Disruption of Balanced Cortical Excitation and Inhibition by Acoustic Trauma

Ben Scholl and Michael Wehr

Institute of Neuroscience and Department of Psychology, University of Oregon, Eugene, Oregon

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Scholl B, Wehr M. Disruption of balanced cortical excitation and inhibition by acoustic trauma. J Neurophysiol 100: 646-656, 2008. First published June 4, 2008; doi:10.1152/jn.90406.2008. Sensory deafferentation results in rapid shifts in the receptive fields of cortical neurons, but the synaptic mechanisms underlying these changes remain unknown. The rapidity of these shifts has led to the suggestion that subthreshold inputs may be unmasked by a selective loss of inhibition. To study this, we used in vivo whole cell recordings to directly measure tone-evoked excitatory and inhibitory synaptic inputs in auditory cortical neurons before and after acoustic trauma. Here we report that acute acoustic trauma disrupted the balance of excitation and inhibition by selectively increasing and reducing the strength of inhibition at different positions within the receptive field. Inhibition was abolished for frequencies far below the trauma-tone frequency but was markedly enhanced near the edges of the region of elevated peripheral threshold. These changes occurred for relatively high-level tones. These changes in inhibition led to an expansion of receptive fields but not by a simple unmasking process. Rather, membrane potential responses were delayed and prolonged throughout the receptive field by distinct interactions between synaptic excitation and inhibition. Far below the trauma-tone frequency, decreased inhibition combined with prolonged excitation led to increased responses. Near the edges of the region of elevated peripheral threshold, increased inhibition served to delay rather than abolish responses, which were driven by prolonged excitation. These results show that the rapid receptive field shifts caused by acoustic trauma are caused by distinct mechanisms at different positions within the receptive field, which depend on differential disruption of excitation and inhibition.

INTRODUCTION

In auditory cortical neurons, excitatory and inhibitory synaptic inputs are balanced across a wide range of stimulus conditions. Throughout the receptive field, tones of different frequencies and amplitudes evoke excitation and inhibition in a nearly constant magnitude ratio for a given neuron (Tan et al. 2004; Wehr and Zador 2003). Even during the suppression caused by repetitive stimuli, this ratio remains essentially unchanged (Wehr and Zador 2005). This suggests that the balance of excitation and inhibition is tightly regulated in cortical circuits (Liu 2004). It remains an open question under what conditions this balance may be disrupted and what effects such a disruption may have on cortical function.

A disruption of the balance of excitation and inhibition has been proposed to underlie the rapid receptive field changes seen in cortical cells after denervation and similar peripheral manipulations. Receptive field expansion, contraction, and shifts have been seen immediately after denervation in the somatosensory cortex (Calford and Tweedale 1991; Rasmus-

son and Turnbull 1983), retinal lesions or artificial scotoma in the visual cortex (Gilbert et al. 1996; Schmid et al. 1995), and acoustic, mechanical, or drug-induced trauma in the auditory cortex (Calford et al. 1993; Norena et al. 2003; Robertson and Irvine 1989; Yang et al. 2007). Following these peripheral manipulations, cortical neurons lose responses to stimuli in the region of the lesion but gain responses to previously ineffective stimuli. These rapid receptive field changes may be related to the phantom ringing in the ears known as tinnitus (Eggermont and Roberts 2004), which can be heard immediately after acoustic trauma (Loeb and Smith 1967). The immediate expansion of receptive fields has been argued to be too fast for structural plasticity such as axonal rewiring. Instead, the unmasking of previously subthreshold excitatory inputs has been widely proposed to be caused by a loss of inhibition (Calford 2002b; Gilbert et al. 1996; Jones 1993). The synaptic mechanisms by which this might occur are unknown.

Here we used in vivo whole cell recordings to study the synaptic mechanisms of rapid receptive field changes by directly measuring tone-evoked excitatory and inhibitory synaptic conductances in the same neurons both before and after acoustic trauma. We found a profound and selective loss of inhibition below the frequency of the trauma-tone, which in some cases unmasked responses to previously subthreshold inputs. Surprisingly, we also found a marked increase in inhibition near the frequency of the trauma. Thus inhibition was selectively increased and decreased in distinct regions of the receptive field.

METHODS

Physiology

We recorded from the left primary auditory cortex of anesthetized (30 mg/kg ketamine, 0.24 mg/kg medetomidine) rats 17-40 postnatal days of age. All procedures were in strict accordance with the National Institutes of Health guidelines as approved by the University of Oregon Animal Care and Use Committee. Recordings were made from primary auditory cortex (A1) as determined by the frequencyamplitude tuning properties of cells and local field potentials. We recorded from all subpial depths (range: 135-770 µm, as determined from micromanipulator travel). For whole cell recordings (a total of 39 cells), we used standard blind patch-clamp methods (Wehr and Zador 2003). Internal solution contained (in mM) 140 Cs- or Kgluconate, 10 HEPES, 2 MgCl₂, 0.05 CaCl₂, 4 MgATP, 0.4 NaGTP, 10 Na₂Phosphocreatine, 10 BAPTA, and 0 or 6 QX-314, pH 7.25, diluted to 290 mOsm, producing a calculated reversal potential of -85 mV for both K⁺ and Cl⁻ conductances. To record spiking and membrane potential responses, we used current-clamp mode (I = 0)and used K⁺ without QX-314 in the internal solution (19 cells). To

Address for reprint requests and other correspondence: M. Wehr, Institute of Neuroscience, 1254 University of Oregon, Eugene, OR 97403 (E-mail: wehr@uoregon.edu).

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record synaptic conductances, we used voltage-clamp mode and included QX-314 and Cs⁺ in the internal solution (20 cells). Note that in addition to blocking fast sodium channels (and thereby blocking action potentials), QX-314 also blocks many other activity-evoked conductances. Auditory brain stem responses (ABRs) were obtained by averaging tone-evoked field potentials (200–500 repetitions) recorded with a teflon-coated silver wire, placed at stereotaxic coordinates 2.5 L, 10 P, and depth 3–5 mm. Across the population, input resistance was 90 ± 55 MΩ, and series resistance was 22 ± 24 MΩ (median ± interquartile range, n = 20 cells). Holding potentials were stepped (using a 1-s ramp) to a pseudorandom sequence of three values using an Axopatch 200b amplifier. At each potential, after a 1-s equilibration period, ten 10-mV voltage pulses were delivered to monitor series and input resistance, followed by pseudorandomly interleaved acoustic stimuli.

Stimuli

We presented 200-ms pure tones and white noise bursts, with 10-ms 10-90% cosine-squared ramps, pseudorandomly interleaved at a rate of 2/s, sampling rate 200 kHz, using a 24-bit Lynx22 soundcard, a Stax SRM-717 driver, and SR-303 speaker, in free-field configuration (speaker located 15 cm lateral to, and facing, the contralateral ear) in a sound isolation chamber with anechoic surface treatment. Frequencies were logarithmically spaced from 1 to 40 kHz at a resolution of either 3/octave (for 31 cells) or 4/octave (for 8 cells). This system was calibrated using a Bruel and Kjaer 4939 microphone positioned where the ear would be, without the animal present. To measure ABR thresholds, we averaged the responses to 200 repetitions of 25-ms tones with 3-ms ramps, logarithmically spaced from 1 to 40 kHz at 4/octave, 7 levels from 20 to 80 dB SPL, or 1-ms white noise bursts with 0.1-ms ramps, presented at a rate of 20/s in pseudorandomly interleaved blocks of 100 (total duration, 26 min). We also used a "fast" ABR protocol with only a single frequency and seven levels (20-80 dB SPL, 200 repetitions, total duration: 3 min) to measure thresholds with higher temporal resolution. Threshold was defined as the minimum sound level at which the N1 component of the ABR (which reflects the auditory nerve compound action potential) could be reliably observed (Calford et al. 1993). If no N1 component was observed after trauma, threshold was defined as the highest level tested (80 dB SPL).

Acoustic trauma

For each cell recorded in voltage-clamp mode, we first characterized the frequency response area at a single holding potential (-65 or-70 mV) using an array of tones (1-40 kHz, 0-80 dB SPL). We defined characteristic frequency (CF) as the frequency at which synaptic currents could be evoked at the lowest sound level. We then characterized synaptic conductances using a tone array with only two levels (1-40 kHz, 60-80 dB SPL) presented at three different holding potentials. We then presented an intense pure tone to induce acoustic trauma during the recording. For 31 cells, trauma-tone frequency was fixed at 20 kHz, and for 8 cells, trauma-tone frequency was selected to be 0.5 octaves below the CF of the cell. The trauma-tone was a continuous pure tone delivered for 10 min using a Beyma CP-22 speaker and a Samson Servo 600 power amplifier. Sound level was measured to be 110-120 dB SPL using a Bruel and Kjaer 4939 microphone positioned alongside the animal's ear. Immediately after trauma-tone presentation, we recharacterized synaptic conductances with the same tone array for the remainder of the recording. We presented the trauma-tone only once per animal; thus each neuron is from a separate animal. For eight of these animals, we characterized peripheral hearing thresholds using the ABR both before and after the whole cell recording. The ABR threshold shift was thus measured with a 26-min stimulus protocol that started \sim 5–70 min after trauma, depending on how long the whole cell recording lasted. For cells recorded in current-clamp mode (19 cells), we followed the same procedure described above, except that we recorded spiking and membrane potential responses instead of synaptic conductances (and ABRs were not recorded). To characterize the time course of the trauma-induced ABR threshold elevation at high temporal resolution, we used a fixed 10-min, 110 dB SPL, 20-kHz trauma-tone frequency in a separate group of six animals and measured ABR thresholds with the fast protocol at a single frequency (28 kHz, or 0.5 octaves above trauma-tone frequency) continuously for 1 h after trauma.

Analysis

We quantified synaptic conductance responses by measuring peak conductance change during the stimulus (relative to a 50-ms baseline period before stimulus onset). We computed series resistance from the peak current transients by taking the average across each group of 10 pulses and taking the median of those averages over an entire stimulus protocol. We corrected holding potentials off-line for series resistance and for a calculated liquid junction potential of 12 mV. We did not use on-line series resistance compensation. We computed total synaptic conductance, corrected for series resistance, assuming an isopotential neuron as described previously (Wehr and Zador 2003). Briefly, we computed the total synaptic conductance from the linear regression between synaptic currents and holding potential. We decomposed total synaptic conductance into excitatory and inhibitory components, assuming linearity, as described previously (Wehr and Zador 2003). Conceptually, this decomposition takes advantage of the fact that at holding potentials near 0 mV (the excitatory synaptic reversal potential), the synaptic current is mainly inhibitory, whereas near -85 mV, the synaptic current is mainly excitatory (see Wehr and Zador 2003 for more details). We used the excitatory and inhibitory conductance waveforms to predict the resulting membrane potential \hat{V}_{m} using the difference equation

$$\hat{V}_{\rm m}(t) = \hat{V}_{\rm m}(t-1) - \frac{dt}{C_{\rm m}} \{g_{\rm r}[\hat{V}_{\rm m}(t-1) - E_{\rm r}] + g_{\rm e}(t)[(\hat{V}_{\rm m}(t-1) - E_{\rm e}] + g_{\rm e}(t)[\hat{V}_{\rm m}(t-1) - E_{\rm e}]\}$$

where dt is the reciprocal of the sampling rate, g_r is the measured resting input conductance, E_r is the calculated resting membrane potential, g_e and g_i are the measured excitatory and inhibitory conductances, respectively, E_e and E_i are the calculated synaptic reversal potentials (0 and -85 mV, respectively), and C_m is the whole cell capacitance. We used E_r as the initial conditions for \hat{V} , and we used a fixed estimate of 200 pF for C_m , although varying C_m across the physiological range (0–500 pF) had no effect on the results.

Latency from stimulus onset was defined as the time at which a signal reached half-maximal height relative to prestimulus baseline. Duration was defined as the time from onset latency until a signal decreased to half its maximal height relative to baseline. Signals were smoothed before estimating latency and duration by low-pass filtering at 100 Hz. Responses that did not exceed 1 SD from baseline were excluded from latency and duration analysis. Spike counts were measured in a 200-ms window following tone onset. We compared group data across conditions using the paired *t*-test except where otherwise noted.

Because we used a variety of recording methods and stimulus protocols, we briefly summarize them here. Each neuron was recorded in a separate animal. We used voltage clamp, with a fixed trauma-tone frequency of 20 kHz, to record from 12 neurons (in 12 animals). We used current clamp, with a fixed trauma-tone frequency of 20 kHz, to record from 19 neurons (in 19 animals). We used voltage clamp, with a variable trauma-tone frequency (set to one half an octave below CF), to record from eight neurons (in 8 animals). We also recorded ABR thresholds before and after trauma in those eight animals, so that

receptive field changes and ABR threshold shifts can be directly compared in those eight neurons. We recorded ABR thresholds at high temporal resolution (at a single frequency) before and after trauma in an additional six animals; no cortical recordings were obtained from those six animals.

RESULTS

We recorded from 39 neurons in primary auditory cortex (A1) of 39 rats, using in vivo whole cell patch methods. For each neuron, we compared the responses to brief tones both before and after an acoustic trauma (10 min of a 110 dB SPL pure tone). This acoustic trauma caused a pronounced peripheral hearing loss, as measured by the ABR in eight of these animals (Fig. 1). ABR threshold elevations [48 \pm 3 (SE) dB, n = 8 animals] were maximal at one half an octave above the trauma-tone frequency. ABR threshold elevations were stable from the first measurement (3 min after trauma) up to at least 1 h after trauma, as measured in a separate group of six animals (Fig. 1*C*).

In auditory cortical neurons, this trauma caused robust changes in tone-evoked synaptic currents. We studied these altered synaptic currents using voltage-clamp methods in 20 cells (an example is shown in Fig. 2, *A* and *B*, CF for this cell was 26 kHz). To improve the isolation of synaptic inputs, we included QX-314 (which blocks spikes) and cesium (which blocks voltage-gated potassium currents) in the pipette and therefore did not measure spiking or membrane potential re-



FIG. 1. Acoustic trauma caused a selective peripheral hearing loss. A: example of auditory brain stem responses (ABRs) to white noise bursts at 8 amplitudes (means of 200 responses, arrow indicates the N1 component). We defined threshold as the minimum amplitude that evoked an identifiable N1, 30 dB SPL in this case. Scale bar = $30 \ \mu$ V, 5 ms. *B*: ABR threshold elevation after acoustic trauma (10 min, 110–120 dB SPL). Gray lines are from 8 individual animals; black line shows the mean across animals. Responses are aligned to trauma-tone frequency (which ranged from 12 to 25 kHz). Maximal threshold elevations occurred 0.5 octaves above trauma-tone frequency (dashed line). *C*: the ABR threshold shift was stable for ≥ 1 h after trauma, shown here for 28-kHz tones, following a 20-kHz trauma-tone in 6 animals. Error bars in this and subsequent figures indicate SE.

sponses in these cells. We clamped cells to three different holding potentials to show the different contributions of excitatory and inhibitory synaptic inputs to the evoked synaptic currents. Before trauma, tones evoked inward currents at hyperpolarized holding potentials and outward currents at depolarized holding potentials for both low- and high-frequency tones (8.8 kHz in Fig. 2A and 20.9 kHz in Fig. 2B). After trauma, the outward currents were abolished for the low tone (8.8 kHz; Fig. 2A) but were enhanced for the high tone (20.9 kHz; Fig. 2B). Evoked currents recorded at depolarized potentials should be dominated by synaptic inhibition, because the holding potential is near the reversal potential for excitation. In contrast, the inward currents recorded at hyperpolarized potentials should be dominated by synaptic excitation, because the holding potential is near the reversal potential for inhibition. This suggests that the synaptic inhibition evoked by the 8.8kHz tone is selectively lost after trauma, whereas in the same cell, the inhibition evoked by the 20.9-kHz tone is selectively enhanced after trauma.

We used the synaptic currents recorded at different holding potentials to decompose the evoked responses into excitatory and inhibitory synaptic conductances (Borg-Graham et al. 1998; Wehr and Zador 2003, 2005; Zhang et al. 2003). Before trauma, excitatory and inhibitory conductances were roughly balanced for both low- and high-frequency tones (Fig. 2, *C* and *D*), consistent with a balance of excitation and inhibition across the width of the receptive field (Tan et al. 2004; Wehr and Zador 2003). However, trauma induced a dramatic shift in this balance, abolishing inhibition for the low tone (Fig. 2*C*) but enhancing it for the high tone (Fig. 2*D*). Excitation was comparatively unchanged for this cell. Thus inhibition was selectively abolished and enhanced in different regions of the receptive field after acoustic trauma.

To examine how the balance of excitation and inhibition was disrupted across the frequency extent of the receptive field for this cell, we measured peak synaptic conductances evoked by a wide range of frequencies, before and after trauma (Fig. 3*A*). Trauma-tone frequency (20 kHz) is indicated by a filled arrowhead, and the frequencies shown in Fig. 2 are indicated by open arrowheads. Before trauma, peak excitation and inhibition were roughly balanced across all frequencies (Fig. 3*A*, dashed lines). After trauma, inhibition was abolished for frequencies below ~ 10 kHz but dramatically enhanced above this frequency. Peak excitatory conductances were comparatively unaffected.

To quantify this disruption of inhibition across the population, we used two complementary strategies. First, we used a fixed trauma-tone frequency of 20 kHz. Figure 3B shows normalized peak excitatory and inhibitory conductances averaged across 12 neurons, which were recorded both before and after trauma (in 12 different animals). These neurons had CFs within 1 octave above trauma-tone frequency (i.e., 20-40 kHz, surrounding the expected peak peripheral threshold shift at one half an octave above trauma-tone frequency). Across this sample, peak inhibition was consistently and dramatically increased near the trauma-tone frequency and strongly diminished for lower frequencies. Excitation showed a similar effect but to a much lesser degree. Both excitation and inhibition were strongly reduced or abolished at the highest frequencies used (32 and 40 kHz). Neurons with CFs <20 kHz showed either inconsistent effects or no effect of trauma and were



FIG. 2. Inhibition could be both abolished and enhanced in the same neuron after acoustic trauma. A and B: synaptic currents evoked by an 8.8-kHz 80 dB SPL tone (A) and a 20.9-kHz tone (B) in an auditory cortical neuron at 3 different holding potentials (-24, -63, and -94 mV), before (left traces) and after (right traces) acoustic trauma (20 kHz, 10 min). Note the loss of outward currents after trauma in A (magenta trace) and the increased outward currents in B. Scale bars = 250 pA, 100 ms for both A and B. Tone presentation indicated by gray bars under traces. C: excitatory (green) and inhibitory (red) synaptic conductance traces evoked by the 8.8-kHz tone for this cell, before (left) and after (right) trauma. Inhibition was selectively abolished after trauma. Scale bars = 10 nS, 100 ms for both C and D. D: excitatory and inhibitory synaptic conductances evoked in the same cell for the 20.9-kHz tone. Inhibition was selectively increased after trauma.

therefore not included in the analysis or cell count. The effects of trauma on peak excitation and inhibition were highly significant (2-way ANOVA, n = 12 cells, df = 1, F = 7, P < 0.01 for excitation; F = 4, P < 0.05 for inhibition), as were the interactions between the effect of trauma and tone frequency (df = 18, F = 3, P < 0.01 for excitation; F = 2, P < 0.01 for inhibition; calculated separately for excitation and for inhibition).

The consistency of these effects across cells may be caused in part by similarity in their characteristic frequencies (mean: 31 ± 8 kHz, range: 21-40 kHz, n = 12). Across the population, trauma caused a loss of inhibition for low frequencies in 10/12 cells and an increase in inhibition for high frequencies in 9/12 cells. In some of these cells (6/10), excitation was also diminished or enhanced along with inhibition. These changes consistently occurred at the same range of frequencies relative



FIG. 3. The balance of excitation and inhibition was disrupted in opposing directions at low and high frequencies. A: peak synaptic conductances as a function of tone frequency for the cell in Fig. 2. Before acoustic trauma (dashed lines), inhibitory (red) and excitatory (green) conductances were approximately balanced throughout the receptive field. After trauma (solid lines), inhibition was abolished for frequencies <10 kHz (downward arrow) but was greatly enhanced for higher frequencies (upward arrow). Tone level = 80 dB. The frequencies for the traces in Fig. 2 are indicated by open arrowheads; the frequency of the trauma-tone (20 kHz) is indicated by the gray arrowhead. Characteristic frequency for this cell was 26 kHz. B: peak synaptic conductances (normalized to peak inhibition for each cell) before (dashed lines) and after (solid lines) acoustic trauma for the population (n = 12)cells in 12 animals). Trauma-tone was 20 kHz, 10 min, 110-120 dB SPL for all cells. Tone level = 80 dB SPL. Inhibition (red) was consistently abolished at low frequencies and enhanced at high frequencies. Excitation (green) was affected to a lesser extent. C: normalized peak synaptic conductances (as in B) for tone levels of 60 dB SPL. Both excitation and inhibition were reduced across all frequencies.

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to the trauma, with a loss of inhibition at low frequencies and a gain of inhibition in a \pm 1-octave region around the traumatone frequency (Fig. 3*B*). For lower level tones (60 dB SPL), both excitation and inhibition were markedly reduced across the width of the receptive field (Fig. 3*C*). Thus the selective increases and decreases in inhibition were seen only for highlevel tones. These changes invariably persisted for the duration of the recordings (median: 31 min, range: 23–90 min, or ~5–70 min after trauma). In a few cells (n = 5), we were able to make measurements at multiple time points after trauma and observed that the effects of trauma seemed to intensify within ~10 min and then stabilize. Because of the limited sample size, however, we were not able to quantify the time course of these effects, which will require further study.

Our second strategy for quantifying the disruption of inhibition across a separate population of eight cells was to vary the trauma-tone frequency (range: 12–25 kHz), such that it was always one half an octave below the CF for each neuron. In this way, the expected peak of the peripheral threshold shift should coincide with CF. To confirm this, we recorded the ABR before and after trauma in each animal to measure the peripheral threshold shift. As expected, the population average peripheral threshold shift (Fig. 4, black line, right ordinate) peaked at one half an octave above trauma-tone frequency, such that it coincided with CF of the cortical neurons. The red and green lines in Fig. 4 show the net change in normalized peak conductance after trauma (i.e., the difference between the dashed and solid lines in Fig. 3). As before, we observed an increase in cortical tone-evoked inhibition (red line) that was centered around the trauma-tone frequency, one half an octave below the peak peripheral temporary threshold shift. This region of increased inhibition coincided with the lower edge of the peripheral lesion. A second region of increased inhibition coincided with the upper edge of the peripheral lesion, >1octave above trauma-tone frequency. For the sample of 12 cells with trauma-tone frequency fixed at 20 kHz, this second region would be expected to occur at >40 kHz, which may explain



FIG. 4. Increased inhibition coincided with the edges of the ABR threshold shift. ABR threshold shift (black, averaged across 8 animals, same data as Fig. 1*B*), superimposed on the change in normalized peak excitatory (green) and inhibitory (red) conductances from 8 cortical neurons recorded both before and after trauma in the same 8 animals. For each cell, trauma-tone frequency was chosen to be half an octave below CF. Note that inhibition was reduced for low frequencies (2–3 octaves below CF) but was increased at the lower and upper edges of the region of increased peripheral threshold.

why we did not observe it in those cells (see Fig. 3*B*). As before, inhibition was decreased for low frequencies ($\sim 2-3$ octaves below CF).

What effects would these selective increases and decreases in inhibition be expected to produce at the level of the membrane potential and spiking output? We expected that decreased inhibition should lead to enhanced or prolonged depolarization, a loss of evoked hyperpolarization, and increased spike output at lower frequencies (below ~ 10 kHz). Conversely, we expected that increased inhibition should lead to reduced depolarization, increased hyperpolarization, and reduced spike output at higher frequencies (above ~ 10 kHz). For the highest frequencies (32–40 kHz), we expected to see little or no response after trauma.

To test these predictions, we used current-clamp methods to record tone-evoked membrane potential and spiking responses in 19 cells before and after a fixed 20-kHz acoustic trauma. We found robust changes in evoked responses after trauma, but to our surprise, these did not match our predictions based on the disruption of inhibition we had observed. Figure 5A shows an example of a response evoked by a low frequency tone (4.6 kHz, CF for this cell was 26 kHz). Before trauma (blue trace), the tone evoked a brief depolarization and spikes, followed by hyperpolarization. After trauma (orange trace), latency was increased, the depolarization was prolonged and diminished in amplitude, and the hyperpolarization was absent. These effects are consistent with the loss of inhibition seen in Figs. 2-4 and are in agreement with our predictions. In contrast, for a high-frequency tone, we expected to see the effects of increased inhibition. The response of the same cell to a highfrequency tone (21 kHz) is shown in Fig. 5B. After trauma (orange trace), latency was increased, the depolarization was prolonged and diminished in amplitude, and the hyperpolarization seen before trauma is absent. These effects were qualitatively similar to those for the 4.6-kHz tone but are difficult to reconcile with the sharply increased inhibitory conductances evoked consistently by high-frequency tones in the voltageclamp recordings (e.g., Fig. 2D).

These effects of trauma were seen across the width of the receptive field. Figure 6A shows tone-evoked responses for this cell across a wide range of frequencies, before and after trauma. Prolonged depolarization and increased onset latency are evident at nearly all frequencies. Responses to the highest frequencies used (32-40 kHz) were largely absent after trauma. To examine how consistent these effects were across the population, we averaged tone-evoked responses across cells with similar characteristic frequencies (mean: 32 ± 6 kHz, range: 26-40 kHz, n = 7 cells). Figure 6B shows tone-evoked responses for a range of frequencies, averaged across cells. After trauma, latency was increased, depolarizing responses were consistently prolonged, and hyperpolarizations were diminished or eliminated. These effects could be seen throughout the receptive field but were most prominent for high frequencies (14-21 kHz), which in voltage-clamp recordings was the region of the receptive field that showed the strongest increase in inhibition after trauma (cf. Fig. 3). Thus effects in the cortex were greater near the trauma-tone frequency but also occurred over a much broader frequency range than did peripheral effects as measured by ABR threshold elevations.



FIG. 5. Tone-evoked membrane potential responses were delayed and prolonged after trauma. A and B: mean membrane potential responses in an auditory cortical neuron evoked by a pure tone (A: 4.6 kHz, B: 20.9 kHz, A and B: 80 dB SPL, 200 ms, indicated by gray bar) before (blue trace) and after (orange trace) acoustic trauma. After trauma, latency was increased, depolarization was prolonged, and hyperpolarization was absent for both tone-evoked responses. Traces are means of 10 trials. Scale bar = 10 mV, 100 ms for A and B.

To quantify these effects of trauma across cells, we measured the latency and duration of tone-evoked depolarizations. For cells with high characteristic frequencies (mean: 32 ± 6 kHz, range: 26-40 kHz, n = 7 cells), latency and duration were increased across a wide range of frequencies (Fig. 7, A and B), most prominently for high frequencies (17-26 kHz) but also at the low-frequency edges of the receptive field (1–2 kHz). For the highest frequencies used (32-40 kHz), responses were strongly diminished or absent. In contrast, for cells with lower characteristic frequencies (range: 2–21 kHz, n = 12cells), trauma had much less effect on membrane potential responses. To examine latency and duration increases across all cells for which we recorded membrane potential responses (n = 19 cells), we measured mean latency and duration increases, averaged across all tone frequencies, for each cell (Fig. 7, C and D). Across all cells and tone frequencies, both latency and duration were significantly increased after trauma (P < 0.001 for duration, P < 0.001







FIG. 7. Membrane potential response latency and duration were increased after acoustic trauma. A: mean increase in onset latency across the population of high-frequency cells (n = 7 cells with CF ≥ 26 kHz) for 80 dB tones, induced by acoustic trauma. Latency was increased across a broad range of frequencies, especially >17 kHz. B: mean increase in response duration across the population of high-frequency cells (n = 7 cells with $CF \ge 26$ kHz) for 80 dB tones, induced by acoustic trauma. Duration was increased across a broad range of frequencies. C: mean increase in onset latency for each cell (combined across tone frequencies) as a function of characteristic frequency (n = 19 cells of all CFs). Latency increase was not correlated with characteristic frequency. D: mean increase in duration for each cell (combined across tone frequencies) as a function of characteristic frequency (n = 19 cells of all CFs). Cells with high CF showed greater duration increase ($r^2 = 0.36$, P < 0.01).

for latency). Duration increases were significantly corre-

lated with CF ($r^2 = 0.36$, P < .01), whereas latency

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FIG. 6. Evoked membrane potential responses were delayed, prolonged, and reduced after acoustic trauma. A: mean membrane potential responses of a neuron to pure tones (200 ms, frequency indicated under each trace) before (blue trace) and after (orange trace) the acoustic trauma. Note the loss of hyperpolarization for tones in the range 9-32 kHz. Higher levels (80 dB SPL) are on the top row; lower levels (60 dB SPL) are on the bottom row. Same neuron as Fig. 5, A and B. Characteristic frequency (CF) for this cell was 26 kHz. Traces are means of 10 trials: action potentials are clipped. Scale bar = 5mV, 250 ms for A and B. B: evoked membrane potential responses averaged across the population of high-frequency cells (n = 7cells with $CF \ge 26$ kHz).

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tone were much stronger for cells tuned above 20 kHz than below.

The effect of trauma on spiking responses was variable. For the subset of cells with high CFs (26-40 kHz), spiking responses were decreased overall after trauma (data not shown). This effect was significant (2-way ANOVA, n = 7cells, df = 1, P < 0.01), as was the interaction between the effect of trauma and tone frequency (df = 18, P < 0.001). This is consistent with the overall decrease in the membrane potential responses averaged across cells (Fig. 6B). Despite this overall decrease, the majority of these cells (6/7) showed increased firing for one or more tones. Figure 8, A and B, shows two examples (from 2 different cells) of robust spiking responses after trauma, which were previously subthreshold. However, the frequency at which this increased spiking was evoked varied from cell to cell and was not well correlated with CF. Spike counts tended to be increased at the low-frequency edges of the receptive fields, but this effect was not significant at the population level after correction for multiple comparisons. This trend is consistent with a small (1/3 octave) receptive field expansion toward low frequencies. Spontaneous firing rates were not affected by the trauma (0.8 \pm 1.1 Hz before, 0.7 ± 1.1 Hz after, n = 19 cells).

How can we reconcile the striking increases and decreases of peak synaptic inhibition in different regions of the receptive field with the marked but relatively homogenous increase in the duration of membrane potential responses? We wondered whether peak excitatory and inhibitory conductances might not accurately predict the resulting membrane potential after synaptic integration. We therefore used a simple model to estimate the membrane potential (\hat{V}_m) that would result from the combination of the full excitatory and inhibitory conductance waveforms and their respective driving forces (see METHODS for details).

Figure 9 shows an example of peak excitatory and inhibitory conductances for a cell tuned to 21 kHz. After trauma, peak inhibition was selectively decreased for low frequencies but strongly increased for high frequencies. The inhibitory conductances evoked by a low tone (3 kHz, Fig. 9*B*) are dramatically decreased, whereas for a high tone (21 kHz), they are dramatically increased. The estimated membrane potential (\hat{V}_m) re-



FIG. 8. Unmasking of previously subthreshold inputs. *A* and *B*: examples of evoked responses (in 2 different neurons) that were subthreshold before trauma but suprathreshold after trauma (A: 2.4 kHz, 60 dB, *B*: 17 kHz, 80 dB). Scale bar = 10 mV, 100 ms for *A* and *B*.



FIG. 9. Peak synaptic conductance did not predict membrane potential. A: peak synaptic conductances in 1 neuron as a function of tone frequency. After trauma (solid lines), inhibition (red) was strongly and selectively decreased for low frequencies but increased for higher frequencies compared with the response before trauma (dashed lines). Excitation (green) was affected to a much lesser extent. Tone levels were 80 dB. B: synaptic conductance traces for this neuron, evoked by 3.0 and 20.9 kHz (80 dB) tones (indicated by open arrowheads in A). Note the strong decrease in peak inhibitory conductance for 3 kHz and the strong increase in peak inhibitory conductance for 20.9 kHz. Note also the increased duration of excitatory conductance (solid green lines) for both tone frequencies (e.g., arrow for 20.9 kHz). Scale bars = 10 nS, 100 ms. C: predicted membrane potential $\hat{V}_{\rm m}$ estimated from the conductance traces in *B* before trauma (blue) and after (orange). Note the similar increases in latency and duration for the predicted membrane potential responses, despite the qualitatively different changes in peak inhibition. Scale bar = 10 mV (B and C are on the same time scale and aligned to the same stimulus).

sulting from these conductances before (blue) and after (orange) trauma is shown in Fig. 9C. Despite the opposing changes in inhibition, the estimated depolarization is increased and prolonged in both cases. This suggests that, despite the far greater amplitude of the initial conductance transients, the later phase of the conductances may be more important in determining the membrane potential response after trauma. For high-frequency tones, the large transient inhibitory conductance at response onset contributed to the increased latency of the membrane potential response, but the smaller and slower excitatory conductance (Fig. 9B, arrow) seemed to contribute much more to the prolonged depolarization. Indeed, in contrast to the significantly increased peak inhibition, mean excitatory conductance averaged across tones and cells was significantly increased in the time window 100-200 ms after tone onset (P < 0.01, n = 12 cells), whereas inhibitory conductance in this time window remained unchanged. Low-frequency tones showed a similar phenomenon (Fig. 8, B and C), although the inhibitory transient was much smaller after trauma and therefore had less impact on membrane potential response latency. This may explain the larger latency increase we observed for high tone frequencies (Fig. 7A).

These increases in latency and duration were consistent across cells and tone frequencies, suggesting that the changes in synaptic conductances could account for the changes in membrane potential responses. Across the population, latencies and durations of estimated membrane potential responses were increased across tone frequencies (P < 0.001 for latency, P <0.01 for duration, n = 12 cells). Likewise, latencies and durations of the underlying conductances were increased after trauma. Mean latency increase was 10 ± 20 ms for excitation and 7 \pm 22 ms for inhibition (n = 12 cells), which was significantly less than that observed for membrane potential responses recorded in current clamp (15 \pm 27 ms, P < 0.05, n = 7 cells). Thus the increased latency in the membrane potential responses seems to be caused in part by increased latency in the underlying conductances but may also include a "delaying" contribution from the inhibitory transients, especially for high-frequency tones (Fig. 9C). Across cells and tone frequencies, the durations of both excitatory and inhibitory conductances were significantly increased after trauma (P <0.001 for inhibition, P < 0.001 for excitation, n = 12 cells). The increased durations of excitatory conductances, inhibitory conductances, and membrane potential responses were not significantly different. This suggests that the increased durations of membrane potential responses can be accounted for by the increased durations of the underlying synaptic inputs.

DISCUSSION

Acoustic trauma, like other peripheral manipulations, causes a rapid expansion of cortical receptive fields. Here we have tested the hypothesis that the mechanism responsible for this expansion in auditory cortical receptive fields is a selective loss of synaptic inhibition. We measured tone-evoked excitatory and inhibitory synaptic inputs in individual cells both before and after acoustic trauma. We found that trauma induced a selective loss of inhibition across the low-frequency half of the receptive field, with excitation affected to a lesser extent. Surprisingly, trauma also induced a dramatic increase in inhibition at higher frequencies at the edges of the peripheral threshold shift. Excitation was also increased to a lesser extent in this region. These changes occurred for relatively high-level tones. Our main conclusion is therefore that acoustic trauma simultaneously caused a selective increase and decrease of synaptic inhibition in distinct regions of the receptive field. Thus the synaptic mechanisms underlying receptive field changes following acoustic trauma do include unmasking by selective loss of inhibition but also include a selective gain of inhibition elsewhere in the receptive field.

We also observed that, despite these opposite effects on inhibition, membrane potential responses were similarly delayed and prolonged throughout the receptive field after trauma. Thus the striking changes in the magnitudes of the inhibitory onset transients had a comparatively subtle effect on the membrane potential response, whereas the most prominent effects on the membrane potential response were caused by comparatively subtle features of the synaptic conductance waveforms. These results emphasize how synaptic integration depends critically on the relative timing and the interaction of excitation and inhibition throughout the entire evoked response. Specifically, these interactions appeared to be qualitatively different in three distinct regions of the receptive field. *1*) At low

frequencies $(1 \sim 10 \text{ kHz})$, the latency and duration of evoked membrane potential responses was increased, because of the increased latency and duration of excitatory synaptic inputs in combination with decreased inhibition. At the lower edge of the receptive field this led to increased depolarization and spiking responses. 2) At the edges of the region of increased peripheral threshold, the latency and duration of evoked membrane potential responses was increased. This was caused primarily by the increased latency, duration, and magnitude of excitatory synaptic inputs. The increased inhibition acted primarily to delay evoked responses rather than to abolish them. 3) At the frequency of peak peripheral threshold shift, both membrane potential responses and the synaptic inputs giving rise to them were strongly diminished or absent. Together, the distinct effects across these three regions caused a small ($\sim 1/3$ octave) receptive field shift toward lower frequencies. Spiking responses were also increased for one or more tone frequencies, which were variable across cells. These results are consistent with the expansion of receptive fields seen in auditory cortex after acoustic trauma (Calford et al. 1993; Kimura and Eggermont 1999; Norena et al. 2003; Robertson and Irvine 1989). They are also consistent with temporary threshold shifts in the auditory periphery following acoustic trauma, which are maximal at 0.5 octaves above the trauma-tone frequency (Cody and Johnstone 1980). It is important to note that the changes in inhibition we report here were evoked by relatively high-level tones (60-80 dB). We did not measure threshold responses after trauma, for which the tuning remains unchanged in cortical neurons after hearing loss (Rajan 1998) and which may evoke less surround inhibition compared with higher level sounds.

The delayed and prolonged membrane potential responses that we observed after trauma could be predicted by a model of the synaptic integration of excitatory and inhibitory conductances recorded in voltage clamp. Because membrane potential changes are minimized in voltage-clamp mode, and the cesium and QX-314 in our internal solution blocked potassium channels and other voltage-gated ion channels, contributions from intrinsic membrane properties are not necessary to explain the prolonged responses after trauma. However, these intrinsic properties could have affected responses in cortical or subcortical neurons presynaptic to those we recorded from.

Measuring absolute conductances using voltage-clamp methods is subject to errors that have been well characterized (Spruston et al. 1993; Wehr and Zador 2003). Here we have avoided the effects of these errors by comparing responses across stimuli, within a given cell. Moreover, there was no significant correlation between series resistance and peak excitatory or inhibitory conductances across cells, suggesting that series resistance had no systematic effect on conductance estimates. Across cells, there were no systematic or significant changes in recording stability before and after trauma, as quantified by series and input resistances (mean series resistance change was $1.5 \pm 8.6 \text{ M}\Omega$, mean input resistance change was $9.9 \pm 27.1 \text{ M}\Omega$), suggesting that changes in recording stability are unlikely to have contributed to the effects of trauma we observed.

Chronic hearing loss is known to cause a loss of surround suppression (evoked from the flanks of the receptive field) but not "in-field" suppression (evoked from within the receptive field) in cortical neurons (Rajan 1998, 2001). Based on these

findings and the observation that the extent of suppressive regions was unchanged, Rajan has proposed a model in which chronic hearing loss causes a loss of surround inhibition, which in turn unmasks in-field inhibition and excitation (Rajan 2001). A rapid unmasking of suppressive responses following denervation has also been shown in the somatosensory cortex (Rasmusson and Turnbull 1983; Turnbull and Rasmusson 1990). Our findings that noise-induced hearing loss caused a loss of synaptic inhibition at the lower edge of the receptive field but increased synaptic inhibition near the center of the receptive field are consistent with these results. The interpretation of forward suppression seen in extracellular recordings is complicated by the contributions of multiple suppressive mechanisms, including the powerful effects of synaptic depression as well as synaptic inhibition (Wehr and Zador 2005). Thus the differential effect of hearing loss on distinct components of suppression (surround and in-field) could be caused by different effects on different suppressive mechanisms (such as synaptic inhibition and depression). We measured synaptic inhibition directly, using voltage-clamp methods and isolated tones that would not be expected to include the effects of synaptic depression or other forms of adaptation. Thus our results show that hearing loss differentially affects synaptic inhibition in distinct regions of the receptive field. These results support the model proposed by Rajan (2001) but leave untested the hypothesis that the loss of surround inhibition itself is directly responsible for the gain of in-field inhibition by means of an unmasking process. We have also shown here that these changes occur immediately after trauma; the results of Rajan for chronic hearing loss (Rajan 1998, 2001) suggest that these effects persist well beyond the durations of our recordings (~ 1 h), lasting at least months if not indefinitely. We also found that responses were decreased at the frequency of peak peripheral threshold shift, which is inconsistent with Rajan's findings (Rajan 1998, 2001). This suggests that these responses may recover sometime between hours and months after trauma and may come to resemble those in the low-frequency region of the receptive field. This view is consistent with the findings of Robertson and Irvine (1989) that rapid receptive field shifts are accompanied by elevated thresholds (as we observed), which return to normal levels after 1-3 mo.

Receptive field expansion following peripheral manipulations has been observed in subcortical structures, raising the issue of whether changes in cortical receptive fields are actually generated within the cortex or reflect changes that occur at lower levels (Calford 2002a; Donoghue 1995). Subcortical receptive field plasticity has been well documented in the visual and somatosensory systems (Calford 2002a; Donoghue 1995), but several lines of evidence have established that changes also occur at the cortical level in these systems (Darian-Smith and Gilbert 1994, 1995; Diamond et al. 1994). In the auditory system, hypersensitivity to low frequencies has been seen in auditory nerve fibers following acoustic trauma (Liberman and Kiang 1978), and receptive field shifts and the emergence of new responses have been seen in the inferior colliculus following acoustic trauma and restricted spiral ganglion lesions (Snyder and Sinex 2002; Wang et al. 1996, 2002). The receptive field changes observed in auditory cortex (Calford et al. 1993; Norena et al. 2003; Rajan 1998) might therefore be passively inherited from these subcortical effects. Here we have shown that acoustic trauma caused substantial

increases and decreases in inhibitory inputs to auditory cortical neurons. Because all inhibition in auditory cortical neurons is intracortical in origin, these results show that the synaptic mechanisms underlying cortical receptive field changes include alterations in synaptic processing within the auditory cortex as well as at subcortical levels. These results provide no evidence for whether or not this involves cortical synaptic plasticity per se. In principal, the affected synapses could be thalamocortical synapses onto cortical interneurons. However, even if cortical synaptic plasticity is not involved in these receptive field shifts, they are not simply passively inherited from subcortical inputs but are actively transformed by intracortical synaptic interactions (Fig. 9).

What are the cortical substrates for these rapid receptive field shifts? In vitro studies using thalamocortical slices from deafened animals have shown that both thalamocortical and intracortical synaptic excitation are increased and that intracortical inhibition is decreased relative to control animals (Kotak et al. 2005). These changes in synaptic efficacy were mediated by both presynaptic and postsynaptic mechanisms. These results are consistent with the decreased inhibition we observed for low frequencies. However, they do not address the possible mechanisms for the increased inhibition we observed for high frequencies. It may be that distinct changes in different receptive field regions, such as those we observed following a pure-tone induced selective hearing loss, are not evoked by total deafening.

We found that a profound loss of inhibition occurred for low tone frequencies at which no peripheral threshold shift was observed. This finding is consistent with the broad spectral integration that is seen in auditory cortex. Individual cortical neurons can receive input covering much of the audible spectrum (Metherate et al. 2005; Ojima et al. 1991; Wehr and Zador 2003). This convergence of spectral information onto individual cortical neurons likely arises from a combination of thalamocortical and intracortical horizontal pathways (Metherate et al. 2005). Disruptions to this horizontal circuitry may be responsible for the changes we observed far from the region of peripheral threshold shift. Indeed, intracortical horizontal connections have been widely proposed to be responsible for receptive field expansion in the visual and somatosensory cortex (Das and Gilbert 1995; Donoghue 1995; Gilbert et al. 1996). In long-term cortical reorganization, these connections show structural modifications (Darian-Smith and Gilbert 1994). During rapid plasticity, however, these connections may instead lose their ability to drive disynaptic inhibition (Hirsch and Gilbert 1991). How or whether these connections lose their ability to drive local inhibitory interneurons after a peripheral manipulation remains unknown, although homeostatic synaptic plasticity (Turrigiano et al. 1998) may be involved. Sensory deprivation has been shown to induce homeostatic synaptic plasticity at both excitatory and inhibitory cortical synapses (Maffei et al. 2004), which can cause both increases and decreases in inhibition (Maffei et al. 2006). Homeostatic synaptic plasticity can also be induced within minutes (Frank et al. 2006) and could therefore be fast enough to account for the rapid changes we observed. An increase in presynaptic release at GABAergic synapses is unlikely to account for the increased inhibition we observed, because the minimal quantal release of GABA is saturating for GABA_A receptors (Edwards et al. 1990). Thus

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if homeostatic synaptic plasticity does act presynaptically to increase inhibition, it is likely to be mediated by the potentiation of excitatory synapses onto inhibitory interneurons. A rapid increase in inhibition could also be mediated by local synthesis of neurosteroids, which can act within minutes to enhance inhibition by prolonging GABA_A currents (Lambert et al. 2001; Saalmann et al. 2006).

Acoustic trauma and related peripheral manipulations can cause both acute and chronic tinnitus in humans and animals (Jastreboff et al. 1988; Loeb and Smith 1967; Yang et al. 2007), but there is still no consensus about the neural mechanisms responsible or the levels of the auditory system at which they operate (Eggermont 2005; Eggermont and Roberts 2004; Norena and Eggermont 2003). In acute salicylate-induced tinnitus in awake rats, tone-evoked cortical responses were enhanced in the region of perceived tinnitus (Yang et al. 2007). Increases in evoked cortical responses have also been reported following acoustic trauma (Norena and Eggermont 2003). These enhancements could be caused by reduced inhibition and prolonged excitation similar to that we observed following acoustic trauma. Increased spontaneous firing rates have been proposed to underlie tinnitus (Kimura and Eggermont 1999; Seki and Eggermont 2003) but are not seen in cortex until a few hours after trauma (Norena et al. 2003). These results are consistent with our observation that spontaneous firing rates did not change during our recordings (up to ~ 1 h after trauma), unlike the immediate changes we observed in tone-evoked inhibition. Tinnitus can occur immediately after acoustic trauma (Loeb and Smith 1967), suggesting that rapid changes such as those we observed could in principle contribute to acute forms of tinnitus. However, acute and chronic tinnitus probably result from a variety of mechanisms acting at different levels of the auditory system. The changes in excitation and inhibition that we report here are therefore likely to be an early event in a cascade of different mechanisms of varying time courses, and it remains unclear which of these are directly or indirectly implicated in tinnitus. Further elucidation of this sequence of events may show opportunities to halt or reverse the procession leading to chronic tinnitus.

$R \mathrel{E} F \mathrel{E} R \mathrel{E} N \mathrel{C} \mathrel{E} S$

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