IC), we exposed rats to an acoustic trauma and let them survive for at least 5 weeks to ensure that we produced a permanent threshold shift. Experiments were carried out in urethane-anesthetized animals 35–296 days after the traumatic exposure. The acoustic lesions were assessed by measuring the compound action potential. We mapped the frequency organization of the IC using multiunit recordings. In addition, we recorded frequency response areas (FRAs) when a single unit was isolated (N=142). The results show that acoustic trauma produces a persistent reorganization of the tonotopic map and that the normal stepwise representation of sound frequency in the IC is profoundly disrupted. Although the reorganization in the IC is similar to that previously described in the cortex and thalamus in that the affected area appears to be invaded by the adjacent normal frequencies, changes in thresholds and FRAs in these regions are different from those in the forebrain. We conclude that most of the changes can be explained by the residual-response hypothesis [Irvine DR, Rajan R, Smith S (2003) Effects of restricted cochlear lesions in adult cats on the frequency organization of the inferior colliculus. J Comp Neurol 467:354–374]. Plastic reorganization of frequency response areas and tonotopic organization does not seem to occur at the midbrain level following acoustic trauma in adult animals in a manner similar to that previously shown in the auditory cortex. Maintaining the stability of the neuronal circuitry for frequency coding in the IC may be important for the treatment of noise-induced hearing loss.

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Abbreviation: BF, best frequency; CAP, compound action potential; CNIC, central nucleus of the inferior colliculus; FRA, frequency response area; IC, inferior colliculus; MU, multiunit; PTS, permanent threshold shift; STC, spatial tuning curve; SU, single unit.

Key words: acoustic trauma, midbrain, spectral analysis, tonotopic organization, plasticity, stability.

A fundamental feature of sensory systems, including the auditory system, is the presence of a topographical representation or map of the sensory receptors in the CNS. For many years it was thought that topographic maps could be modified by experience only during development, notably during "sensitive" or "critical" periods of limited duration (de Villers-Sidani et al., 2007; Nakahara et al., 2004; Zhang et al., 2001), and that this organization was fixed in the adult brain. However, it is now well-established that topographical maps have the capacity to reorganize if the mature sensory system is chronically deprived of its normal input, for example, through damage of the sensory receptors.

The primary somatosensory and visual cortices of adult mammals exhibit a remarkable capacity for plastic change when patterns of input are altered by peripheral denervation (Buonomano and Merzenich, 1998; Gilbert, 1998; Kaas, 2000). In the auditory system, unilateral mechanical lesions of a restricted frequency region in the adult cochlea results in a reorganization of the normal frequency map in the contralateral cortex. Cortical neurons which would usually be tuned to the frequency corresponding to the lesioned section of the cochlea (termed lesion projection zone; Schmid et al., 1996) retune so that their new best frequencies correspond to the edge of the cochlear lesion (Robertson and Irvine, 1989; Rajan et al., 1993; Schwaber et al., 1993; Rajan, 1998). It is not clear to what extent, plastic changes occur within the excitatory response area following different forms of deafferentation.

Cortical plasticity is well-documented (Irvine and Wright, 2005; Irvine, 2007); however, it is unclear to what extent subcortical nuclei contribute to cortical reorganization. Studies carried out in the cochlear nucleus have failed to demonstrate plastic changes in frequency reorganization (Kaltenbach et al., 1992; Rajan and Irvine, 1998a); however, a single study of the auditory thalamus has shown evidence for genuine plastic reorganization of the tonotopic map similar to that seen in the auditory cortex (Kamke et al., 2003).

Since the inferior colliculus (IC) is an obligatory relay center for most input from lower auditory centers going to the thalamus (Anderson et al., 2006; Malmierca et al., 2002; Malmierca, 2003) understanding its contribution to thalamic and cortical plasticity in frequency coding is critical. The effects of partial ablation of the auditory periphery, including mechanical disruptions of the organ of Corti

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(Rajan et al., 1993; Rajan and Irvine, 1998b; Rajan, 1998, 2001; Robertson and Irvine, 1989), administration of ototoxic drugs (Harrison et al., 1993a,b, 1995; Harrison, 2001; Schwaber et al., 1993) or genetically induced progressive hearing loss (Willott, 1984; Willott et al., 1993; Willott and Bross, 1996), have been reported at the level of the auditory cortex in a wide variety of experimental models. However, fewer studies have described the effects at the level of the IC and the results are controversial. For example, while Harrison et al. (1998) reported some tonotopic map plasticity in the IC, Irvine et al. (2003) reported only a patchy reorganization in the central nucleus where most changes seem to be due to residual responses ("pseudoplastic").

The present study aimed to shed light on the issue of subcortical plasticity in the auditory system with special emphasis on the role of the midbrain in frequency coding. We exposed young adult rats to acoustic trauma in order to produce moderate to severe noise-induced hearing loss. This cochlear insult resulted in a profound reorganization of the tonotopic map in the IC. However, in most cases, the reorganization was accompanied by increases in neuronal thresholds. Preliminary reports have been presented elsewhere (Izquierdo et al., 2006, 2007).

EXPERIMENTAL PROCEDURES

Experiments were performed on a total of 51 healthy young-adult rats (*Rattus norvegicus*, Rj: Long Evans) of both sexes. Rats weighed between 170 and 430 g, were between 96 and 341 days old and were free from any signs of external- or middle-ear pathology. The care and use of animals reported on in this study were approved by the University of Salamanca Animal Care and Use Committee and conformed to the guidelines of the EU directive 2003/65/CE and the Spanish RD 1201/2005. All efforts were made to minimize the number of animals used and their suffering.

Experimental groups and experimental design

Animals were randomly assigned to one of three groups: 1) seven control animals (3–7 months old) were used to establish a mean baseline compound action potential (CAP, Fig. 1A); 2) 32 animals in the same age range as the control group were used to obtain detailed tonotopic response maps from the "normal" IC (Fig. 1B) and to collect control frequency response areas (FRAs, Fig. 1C); and 3) 17 animals were exposed to intense pure tone stimuli (see Table 1 for parameters). The animals in the third group were first tested for permanent threshold shift (PTS) of the CAP audiogram. (In order to assess possible differences after longer recovery periods they were tested at variable periods after the exposure.) Following the CAP measurements, group 3 underwent a recording protocol similar to that described for group 2. The three groups of experiments were randomly conducted.

Acoustic trauma

Animals in group 3 were exposed to continuous pure tones of either 5 or 8 kHz, at intensities between 110–121 dB SPL. In order to induce different degrees of cochlear damage the duration of exposure ranged from 3.3–16 h (Table 1). Throughout the exposure, the animals were unanesthetized and unrestrained within individual cages which were suspended inside a small reverberant sound-exposure box with non-parallel sides (e.g. Liberman and Gao, 1995; Yoshida et al., 2000). The exposure stimulus was generated by a custom-made noise source, amplified (Magnat

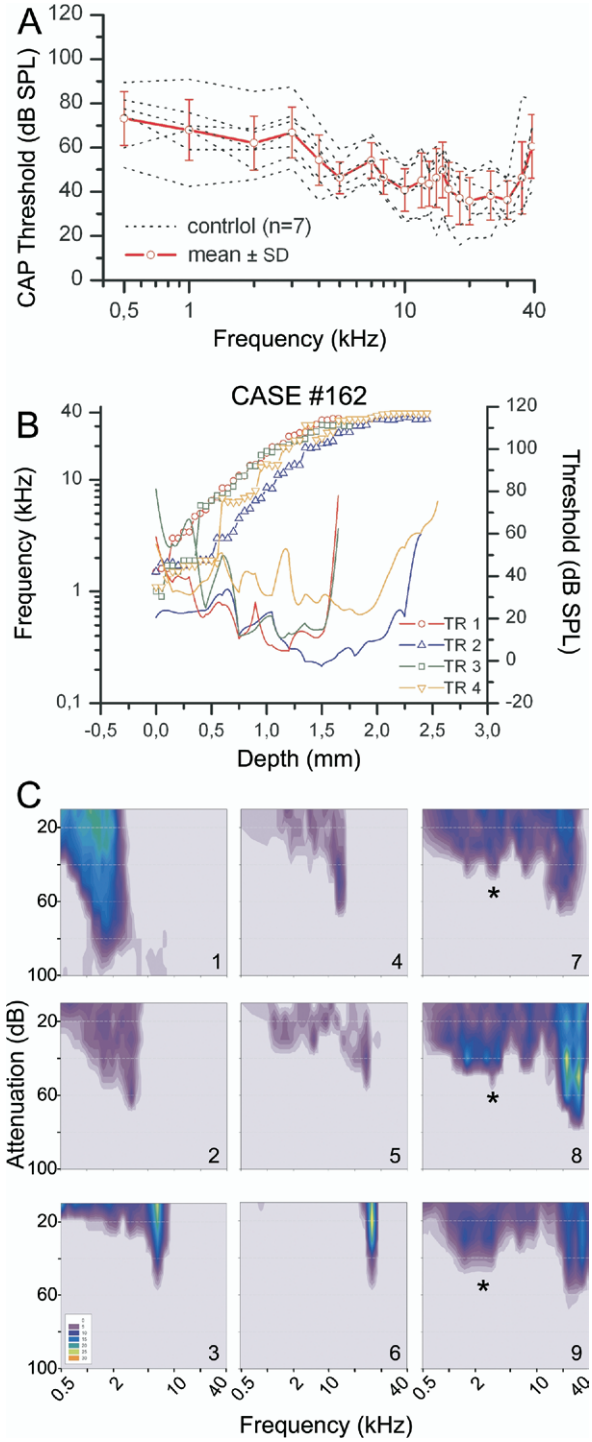

Fig. 1. Control data. (A) CAP audiograms for seven normal individual cases (dashed lines) and the corresponding mean CAP audiogram (mean±S.D.; open circles; red line). (B) Normal MU frequency organization from four penetrations across the CNIC for one normal animal (open symbols) and their corresponding thresholds (solid lines) as a function of recording depth. All tracks show a staircase pattern of progression of BFs. (C) Nine control FRAs from well isolated SUs (1–9) recorded from three different tracks across the CNIC. Asterisks indicate low frequency tails observed in high frequency FRAs. Color scale indicates number of spikes fired in response to two stimulus presentations. SPL, sound pressure level.