Neural Changes in Cat Auditory Cortex After a Transient Pure-Tone Trauma

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INTRODUCTION

It is now well known that cochlear damage can lead to profound CNS changes. For instance, a few weeks or months after a hearing loss induced by a mechanical lesion of the cochlea (Rajan et al. 1993; Robertson and Irvine 1989) or by an exposure to a traumatizing tone (Eggermont and Komiya 2000) the tonotopic organization in the primary auditory cortex (AI) is dramatically modified or reorganized. Moreover, a similar modification of the tonotopic map has been observed after a progressive high-frequency hearing loss (Willott et al. 1993). Cortical reorganization is defined as a shift in characteristic frequency (CF) of neurons with preloss CFs within the frequency band of the hearing loss, toward the edge frequencies of the hearing loss range that have near-normal thresholds. Importantly, cortical tonotopic maps are considered as reorganized only when the thresholds at each “new” CF are close to the peripheral threshold at that frequency. The definition of reorganization thus excludes shifts in CF resulting from residual low-frequency sensitivity of neurons at high intensities (Kaltenbach et al. 1992; Rajan and Irvine 1998). Changes in frequency tuning can be the result of unmasked inputs that were previously inhibited. Indeed, it has been demonstrated that cortical neurons receive divergent inputs coming from a relatively broad frequency band (Noreña and Eggermont 2002; Wang et al. 2000) and intracortical inhibition has been hypothesized to inhibit or “mask” some of these inputs (Noreña and Eggermont 2002; Phillips and Hall 1992; Rajan 1998, 2001; Wang et al. 2000). The inhibited inputs are usually those from frequency bands relatively remote from the neuron’s CF. The net effect of this balance between excitation and inhibition is a narrowing of the frequency response area. In addition, the inhibition/excitation balance also accounts for the neuron’s intensity selectivity by causing the rate–intensity function in some cases to be nonmonotonic. This can be quantified by a best intensity (BI), the intensity at which the firing rate (FRmax) is maximal (Rajan 1998, 2001; Salvi et al. 2000; Wang et al. 2000, 2002b). After a hearing loss, regions in the frequency band of the peripheral damage are hypothesized to provide less inhibition to neighboring and remote frequency regions (Salvi et al. 2000; Wang et al. 2002a). As a consequence, the thalamic inputs coming from regions remote from the initial CF are no longer—or substantially less—inhibited. This release from inhibition “unmasks” excitatory inputs at new frequency–intensity combinations of the stimulus and so may alter the neuron’s CF (Eggermont and Komiya 2000; Rajan et al. 1993; Robertson and Irvine 1989; Willott et al. 1993).

The time course of the central changes leading to tonotopic reorganization is still a matter of debate. This question is important because it pertains to the understanding of cortical plasticity. That is, if cortical reorganization is induced immediately (or within a short period) after a peripheral damage, then the central changes may solely reflect the modification of the balance between excitatory and inhibitory inputs. In other words, an immediate reorganization after a hearing loss would suggest that no additional mechanisms are needed beyond the unmasking phenomena described above (Salvi et al. 2000; Wang et al. 2002a). On the other hand, if cortical reorganization occurs only several weeks or months after the peripheral damage, it suggests that reorganization involves, in addition to the passive unmasking phenomenon, use-dependent plasticity potentially leading to long-term synaptic potentiation or even axonal sprouting (Buanomono and Merzenich 1998; Gilbert et al. 1996). A way to address this question is to study the immediate effect of a peripheral hearing loss on cortical tonotopic organization. To date, only one study (Calford et al. 1993) has addressed the question how a transient threshold shift caused by a few-minute exposure to a traumatizing tone induces complex changes in AI. In 12% of the neurons the cortical changes were related to the peripheral damage. How-
ever, 41% of the neurons showed an expansion of their frequency-response area and 18% showed a contraction. These latter changes suggested central modifications. Nevertheless, these latter central changes were much less dramatic than those observed several months after a large peripheral lesion (i.e., a systematic shift of CF was not observed). These findings thus suggest that additional mechanisms beyond the modification in the balance of inhibition and excitation are involved in the long-term tonotopic reorganization that follows a hearing loss.

On the other hand, a recent study (Snyder et al. 2000) showed that an acute lesion of the spiral ganglion induces an immediate and dramatic modification of the tonotopic map in the inferior colliculus (IC) similar to that observed in AI after chronic cochlear damage. Contrary to the study of Calford et al. (1993), Snyder et al.’s study suggests that no additional mechanisms beyond the change in the balance between excitation and inhibition are involved in the tonotopic reorganization after a hearing loss. The discrepancy between the 2 studies—the different amount of central changes—might be related to the degree of sensory deafferentation. In the study of Snyder et al. (2000), the mechanical lesions of a sector of the spiral ganglion resulted in the local removal of cochlear inputs coming from this region, a local or partial deafferentation. On the other hand, in the study of Calford et al. (1993), the exposure to the traumatizing tone was short and induced a small hearing loss, and thus only a local decrease of sensitivity.

To gain insight into the mechanisms involved in cortical tonotopic reorganization after a hearing loss, the nature of the cortical changes that followed an acute pure tone–induced hearing loss was assessed. We report the effects of an acoustic stimulation (SPL for 1 h), which produced a substantial hearing loss, on the hearing loss was assessed. We report the effects of an acoustic cortical changes that followed an acute pure tone loss, and thus only a local decrease of sensitivity.

Peripheral threshold estimation

Before acute recordings and in one-third of the cases after the end of the experiment, approximately 6 h after the exposure, peripheral hearing sensitivity was determined from auditory brain stem response (ABR) thresholds. ABRs were recorded in response to tone pips, with needle electrodes positioned in the ipsi- and contralateral muscles covering the mastoids with a ground electrode placed subcutaneously in the dorsal part of the neck region. Auditory stimuli were presented from a speaker 45° (at a distance of 55 cm) from the animal’s head. Calibration and monitoring of the sound field was accomplished with a Bruel and Kjær (type 4134) microphone positioned above the animal’s head and facing the loudspeaker. The gamma-shaped tone pips, with an effective duration of 15 ms at 50% from peak, were presented at frequencies of 3, 4, 6, 8, 12, 16, 24, and 32 kHz, at a rate of 10 times/s. The ABR signal was amplified (10,000×) between 300 and 3,000 Hz with a DAM 500 (WPI) differential amplifier and averaged with a Bruel and Kjær (type 2034) dual-signal analyzer in the signal enhancement mode. Artifact rejection, based on an amplitude criterion of 20 μV, and local lidocaine infusion (when required) were used to avoid contamination of ABR by muscle action potentials. The threshold was determined based on visibility and reproducibility of negative–positive waves, using 20–50 averages at high intensities, whereas at near-threshold intensities about 400 averages were obtained and repeated once. The step size was 10 dB, except around threshold where it was 5 dB. Threshold was defined as the lowest sound level that yielded a reproducible response.

Acoustic stimulus presentation

Stimuli were generated in MATLAB and transferred to the DSP boards of a TDT-2 (Tucker Davis Technologies) sound delivery system. Acoustic stimuli were presented in an anechoic room from a speaker system [Fostex RM765 in combination with a Realistic Super-Tweeter that produced a flat spectrum (±5 dB) ≤40 kHz measured at the cat’s head] placed approximately 30° from the midline into the contralateral field, about 50 cm from the cat’s left ear. Calibration and monitoring of the sound field was accomplished with a condenser microphone (Bruel and Kjær 4134) placed above the animal’s head, facing the speaker, and a measuring amplifier (Bruel and Kjær 2636).

The characteristic frequency and tuning properties of individual
neurons were determined using gamma-tone pips (Eggermont 1996). These tone pips with a half-peak–amplitude duration of 15 ms, and a gamma-function–shaped envelope, were presented at a rate of 1/s in a pseudo-random frequency order at fixed intensity level. The stimulus ensemble consisted of 5 identical sequences of 81 tone pips covering 5 octaves (with a tone separation of 1/16 octave), from 625 Hz to 20 kHz or from 1250 Hz to 40 kHz. The intensity series generally covered the range from 75 or 65 dB SPL to threshold in 10-dB steps. All the data in this study concerning the frequency–tuning properties and the driven firing rate of the neurons were derived from this procedure. Importantly, this time-consuming procedure was utilized ≥ 1 h after the trauma, when the neuronal responses were stable.

However, a fast procedure to estimate frequency-tuning curves was also used to assess immediate changes after the acoustic trauma. Here, 27 tone frequencies covering 5 octaves were presented at 6 different intensities (i.e., 5–55, 15–65, or 25–75 dB SPL), and each intensity–frequency combination was repeated 5 times. The rate presentation was 2/s, so this procedure lasted about 7 min.

The trauma-tone frequency was set at 5 or 6 kHz and presented for 1 h at the maximum output level. We used a power amplifier (Samson Servo 240) and speaker (Yorkville YS-112) positioned 75 cm to the left of the cat’s head. Measured at the cat’s head, the trauma tone fundamental frequency had a level of 115–120 dB SPL; whereas the second and third harmonics had a level 25 and 38 dB lower than that of the fundamental frequency, respectively.

Recording and spike separation procedure

Two arrays of 8 electrodes (Frederic Haer) each with impedances between 1 and 2 MΩ were used. The electrodes were arranged in a 4 × 2 configuration with interelectrode distance within rows and columns equal to 0.5 mm. Each electrode array was oriented such that all electrodes were touching the cortical surface and then were manually and independently advanced using a Narishige M101 hydraulic microdrive (one drive for each array). The signals were amplified 10,000 times using a Frederic Haer HiZx8 set of amplifiers with filter cutoff frequencies set at 300 Hz and 5 kHz. The amplified signals were processed by a DataWave multichannel data acquisition system. Spike sorting was done off-line using a semiautomated procedure based on principal component analysis (Eggermont 1990) implemented in MATLAB. The spike times and waveforms were stored. The multiunit data presented in this report represent only well-separated single units that, because of their regular spike waveform, likely are dominantly from pyramidal cells (Eggermont 1996). For statistical purposes, the separated single-unit spike trains were added again to form a multiunit spike train, thereby eliminating potential contributions from thalamocortical afferents or interneurons.

Data analysis

To assess frequency-tuning properties using the standard method, the peak number of action potentials in the poststimulus time histogram (PSTH, 5-ms bins) calculated over the first 100 ms after gammatone presentation was estimated. The peak counts for 3 adjacent frequencies were then combined, to reduce variability, and divided by the number of stimuli and presented as a firing rate per stimulus. This resulted in 27 frequency bins covering 5 octaves so that the final frequency resolution for determining the CF was about 0.2 octave. The results were calculated per stimulus intensity, and were combined into an intensity–frequency–rate profile from which tuning curves, rate–intensity functions, and isointensity rate–frequency contours could be derived (Eggermont 1996) using routines implemented in MATLAB. The frequency-tuning curve was defined for a firing rate at 25% of the maximum peak firing rate (FRmax). This was about 10–20% above the background firing rate, but because the latter was dependent on the level of stimulus-induced suppression, the tuning curve criterion based on a percentage of peak firing rate was preferred over that based on an increase over background activity. The values of firing rate given in this study are in spikes/s (sp/s). The number of spikes in a 5-ms bin is divided by the number of repetitions (5 repetitions over 3 frequencies = 15) times the bin size in seconds (0.005 s) (i.e., by 0.075). This gives very high values of FRmax when the MU spikes are well synchronized to the onset of stimulus. For the fast method, the same procedure was used.

The threshold was determined as the lowest intensity that produced visible time-locked responses to the tone pip. The tuning curve bandwidth (BW20dB) was measured at 20 dB above threshold and expressed in octaves. The 2 frequencies at the low and high side of the tuning curve (Flow20dB and Fhigh,20dB, respectively) at 20 dB above threshold were also analyzed. The best frequency (BF) and best intensity (BI) were defined as the frequency and intensity for which the firing rate was maximal, respectively. The index of monotonicity (IM) was obtained by dividing the maximum firing rate by the firing rate at the highest intensity level (Sutter et al. 1999).

All statistical analyses were performed using Statview 5 (SAS Institute, Cary, NC). Illustrations were made with SigmaPlot and Matlab.

RESULTS

Recordings were made from the right auditory cortex in 16 cats. The age of the cats ranged from 90 to 202 days (mean = 154 days, SD = 30.8 days). We recorded neural activity continuously from 124 MU clusters several hours before and up to 6 h after the pure-tone trauma. In 5 cats, ABR thresholds observed about 6 h after the induction of the acoustic trauma and compared with the pretrauma measures resulted in a broad hearing loss range from 6 to 32 kHz with an average 40 dB threshold increase (Fig. 1). However, in one animal the hearing loss region was separated by a normal patch around 12 kHz (filled triangles).

Individual examples

DOT DISPLAYS ACCORDING TO TIME AFTER THE PURE-TONE TRAUMA. As described in METHODS, the procedure used to measure the intensity–frequency responses of MUs (81 frequencies, between 4 and 9 intensities, 5 repetitions for each intensity–frequency combination) is relatively time-consuming. However, we wanted to address the stability of the MU

FIG. 1. Hearing loss about 5 h after exposure to loud pure tone in 5 individual cats. Mean curve (fat line) is also drawn in. In 4 of 5 cats hearing loss covered a large frequency range, but in one cat it consisted of 2 frequency regions separated by normal range about 12 kHz.
The panels represent the neural activity for the induced by a 5-kHz tone with this procedure is shown in Fig. 2. The panels represent the neural activity for the first 100 ms after tone pip onset (horizontal axis) as a function of frequency (vertical axis). The 3 panels in a column correspond to simultaneous recordings made from 3 different electrodes in the same array, and each panel in a row corresponds to recordings from the same electrode made at different times.

Immediately after the trauma (starting at 1 min), the response was strongly decreased for all 3 electrodes. Within 0.5 h after the trauma, the responses improved somewhat (compared with responses at 1 min). At 1 min after the trauma, Fig. 2, B and C both show the emergence of new responses, originating from a frequency band lower than the pretrauma response area (for 65 dB SPL at frequencies below \( \approx 6 \) kHz in Fig. 2B and below \( \approx 2 \) kHz in Fig. 2C). This example illustrates the very short time-course process involved in the appearance of new responses after an acoustic trauma. Furthermore, the increase in responses to frequencies below the pretrauma response area suggests a decrease in lateral inhibition. The MU responses recorded 23 min after the trauma are roughly similar to those recorded at 43 min and about 1.5 h after the trauma. This is typical of the observations in our study: the neural responses are initially decreased after the trauma, and then recover to some extent and/or change (increase in neural responsiveness, appearance of new responses) over the first 0.5 h after the trauma. Then, about 0.5 to 1 h after the trauma the pattern of responses stabilizes. Furthermore, it is interesting to note that different recording sites, even if they are spatially close, can be differentially affected by the trauma. For instance, the MU activity recorded from electrode 3 (Fig. 2A) is much decreased after the trauma compared with electrodes 5 and 6 (see inset), which are 0.5 and 0.7 mm away, respectively (Fig. 2, B and C). On the other hand, from 23 min after the trauma the responses are similar across the 3 electrodes.

**FREQUENCY-TUNING CURVES BEFORE AND AFTER THE PURE-TONE TRAUMA.** The following posttrauma data were all obtained several hours after the end of the exposure, when “asymptotic” values were reached. Figure 3 shows the tuning curves of two MU recordings with a CF below the trauma frequency, before the trauma (Fig. 3, A and D) and after the trauma (Fig. 3, B and E). Figure 3, C and F show the difference in firing rates post- and pretrauma, respectively. The 2 examples again illustrate that the acoustic trauma is followed by the emergence of new responses. For the MU recording shown in the top panels of Fig. 3, the new responses emerge in the same general frequency range as that of the pretrauma response area but are stronger and show reduced thresholds. For the MU recording shown in the bottom panels of Fig. 3, the new responses emerge to lower and higher frequencies (at intensities above 60 dB SPL and frequencies below \( \approx 2 \) kHz and above \( \approx 4 \) kHz; Fig. 3, E and F).

Figure 4 shows a set of tuning curves obtained before (top panels) and after (bottom panels) the trauma for MUs with a CF above the trauma-tone frequency. The dot displays previously shown in Fig. 2C correspond to the tuning curves shown in Fig. 4, B and F. A common feature encountered after a trauma was a decrease in CF for MUs with a pretrauma CF above the trauma-tone frequency; this change is illustrated in Fig. 4, A and E. Interestingly, this decrease in CF is not associated with an elevation of threshold. In some rare cases, the threshold at CF is even improved after the trauma (Fig. 4, C and G). As already illustrated in Figs. 2 and 3, a large number of recordings showed the emergence of new responses after the trauma. New responses appear more frequently within the frequency band below that of the former response area (Fig. 4, A and E and B and F). However, the new responses can also occur within the frequency band above the pretrauma response area (Fig. 4, D and H).

Figure 5 shows the difference in firing rate between the post- and pretrauma conditions for cases shown in Fig. 4. Figure 5 is
In Fig. 5, A and B a decrease in response for frequencies above the trauma-tone frequency is found; this probably reflects the cochlear damage induced by the trauma. On the other hand, firing rates are increased in the frequency band below the trauma frequency; this increase can extend to regions just above the trauma-tone frequency as shown in Fig. 5B. In Fig. 5C (note different frequency scale) one observes that the responses are increased at all intensity–frequency combinations of the pretrauma tuning curve. This increase in responsiveness is pronounced at a relatively low intensity level (between 30 and 40 dB SPL). In Fig. 5D, the responses are increased in the frequency band above the trauma frequency.

Figure 6 shows tuning curves that illustrate a contraction of the response area that is sometimes noted after the trauma. The top row shows a case where the CF (Fig. 6A) was below the trauma-tone frequency; the tuning curves are narrower after the trauma, whereas the threshold at CF is decreased (Fig. 6B). Figure 6C shows the difference in firing rates post- and pre-trauma and illustrates a decrease of responsiveness (contraction) within the frequency region <2 kHz. On the other hand, the responses were slightly increased above 2 kHz. The response areas shown in Fig. 6, D and E also illustrate a strong contraction of the response area with a slight increase in CF and threshold resulting from a decrease in response throughout the pretrauma response area (Fig. 6F).

**Group data**

The following averaged posttrauma data were all obtained several hours after the end of the exposure, when “asymptotic” values were reached.
Changes in Frequency Tuning. Figure 7A shows the difference between post- and preexposure thresholds at CF (CF threshold shift) as a function of the difference between the preexposure CF and the trauma-tone frequency. Figure 7B shows the threshold shift averaged into 3 frequency bands. The “Below” group (Be) corresponds to MU recordings with a CF below the trauma-tone frequency. The Ab1 group corresponds to MU recordings with a CF ≤1 octave above the trauma-tone frequency and the Ab2 group corresponds to MU recordings with a CF more than one octave higher than the trauma-tone frequency. One notes, first, that the threshold is increased in all groups, and second that the elevation of MU thresholds is largest for the Ab2 group. The threshold shift was statistically tested using a one-sample t-test with a hypothesized mean of zero. Furthermore, because we made 3 comparisons (1 for each group), we applied a Bonferroni correction to the statistics. That is, we considered the results as significantly different from 0 only if \( P < 0.017 \) (0.05/3). The same correction was applied to the other statistical tests used later on in this study. All groups showed a significant elevation of the threshold [Be: \( t(42) = 2.864, P = 0.0065 \); Ab1: \( t(42) = 4.359, P < 0.0001 \); Ab2: \( t(34) = 6.768, P < 0.0001 \)].

Figure 8, A and D show the pre- and posttrauma BF as a function of the pre- and posttrauma CF, respectively. One notes that before the trauma, CF and BF are very similar, whereas they can be largely different after the trauma. Figure 8, B and E show the CF and BF changes as a function of the difference between the preexposure CF and the trauma-tone frequency. Figure 8, C and F show the CF and BF changes averaged into the 3 frequency bands described above. The CF was not significantly changed for Be and Ab1 groups, whereas it was significantly decreased for the Ab2 group \( t(33) = -3.822, P = 0.0006 \). For the BF, the changes were also significant only for the Ab2 group; the BF decreased significantly \( t(33) = -3.69, P = 0.0008 \).

Figure 9A shows the pre- and postexposure BW_{20dB} as a function of pre- and postexposure CF, respectively. One notes, as shown before (Noreña and Eggermont 2002) that there is no dependency between MU CF and BW_{20dB} expressed in octaves. Figure 9B shows the change in BW_{20dB} (ratio between post- and pre-BW_{20dB}) as a function of the difference between the preexposure CF and the trauma-tone frequency. Figure 9C shows the changes in BW_{20dB} averaged into 3 frequency bands. The BW_{20dB} did not significantly change for the Be group. On the other hand, the BW_{20dB} increased by a factor of about 1.5 and 1.6 after the traumatizing exposure for Ab1 and Ab2 groups, respectively. However, the change in BW_{20dB} was significant only for the Ab1 group \( t(39) = 2.6, P = 0.013 \).

The changes of the 2 frequencies at the low and high side of the tuning curve at 20 dB above threshold (Flow_{20dB} and Fhigh_{20dB}, respectively) were also analyzed. In the Ab2 group, the Flow_{20dB} and Fhigh_{20dB} were significantly decreased \( t(25) = -5.4, P < 0.0001, t(23) = -4.26, P = 0.0003, \) respectively, corroborating the already suggested downward shift of the entire tuning curve (cf. Figs. 2, 4, and 8). For Be and Ab1 groups, the averaged changes were small and not significant.

Changes in CF and Fhigh_{20dB} were not significantly correlated with the threshold shift (R^2 = 0.008 and 0.011, P = 0.34 and 0.32, respectively), whereas the BF was only slightly correlated with threshold shift (R^2 = 0.038, P = 0.034). On the other hand, Flow_{20dB} changes were negatively correlated with the threshold shift (R^2 = 0.23, P < 0.0001), whereas BW_{20dB} changes were positively correlated with the threshold shift (R^2 = 0.14, P = 0.0002).
CHANGES RELATED TO DRIVEN FIRING RATE. Figure 10 shows the change (ratio) in the IM (a larger value indicates increased monotonicity) averaged into 3 frequency bands (see METHODS). Figure 10, B and C show the difference in the BI (the intensity at which the firing rate is maximal) and the change (ratio) in maximum firing rate ($FR_{\text{max}}$), respectively. The IM increased on average for the 3 groups but the increase was significant only for the Be group [$t(39) = 4.02, P = 0.0003$]. The BI and $FR_{\text{max}}$ were significantly increased only for the Be [$t(38) = 3.04, P = 0.0043, t(43) = 2.57, P = 0.0139$, respectively] and Ab2 [$t(33) = 2.89, P = 0.0069, t(34) = 3.28, P = 0.0024$, respectively] groups.

CHANGES IN THE TEMPORAL PATTERN OF MU DISCHARGES. The results presented above indicate that the neural properties, in terms of averaged peak driven firing rates, are changed after an exposure to a loud tone. In addition, as illustrated in Fig. 11, the temporal pattern of the evoked discharges is also changed after an acoustic trauma. The dot displays of MUs recorded before (top panels) and after the trauma (bottom panels) at 7 intensity levels (from 5 to 65 dB SPL, in 10-dB steps) corresponds to those for which the tuning curves were shown in Fig. 4, D and H. At higher intensities (>25 dB SPL), the tone-evoked response is much shorter in duration after the trauma compared with that before the trauma. Indeed, before the trauma, a stimulus-locked response around CF is noted ≤60 ms after the onset of the stimulus, whereas after the trauma, the response lasts up to only 35 ms (with a minimum latency of 20 ms, dotted vertical lines). In this example the changes in the temporal pattern of the firing rate were not accompanied by a CF shift (see also Fig. 4, D and H). The shorter response duration after the trauma combines with a strong and long-lasting inhibition of the spontaneous firing rate (SFR) that follows the response (postactivation suppression). Figure 12 shows the PSTHs (5-ms bins) of the dot displays represented in Fig. 11 taken at CF (11.9 kHz). After the trauma (full line), the peak MU activity is higher than that before the trauma (dotted line) for bins with a starting time window at 15, 20, and 25 ms. On the other hand, between 35 and 65 ms after the stimulus onset the MU activity is lower after the trauma than before. The FR calculated over a 100-ms time window after stimulus onset is higher for the before condition (horizontal dotted line) than for the after condition (horizontal full line), largely because of spontaneous firings.

To further analyze the potential effect of the trauma on the temporal pattern of MU discharges at BF, we averaged the PSTHs of all MU recordings used in the previous analyses (frequency-tuning properties). The averaged PSTHs before and after the trauma were grouped in relation to the frequency band
and intensity. We distinguished 3 intensity groups: Int1 ($\leq 40$ dB SPL), Int2 (45–60 dB SPL), and Int3 (65 dB SPL). Figure 13 shows the averaged PSTHs at each intensity group, before and after the acoustic trauma, for the Be group (Fig. 13, A, D, and G), Ab1 group (Fig. 13, B, E, and H), and the Ab2 group (Fig. 13, C, F, and I), respectively. Figure 14 show the average difference between the pre- and posttrauma PSTHs at each intensity group, for the Be group (Fig. 14, A, D, and G), Ab1 group (Fig. 14, B, E, and H), and the Ab2 group (Fig. 14, C, F, and I), respectively. For each bin, the changes in PSTH (after vs. before the trauma) were statistically tested using a one-sample t-test analysis with a hypothesized mean of 0. Because we compared PSTHs for 20 different bins, we carried out a Bonferroni correction and a difference between the pre- and postexposure was considered as significantly different from 0 only if $P < 0.0025$ (0.05/20). For the Be group at Int3 (Fig. 13G), one observes that the averaged FR$_{\text{max}}$ is increased by about a factor of 2 after the tone exposure. The firing rate increase was statistically significant for bins with a starting time at 20 ms [$r(72) = 3.596, P = 0.0006$], 25 ms [$r(72) = 4.37, P < 0.0001$], and 30 ms [$r(72) = 4.074, P = 0.0001$, Fig. 14G]. However, in this intensity group, the temporal pattern of the response is not shortened; that is, there is no significant decrease in any bin after the trauma. In other words, the postactivation suppression is not significantly different between the pre- and the posttrauma condition. On the other hand, in the Be and Ab1 groups at Int2 (Figs. 13D, 14D and 13E, 14E, respectively), the sustained (increased) activity related to the presentation of the stimulus lasts longer before the trauma than after the trauma. For this intensity group (Int2), the shorter activation of neurons after the trauma occurs without any change in the maximum value of the averaged FR, which is not significantly different between the pre- and postexposure conditions (bins 30–35 ms in the Be group and bins 20–25 and 25–30 ms in the Ab1 group). In the Be group at Int2 (Fig. 14D), the preexposure FR is significantly higher than the postexposure FR for bins with a starting time at 40 [$r(80) = -3.66, P = 0.0005$], 45 [$r(80) = -5.32, P < 0.0001$], and 50 ms [$r(80) = -3.616, P = 0.0005$]. Similarly, for the Ab1 group at Int2 (Fig. 14E), the preexposure FR is significantly higher than the postexposure FR, for the 6 bins with starting times from 30 and 55 ms ($-4.492 < r(81) < -3.254, 0.0001 < P < 0.0017$). Changes in FR for the Ab2 group at Int2 were not significant (Fig. 14F). Finally, the FR is significantly decreased for the Be (Fig. 14A) and Ab2 groups at Int1 (Fig. 14C), that is, between 25 and 45 ms for the Be group ($-4.761 < r(64) < -3.323, 0.0001 < P < 0.0015$), and
The results of the present study can be summarized as follows. First, the frequency tuning of cortical neurons is changed after a pure-tone–induced hearing loss. This hearing loss was initially fairly severe, judging from the threshold increase of the MU recordings, but recovered so that about 5 h after the exposure it was on average 40 dB in the frequency range above 6 kHz as estimated by auditory brain stem recordings. For neurons with a CF more than one octave above the trauma-tone frequency, the CF and BF are shifted on average toward the trauma-tone frequency. Second, the input–output properties of neurons are also modified after a noise trauma; that is, the degree of monotonicity increases for neurons with a CF below the trauma-tone frequency, and maximum evoked firing rate and the best intensity are significantly increased for neurons with CFs below and more than one octave above the trauma-tone frequency. Finally, the onset response produced by the presentation of the gamma tones is on average much shorter after the trauma than before, whereas its peak value stays the same or is increased.

**DISCUSSION**

Our recordings, after spike sorting and adding the sorted units together, are not specific to what happens to single-unit activity. However, several facts suggest that during our long recording sessions from the same electrode sites, ≥75% of the single units recorded from were the same across the entire time span. A difficulty in assessing the continuous recording of the same units is that we had to cease recording during the exposure because of electrical interference from the speaker. Thus we could rely only on the spike waveforms and amplitudes. Another difficulty is that we periodically resorted the spike trains (typically every 2–3 h). This resorting of spikes recorded over 2- to 3-h blocks of recorded data allowed us to adapt to slowly changing spike amplitudes. Cortical regular spiking neurons, the only ones that could be recorded for long periods of time, tend to have fairly similar, negative–positive–negative, spike waveforms with the units characterized mainly by differences in amplitude. After about 1 h of recording at the same site, very little change in the makeup of the spike waveforms was found. All recordings used in the pre-/posttrauma comparison were obtained after that initial period. In an uninterrupted 2-h block of recordings ≥90% of the units stayed the same, as based on amplitude distributions. However, after new spike sorting for data collected in the next 2- to 3-h block, units could be assigned to a different class (without being a different neuron). We did not attempt to relabel neuron classes. However, the frequency-tuning properties did not change. Of course, as a function of time after the trauma, thresholds could between 35 and 45 ms for Ab2 groups (−4.492 < t(66) < −3.281, 0.0001 < P < 0.0017).

**Stability of recordings**

The results of the present study can be summarized as follows. First, the frequency tuning of cortical neurons is changed after a pure-tone-induced hearing loss. This hearing loss was initially fairly severe, judging from the threshold increase of the MU recordings, but recovered so that about 5 h after the exposure it was on average 40 dB in the frequency range above 6 kHz as estimated by auditory brain stem recordings. For neurons with a CF more than one octave above the trauma-tone frequency, the CF and BF are shifted on average toward the trauma-tone frequency. Second, the input–output properties of neurons are also modified after a noise trauma; that is, the degree of monotonicity increases for neurons with a CF below the trauma-tone frequency, and maximum evoked firing rate and the best intensity are significantly increased for neurons with CFs below and more than one octave above the trauma-tone frequency. Finally, the onset response produced by the presentation of the gamma tones is on average much shorter after the trauma than before, whereas its peak value stays the same or is increased.

**FIG. 9.** Effects of acoustic trauma on BW$_{20\text{dB}}$. A: pre- (open symbols) and posttrauma (closed symbols) BW$_{20\text{dB}}$ as function of pre- and posttrauma CF. B: changes in BW$_{20\text{dB}}$ as function of difference between pretrauma CF and trauma-tone frequency. C: changes in BW$_{20\text{dB}}$ averaged into 3 frequency bands (±SE; *P < 0.017).

**FIG. 10.** Effects of acoustic trauma on index of monotonicity (IM), best intensity (BI), and peak firing rate (FR$_{\text{max}}$). A, B, and C: changes in IM, BI, and FR$_{\text{max}}$ averaged into 3 frequency bands, respectively (±SE; *P < 0.017).
change and so could firing rate. Occasionally, new units emerged and this was always accompanied by a sudden change in firing rate for the MU recording. These new units invariably had the same tuning properties as the remaining ones. Similarly a sudden drop in MU firing rate announced the loss of one or more units. A worst-case scenario (change of one unit out of the 4 sorted on any given electrode), would still have ≥75% of the units the same hours after the trauma to those before the trauma.

Comparison to other studies

To our knowledge, only two studies have studied the immediate effect of an acoustic trauma on neural properties in AI (Calford et al. 1993; Kimura and Eggermont 1999). The pioneering study of Calford et al. (1993) showed complex neural changes after a short exposure to a traumatizing tone with a frequency set at 0.5 octave below the CF of the studied neurons. On the one hand, 12% of the neurons were classed as “auditory-nerve like” because the peripheral hearing loss accounted for the changes in response area, just as it would for auditory nerve fibers. On the other hand, 59% of the neurons showed changes after the trauma that could not be accounted for by peripheral hearing loss alone. Indeed, the tuning curve was expanded in 41% of the neurons after the trauma and contracted in 18% of the neurons after the trauma. Our findings
are largely consistent with those of Calford et al. (1993) showing that the major effect of an acoustic trauma is to induce an expansion of the neurons’ response area, that is, the emergence of unmasked responses (Figs. 2, 3, 4, and 5). In addition, we also noted for some MUs a contraction of the response area (Fig. 6). These results suggest that both an increase and a decrease in inhibition follow an acoustic trauma.

In another study, Kimura and Eggermont (1999) focused on the effect of an acoustic trauma induced by a pure tone with a frequency set at about 0.5 octave above the highest neuron’s CF. In this case, the traumatizing tone is not supposed to induce major peripheral damage in the frequency band corresponding to the neurons’ response area (at least around the neuron’s CF). After the trauma, the thresholds at CF were only slightly elevated (6 dB in average) but the CF was significantly shifted toward lower frequencies. These results can be compared with those of the Be group in our study. The threshold shift is very similar in the 2 studies, but in our study the CF was not significantly changed. It is important, however, to point out that the difference reported by Kimura and Eggermont (1999) was very small (0.1 octave in average). More important, it was noted that neural responsiveness increased after the trauma, corroborating our finding that the FR max is significantly increased in the Be group. Interestingly, MU activity and local field potentials (LFPs) were recorded simultaneously. Because the locally negative phase of the LFPs reflect summed excitatory postsynaptic potentials of cortical cells (Mitzdorf 1985) evoked by thalamic input, the comparison between LFP and MU activity then allowed intracortical inhibition to be inferred (Noreña and Eggermont 2002). When LFP responses were enhanced after the trauma, MU response areas were usually similarly affected. Consequently, these results suggest that cortical changes after an acoustic trauma may involve a release from inhibition both at cortical and subcortical levels.

**Subcortical findings after noise trauma**

Numerous studies have focused on the immediate effect of a peripheral damage at subcortical levels, that is, at auditory nerve (Lonsbury-Martin and Meikle 1978), cochlear nucleus (Lonsbury-Martin and Martin 1981; Salvi et al. 1996; van Heusden and Smoorenburg 1983), and inferior colliculus (Snyder and Sinex 2002; Wang et al. 1996) levels. One has to keep in mind that the procedures used to induce a peripheral damage (duration and intensity level of the traumatizing stimulus, for instance) as well as the anesthetic used differ over the different studies making a comparison between the various results difficult. However, it is interesting to address at each level, the type and the extent of the neural changes caused by the peripheral lesion, to determine the potential contribution from each central station to the changes we observed in AI.

At the auditory nerve level, cochlear damage is usually followed by a decrease in the driven firing rate and the SFR (Dallos and Harris 1978; Kiang et al. 1970; Liberman and Dodds 1984; Lonsbury-Martin and Meikle 1978; Salvi et al. 2000). These changes reflect the loss of sensitivity at the cochlear level attributed to the induced damage. Both in acute and chronic conditions, a noise trauma is known to damage inner and outer hair cells around and above the trauma frequency (Kaltenbach et al. 1992; Liberman 1987; Liberman and...
Moreover, a noise trauma has been shown to induce a massive destruction (sometimes reversible) of the auditory nerve fiber neurites synapsing with the inner hair cells that are strongly excited by the trauma stimulus (Puel 1995). The large amount of glutamate release is likely responsible for this type of damage (excitotoxicity). It is important, however, to mention here that sound exposure in the present study using ketamine, an NMDA antagonist, produced much less damage (Giraudet et al. 2002), potentially by a reduced excitotoxicity. In summary, the changes at the auditory nerve level do not account for some of the changes we observed in AI (e.g., an increase in the driven firing rate). Thus at more central levels, the changes in neural responses after peripheral damage are more complex and suggest the involvement of additional changes. For instance, as early as the cochlear nucleus, an acoustic trauma can induce an increase in the driven firing rates. In the ventral cochlear nucleus (VCN), Boettcher and Salvi (1993) showed that a traumatizing tone above the neurons’ CF could enhance the maximum driven firing rate at CF by a factor of ≈1.25. This increase was observed in <20% of all the neurons and occurred only in neurons with inhibitory sidebands above CF. Furthermore, an exposure to a 105-dB SPL-pink noise over 0.5 h (causing a threshold shift of 30 dB in average) did not significantly change the SFR (van Heusden and Smoorenburg 1983). The shape of the PSTH also was not changed after the trauma (Boettcher and Salvi 1993).

In the dorsal cochlear nucleus (DCN), a subset of neurons (about 20–25%) with a CF below the trauma-tone frequency showed an increase in their responsiveness after an acoustic trauma (Salvi et al. 1996). The threshold in the low-frequency tail of the tuning curve could be decreased by as much as 40 dB, whereas these changes were not observed in VCN (Boettcher and Salvi 1993). Moreover, the discharge rate in the latter frequency band could be increased by a factor of ≈4. Similarly to the VCN, neurons in the DCN showing increased responses after the trauma were those with strong inhibitory sidebands. In some cases, the SFR increased (Salvi et al. 1996).

In the inferior colliculus (IC), some studies have focused on the immediate effect of an acoustic trauma (Salvi et al. 1990; Wang et al. 1996) or a lesion of the spiral ganglion (Snyder and Synex 2002; Snyder et al. 2000) on the response properties of neurons. Salvi et al. (1990) showed that the amplitude of LFP, at frequencies below the trauma-tone frequency, increased after an acoustic trauma by as much as a factor of 4. Interestingly, the LFP amplitude was sometimes slightly increased at moderate intensity level within the frequency band above the trauma frequency (i.e., in the frequency band of the hearing loss). In the study of Wang et al. (1996), single-unit recordings were obtained before and after an exposure to a trauma tone with a frequency above the neuron’s CF. The results revealed that the driven firing rate was enhanced in 70% of all neurons studied after the trauma (93% of neurons with strong non-monotonic discharge rate-level functions) by a factor of ≈5. The increase in driven firing rate was found at both the low- and high-frequency edge of the tuning curve. In addition, the maximum driven firing rate was also increased by a factor of ≈1.5. In contrast, neurons with V-shaped tuning curve were generally unaffected by the trauma. Finally, the SFR was not significantly changed after the trauma.
In summary, some changes seen in the DCN and IC (occurrence of a hypersensitive low-frequency tail after a trauma) are consistent with, but likely different from, our observations (Figs. 2, 3, 4, and 5). However, other changes in the DCN are too small to account for those occurring in the IC and AI. That is, the increase in driven firing rate is on average greater in IC and AI and more neurons show changes in their discharge properties (Wang et al. 1996). Subsequently, one can ask whether the changes observed in IC can account for those in AI. Because the studies described above focused on the effect of damage induced by a trauma tone with a frequency above the neuron’s CF, we will limit the comparison of these results to the Be group of our study. Similarly to what was found in the IC, we observed in our study an increase in the evoked firing rate at the low- and high-frequency edge of the neurons’ tuning curve after the trauma. The maximum driven firing rate was on average also increased by the same amount, a factor of 1.6 in our study and 1.5 in that of Salvi et al. (1996). Thus at least some of the cortical changes observed after an acoustic trauma reflect subcortical changes, especially those occurring in the IC.

The changes in CF that follow peripheral damage are usually attributed to an unmasking of existing inputs (Calford et al. 1993; Kimura and Eggermont 1999; Salvi et al. 2000; Wang et al. 1996, 2002a). Indeed, it is known that the response area of central neurons is narrower than that of their excitatory inputs (Noreña and Eggermont 2002; Wang et al. 2000). A stimulus-dependent central inhibition is involved in the relative sharp frequency tuning of neurons (Muller and Scheich 1988; Noreña and Eggermont 2002; Rajan 1998, 2001; Shamma and Symmes 1985). Moreover, a tonic central inhibition from neighboring and remote frequency bands also participates in the frequency-tuning properties of neurons. This tonic inhibition is considered to depend on the spontaneous firing rates of the excitatory neurons that drive the inhibitory interneurons (Jones 1990). When a portion of the peripheral receptor is damaged, the excitatory inputs coming from the periphery are decreased, inducing at a central level a decrease in the tonic inhibition. The net, and paradoxical, effect of this imbalance between excitation and inhibition could then be an increase in excitation (Salvi et al. 2000; Wang et al. 2000, 2002b). This hypothesis can account for the expansion of the response area and for the increase in firing rate that we observed in our study.

Comparison to chronic trauma effects

One can wonder now, whether in our study, the acoustic trauma is followed by tonotopic reorganization similar to that after chronic cochlear damage (Eggermont and Komiya 2000; Rajan et al. 1993; Robertson and Irvine 1989; Willott et al. 1993). Figure 8, B and E and C and F suggests that the tonotopic map is disturbed between one and 2 octaves above the trauma-tone frequency (i.e., between 10 and 20 kHz). In this frequency region both the CF and BF are reduced by 0.64–0.74 octave. However, this potential “reorganization” clearly does not match that induced after a chronic cochlear lesion. First, the threshold is significantly increased in the Ab1 and Ab2 groups and there is not a clear overrepresentation of a narrow frequency band at the edge of the hearing loss (between 5 and 10 kHz). Nevertheless, it is important to emphasize that the modification of the tonotopic map a few hours after transient trauma is not explicable in terms of the residual sensitivity of the neurons (Kaltenbach et al. 1992; Rajan and Irvine 1998). Indeed, we showed that the changes in frequency tuning were not correlated with the threshold shift. In addition, examples shown in Fig. 4 also argue against residual responses in explaining the CF shift. Indeed, in these examples, the CF is shifted toward lower frequencies, whereas the threshold at CF is not changed (Fig. 4, A and E) or even improved (Fig. 4, C and G). In conclusion, it is suggested that the neural changes observed after an acute acoustic trauma mostly reflect the unmasking of previously inhibited responses caused by the change in balance between excitation and inhibition. However, as already suggested by Calford et al. (1993), it appears that the tonotopic reorganization observed after chronic cochlear damage involves use-dependent plasticity beyond the simply unmasking phenomena.

The hypothesis stating that tonotopic reorganization induced by peripheral damage necessitates weeks or months to occur is not corroborated by 2 recent studies (Snyder and Sinex 2002; Snyder et al. 2000). In these latter studies, a small portion of the spiral ganglion was damaged, inducing a local deafferentation (i.e., a local removal of afferent inputs coming from this frequency band). Interestingly, such an acute spiral ganglion lesion changed the tonotopic organization in the IC (Snyder et al. 2000) in such a way that the new organization was similar to that obtained in AI after a chronic mechanical lesion in the cochlea (Rajan et al. 1993; Robertson and Irvine 1989). This result suggests that modification of the tonotopic map can occur immediately after peripheral damage, and that these changes do not necessarily involve use-dependent plasticity (Snyder et al. 2000). A major difference between the latter studies and our study is the amount of induced deafferentation, which is of lesser extent after an acoustic trauma. The critical variable to induce an immediate tonotopic reorganization may then be the amount of sensory deafferentation. In Snyder et al.’s study, a portion of the nerve fibers are destroyed (i.e., the inputs coming from the corresponding frequency region are removed). On the contrary, an acoustic trauma (as that used in the present study) does not destroy all hair cells or auditory nerve fibers within the damaged region (Kaltenbach et al. 1992; Liberman 1987; Liberman and Dodd 1984, 1987; Salvi et al. 1990). The best demonstration of this is the fact that cortical neurons are still responding in the frequency region above the trauma-tone frequency. Nevertheless, Eggermont and Komiya (2000) showed that a permanent moderate hearing loss induced tonotopic reorganization in AI. This study suggests that use-dependent plasticity is necessary to account for the cortical tonotopic reorganization when the hearing loss is only moderate.

Changes in inhibition

Our finding of unmasking phenomena suggests that the acoustic trauma-induced hearing loss caused a decrease in lateral inhibition. However, some of our findings can be paradoxically interpreted as reflecting an increase in inhibition. First, the response area was sometimes contracted at frequencies below the trauma frequency, that is, within a frequency band where it is unlikely that the trauma induced peripheral damage (Fig. 6). Second, the duration of the response related to the presentation to the gamma tones was significantly shorter.
after the trauma than before (Figs. 11–14). Interestingly, an unmasking and a contraction of responses can be observed in the same MU (Fig. 6, A and B), as well as an unmasking of responses, an increase in the driven firing rate, and a shortening of the sustained responses (Figs. 4, D and H, 11, and 12). These results then suggest that both an increase and a decrease in inhibition can coexist, affecting in parallel the same MU.

A recent study, focusing on the effects of bicuculline (GABA \(_\text{A}\) blocker) in AI, showed PSTH changes in onset-rebound similar to ours after a trauma (Wang et al. 2002b). That is, bicuculline induced an increase in the onset response (in terms of firing rate), suggesting a release from inhibition and an elongation of the quiet period after the onset response. This result strongly suggests that GABAergic mechanisms play an important role in the PSTH changes we observed in our study.

At first sight, the shortening of the sustained response could be accounted for by a delayed feed-forward or feed-back inhibition related to the amount of the onset response. That is, inhibition related to the amount of the onset response. That is, bicuculline induced an increase in the onset response (in terms of firing rate), suggesting a release from inhibition and an elongation of the quiet period after the onset response.

This result strongly suggests that GABAergic mechanisms play an important role in the PSTH changes we observed in our study.

Rajan (2001) proposed a model in which surround and in-field inhibitions are differentiated. He hypothesized that a (moderate) hearing loss decreases the surround inhibition. He further suggested that a release from surround inhibition could unmask in-field inhibition. The release from surround inhibition after a cochlear damage (supposed to be tonic in this case) might then explain the unmasking of excitatory responses, and potentially the tonotopic reorganization, within and at distance from the peripheral lesion as well as the increase in \(\text{FR}_{\text{max}}\) and index of monotonicity. The unmasking of in-field inhibition might also account for the contraction of the neurons’ response area observed in our study (Fig. 6) and that of Calford et al. (1993) after the trauma. Moreover, if the occurrence of in-field inhibition is delayed compared with the excitatory onset response (Volkov and Galazuk 1991), the sustained response should be shortened whatever the strength of the onset response.

In summary, it has been shown that an acute acoustic trauma changed the neural responses in cat AI, in terms of their frequency-tuning properties and driven discharges. Importantly, the frequency-tuning changes did not match those observed after long-standing cochlear damage. In particular, above the trauma frequency the CF changes were not systematic and thresholds were on average elevated. Additional mechanisms may thus be involved in the tonotopic map reorganization, at least that induced after an acoustic trauma (Eggermont and Komiya 2000). The acoustic trauma also induced a contraction of the neurons’ response area and a shortening of the increase in discharge produced by the presentation of a tone at the neurons’ BF. These results suggest that, in addition to a release from a tonic inhibition, an acoustic trauma may also increase certain types of inhibition.

**REFERENCES**


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