Degradation of Temporal Resolution in the Auditory Midbrain After Prolonged Deafness Is Reversed by Electrical Stimulation of the Cochlea

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Submitted 30 August 2004; accepted in final form 13 January 2005


In an animal model of prelingual deafness, we examined the anatomical and physiological effects of prolonged deafness and chronic electrical stimulation on temporal resolution in the adult central auditory system. Maximum following frequencies ($f_{max}$) and first spike latencies of single neurons responding to electrical pulse trains were evaluated in the inferior colliculus of two groups of neonatally deafened cats after prolonged periods of deafness (>2.5 yr): the first group was implanted with an intracochlear electrode and studied acutely (long-deafened unstimulated, LDU); the second group (LDS) received a chronic implant and several weeks of electrical stimulation (pulse rates $\geq$300 pps). Acutely deafened and implanted adult cats served as controls. Spiral ganglion cell density in all long-deafened animals was markedly reduced (mean $<5.8\%$ of normal). Both long-term deafness and chronic electrical stimulation altered temporal resolution of neurons in the central nucleus (ICC) but not in the external nucleus. Specifically, LDU animals exhibited significantly poorer temporal resolution of ICC neurons (lower $f_{max}$, longer response latencies) as compared with control animals. In contrast, chronic stimulation in LDS animals led to a significant increase in temporal resolution. Changes in temporal resolution after long-term deafness and chronic stimulation occurred broadly across the entire ICC and were not correlated with its tonotopic gradient. These results indicate that chronic electrical stimulation can reverse the degradation in temporal resolution in the auditory midbrain after long-term deafness and suggest the importance of factors other than peripheral pathology on plastic changes in the temporal processing capabilities of the central auditory system.

INTRODUCTION

Sensorineural hearing loss in the mammalian cochlea as a result of hair cell loss leads to anatomical and functional changes both in the cochlea and in the central auditory system. Within the cochlea the changes include progressive demyelination of spiral ganglion neurons, loss of their peripheral processes, and degeneration of their somata. Within the central auditory system, the changes include reduction in the volume of the cochlear nuclei, shrinkage or loss of auditory brain stem neurons, a reduction in the synaptic density within the central nucleus of the inferior colliculus (ICC), and a degradation in the temporal resolution and spatial selectivity of physiological responses (Hardie et al. 1998; Nadol et al. 1989; Nishiyama et al. 2000; Otte et al. 1978; Snyder et al. 1995; Vollmer et al. 1999, 2000). The age at onset of deafness is an important factor determining the extent of these pathological changes, suggesting a critical period for normal development of the auditory system (human studies: Eggermont and Bock 1986; Ruben and Rapin 1980; animal studies: Silverman and Clopton 1977; Webster 1983, 1988).

Animal studies have shown that sensorineural hearing loss before the onset of hearing or during early postnatal periods results in more profound anatomical degeneration (e.g., Moore 1990; Nishiyama et al. 2000; Nordeen et al. 1983) and functional degradation or reorganization as compared with changes observed after auditory deprivation later in life (e.g., Hardie and Shepherd 1999; Hardie et al. 1998; Moore 1994; Raggio and Schreiner 1999; Shepherd et al. 1997; Silverman and Clopton 1977; Trune 1982).

Clinical studies also suggest that the acquisition of speech and language in humans has a critical period within the first few years of life (Eggermont and Bock 1986; Ruben and Rapin 1980). The deficits in speech and language acquisition are generally more pronounced with earlier and more extensive auditory deprivation. The greatest deficits are observed when deafness occurs around birth (Ruben 1986).

Several studies indicate that early chronic electrical stimulation of the auditory system during maturation can ameliorate or prevent some of these negative effects of auditory deprivation. Histological studies have shown that chronic electrical stimulation of the cochlea prevents or delays the degeneration of spiral ganglion cells (SGC) (e.g., Hartshorn et al. 1991; Leake et al. 1991, 1992, 1999) and ameliorates degenerative changes in the cochlear nucleus (Lustig et al. 1994; Matsushima et al. 1991) that occur after deafness. Electrophysiological studies have demonstrated that early introduction of chronic electrical stimulation in neonatally deafened cats either maintains or increases temporal resolution of neurons in the ICC (Snyder et al. 1995; Vollmer et al. 1999) depending on the stimulus frequency.

Moreover, clinical studies indicate that deaf children implanted at a younger age demonstrate better speech recognition than those implanted at an older age (Hassanzadeh et al. 2002; Miyamoto et al. 2003; Moog and Geers 1999; Osberger 1995). Congenitally and prelingually deaf cochlear implant (CI) users who are implanted as adults generally demonstrate particularly poor speech discrimination (Busby et al. 1991). Other studies suggest that the immature deaf auditory system may be more plastic or adaptable to the electrical information provided by a CI than the mature, long-deafened auditory system (e.g.,...
Blamey et al. 1996; Dawson et al. 1992; Osberger et al. 1998; Tyler et al. 1997; Waltzman 1997). These studies highlight the important role of age at implantation and duration of deafness for speech recognition performance in CI users. However, even prelingually deafened individuals implanted as adults demonstrate gradual improvements in speech recognition over time, indicating that auditory experience and implant use are important factors for enhanced performance (Busby et al. 1991). These results suggest that reorganization of auditory processing capacities even after prolonged periods of deafness is presumably a reflection of plastic mechanisms in the central auditory system.

The goal of the present study was to examine temporal processing in the inferior colliculus (IC) in an adult animal model of congenital deafness. Specifically, we assessed the temporal response properties [maximum following frequencies (Fmax) and first spike latencies] of single IC neurons to address the following questions: first, how is temporal resolution affected by long-term auditory deprivation? We hypothesized that the severe cochlear pathology induced by prolonged periods of deafness would impair temporal processing in the IC. The present study extends the very limited data set reported in a previous investigation on temporal response properties of IC neurons in a single long-deafened animal (Shepherd et al. 1999) and examines neuronal responses in neonatally deafened, unstimulated animals that were studied after long durations (>2.5 yr) of deafness (LDU). Second, what is the effect of chronic electrical stimulation on temporal processing in the neonatally deafened adult auditory system? The current study reports for the first time temporal resolution data of IC neurons obtained from long-term (>3.5 yr) neonatally deafened animals that received chronic electrical stimulation as adults (LDS). Earlier studies using chronic stimulation with identical signals indicated a significant increase in temporal resolution of ICC neurons in the developing auditory system (Vollmer et al. 1999). Thus these data provide a valuable basis for a comparison of functional alteration after chronic electrical stimulation between the mature and developing auditory system.

In addition, SGC density was determined for the individual animals to evaluate the effects of long-term deafness on peripheral cochlear pathology and the consequences of severe spiral ganglion cell loss on temporal resolution in the central auditory system.

**METHODS**

All procedures described in the present study followed National Institutes of Health and University of California, San Francisco, guidelines for care and use of laboratory animals.

**Deafening and implantation**

Before all surgical procedures, animals were sedated with an intramuscular injection of ketamine (22–33 mg/kg) or initial anesthesia was induced with inhaled isoflurane. An intravenous catheter was inserted into the cephalic vein for fluid or drug administration. General anesthesia was induced with pentobarbital sodium (7–10 mg/kg iv) and maintained at a surgical areflexic level with supplementary intravenous infusion of pentobarbital sodium (2–6 mg· kg⁻¹· h⁻¹) in Ringer solution. Vital functions (heart rate, respiration, CO₂, or O₂ saturation, body temperature) were monitored continuously and maintained at physiological levels.

Two experimental groups of neonatally deafened animals (n = 11) were studied after prolonged periods of neonatal deafness (>2.5 yr): six unstimulated cats received a unilateral cochlear implant as adults and were studied acutely (LDU group); the other five cats were also implanted as adults and received several weeks to months of chronic electrical stimulation prior to study (LDS group; Table 1). All long-deafened animals were deafened as newborns by systemic administration of neomycin sulfate (40–70 mg/kg im/SID) beginning 24 h after birth and continuing for the first 14–25 days after birth. Neomycin injections were terminated when profound hearing loss (>108 dB) was confirmed by the absence of auditory brain stem responses to clicks (0.2 ms/ph, 20 pps) and frequency following responses to tonal stimuli (500 Hz). None of the animals demonstrated any residual hearing. All animals in both long-deafened groups were maintained for periods ranging from 2.5 to 7.2 yr prior to study. Two of the LDS animals (K13 and K24) were implanted immediately before study, the others were implanted ≥1 wk before the electrophysiological experiment to allow thresholds to stabilize. LDS animals were implanted, and electrical stimulation of the auditory nerve was initiated at ages ranging from 3.5 to 7.0 yr with an average of 5.3 yr.

**TABLE 1. Durations of deafness and stimulation histories for all long-term neonatally deafened animals**

<table>
<thead>
<tr>
<th>Animal ID</th>
<th>Age at Initial Stimulation, mo</th>
<th>Duration of Stimulation, wk</th>
<th>Age at Study, mo</th>
<th>Spiral Ganglion Survival (% normal)</th>
<th>Stimulation Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long deafened unstimulated (LDU)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K16</td>
<td>NA</td>
<td>NA</td>
<td>44</td>
<td>4.5</td>
<td>NA</td>
</tr>
<tr>
<td>K24</td>
<td>NA</td>
<td>NA</td>
<td>30</td>
<td>3.1</td>
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<tr>
<td>K33</td>
<td>NA</td>
<td>NA</td>
<td>51</td>
<td>5.1</td>
<td>NA</td>
</tr>
<tr>
<td>K51</td>
<td>NA</td>
<td>78</td>
<td>4.9</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>K73</td>
<td>NA</td>
<td>38</td>
<td>18.3</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>K11</td>
<td>NA</td>
<td>38</td>
<td>11.9</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>46.5</td>
<td>7.97</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long Deafened Stimulated (LDS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH611</td>
<td>42</td>
<td>28</td>
<td>50</td>
<td>3.1</td>
<td>300/30 SAM, 80 pps, SP; Beh</td>
</tr>
<tr>
<td>CH618</td>
<td>52</td>
<td>34</td>
<td>60</td>
<td>1.3</td>
<td>300/30 SAM, SP; Beh</td>
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<tr>
<td>CH539</td>
<td>65</td>
<td>13</td>
<td>69</td>
<td>2.7</td>
<td>SP, 300/30 SAM; Beh</td>
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<tr>
<td>K56</td>
<td>84</td>
<td>7</td>
<td>86</td>
<td>5.1</td>
<td>300/30 SAM; Beh</td>
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<tr>
<td>CD393</td>
<td>73</td>
<td>24</td>
<td>79</td>
<td>3.5</td>
<td>300/30 SAM</td>
</tr>
<tr>
<td>Mean</td>
<td>63.2</td>
<td>21.4</td>
<td>68.8</td>
<td>3.1</td>
<td></td>
</tr>
</tbody>
</table>

The average age at study was 46.5 months for the LDU animals and 68.8 months for the LDS animals. SP denotes chronic stimulation using an analogue speech processor; Beh indicates behavioral training; 80 pps indicates chronic stimulation with an unmodulated 80 pps continuous train of electrical pulses; 300/30 indicates chronic stimulation with pulses delivered at a carrier rate of 300 pps with 100% SAM at 30 Hz.
Fourteen adult cats with normal auditory experience prior to the experiment served as controls. These animals served also as the control group in a previous study (Vollmer et al. 1999). Control cats usually were deafened 1.5–3.5 wk before study by intraveneous administration of kanamycin and ethacrynic acid (Xu et al. 1993). About half of the control animals were implanted immediately before the experiment, the others were usually implanted 1–2 wk before study.

Comparison of temporal resolution data from cats studied directly after implantation and those studied ≥1 wk after implantation did not show any statistically significant differences in either the LDU or the control group. The immediate and delayed implantation data were therefore pooled for subsequent analysis.

All electrode arrays were inserted through the round window into the left scala tympani. Chronic implantations were carried out under sterile conditions. Implants consisted of four platinum-iridium ball-shaped electrode contacts (≈300 mm diam) in a molded silicone rubber carrier that was custom designed for the cat cochlea (Rebscher et al. 1988). Electrode contacts were designated 1–4 from apical to basal cochlear locations and were arranged as two bipolar offset-radial pairs (apical pair: 1,2; basal pair: 3,4). The separation between the electrodes comprising a pair was 1 mm, and the two pairs were separated by 3 mm. A percutaneous connector allowed direct electrical connection to the electrodes.

Chronic stimulation

Chronic electrical stimulation was applied for 4 h/d, 5 days/wk for a mean duration of 21 ± 11 (SD) wk, with maximum signal intensity adjusted to 2 dB above electrically evoked auditory brain stem thresholds (EABR) threshold for each individual subject. All LDS animals were stimulated with the apical electrode pair 1,2. Due to lead failure, however, subjects CD393 and CH539 were stimulated with electrode pairs 2,3 and 1,4, respectively, during the final weeks of stimulation. Because the level of chronic stimulation generally exceeded the dynamic range of IC neurons both for widely and narrowly spaced electrode pairs and leads to an activation of virtually the entire IC (unpublished data), it seems unlikely that the wider spacing of the stimulating electrodes in CH539 affected temporal resolution in this animal.

Electrical stimulation was delivered either by an analogue speech processor (SP) that transduced ambient environmental sounds or by computer-generated amplitude modulated pulse trains. For stimulation with the analogue speech processor, the frequency spectrum of the analogue stimulation was band-pass filtered from 250 Hz to 3 kHz with a roll-off at the shoulder frequencies of 6 dB/octave. The computer-generated signal was a continuous train of electrical pulses (200 μs/phase, charge-balanced biphasic square-wave pulses) delivered at a 300 cps carrier rate and sinusoidally amplitude modulated (SAM) at a frequency of 30 Hz with a modulation depth of 100% (300/30 SAM). The choice of these stimuli was based on previous studies showing that chronic electrical stimulation of the developing auditory system using these signals resulted in a significant increase in temporal resolution of IC neurons (Snyder et al. 1999; Vollmer et al. 1999).

One animal (CH611) received stimulation with 80 pps delivered by a backpack stimulator for a period of 2 wk. This animal did not tolerate stimulation outside its home cage, and the 80 pps stimulation was used until an analogue SP became available as a backpack stimulator for use in the home cage.

All but one cat received additional stimulation during behavioral training sessions (Table 1; 5 day/wk). The total duration of supra-threshold stimulation during the behavioral sessions was very brief (a total of usually <30 s) and, therefore very limited compared with the duration of chronic passive stimulation (4 h/day at supra-threshold level).

Acute electrophysiological experiments

The anesthetic procedures were virtually identical to those already described for implantation. The animal’s head was stabilized in a head holder, and the IC contralateral to the cochlear implant was exposed. Neuronal responses were recorded differentially using two tungsten microelectrodes matched in impedance (0.8–1.5 MΩ). The active electrode was advanced through the IC from dorsolateral to ventromedial parallel to the tonotopic gradient (Brown et al. 1997) with low frequencies represented more superficially and high frequencies at progressively deeper locations within the ICC. Biphasic square-wave pulses (0.2 ms/phase, 3 pps) were used as a search stimulus. Neural activity was recorded differentially, band-pass filtered, amplified, and monitored on an oscilloscope (Tektronix 565) and an audio monitor.

At intervals of 100 μm along each penetration, the minimum response threshold levels for three cycles of a 100-Hz sinusoidal signal and for pulses (0.2 ms/phase, 3–10 pps) were determined audiovisually for either single- or multiple-neuron responses. Thresholds were plotted as a function of IC depth to obtain a spatial tuning curve (STC; Fig. 1). As reported previously, STCs were typically W-shaped (Vollmer et al. 1999). The highest threshold region between the two locations of minimum thresholds was defined as the border between the two nuclei (see Fig. 1, - - -) and allowed neurons to be assigned to either the external nucleus of the IC (ICX) or the ICC. Due to the difference in charge per phase of the 100-Hz sinusoidal (5 ms/phase) and pulsatile (0.2 ms/phase) signals, STCs obtained with sinusoidal stimuli generally had lower thresholds, markedly sharper tuning, and greater dynamic ranges than those obtained with pulses. Therefore in most penetrations the border between ICX and ICC was determined by the STCs for sinusoidal stimuli.

When a single neuron was isolated, threshold was determined audiovisually. Stimuli were then presented at intensities of 2–6 dB above threshold, and responses to pulse trains (0.2 ms/phase) of increasing frequencies (starting with 10 pps; increments of 5–20 pps) were recorded until the neuron no longer responded to the sustained stimulus. The duration of the recording window was 320 ms after...
stimulus onset followed by an interstimulus interval of 1,000 ms, and neuronal responses were recorded for 20 repetitions of each stimulus condition. Action potentials (spikes) were isolated from background noise and stimulus artifact using a window discriminator (BAK-DIS-1). The number of spikes and the latency of each response after stimulus onset were stored in a computer and displayed on a monitor.

To assess the temporal processing capabilities of isolated neurons, peristimulus-time histograms (PSTHs) were plotted, and the maximum stimulus frequency \( F_{\text{max}} \) to which each neuron phase locked \((P < 0.01, \text{Raleigh-test; Mardia 1972})\) was determined. Figure 2A illustrates examples of PSTHs constructed for one single neuron responding to intracochlear pulse trains of increasing frequencies (10–90 pps). Vector strength (VS) and significance \((P)\) of phase-locking are noted to the right of each histogram. The response to the first pulse in each pulse train, i.e., the onset response, was excluded from the analysis. In this example, the highest frequency to which the neuron responded in a phase-locked manner \((P < 0.01, \text{Raleigh-test})\) was 70 pps. In addition, the entrainment, i.e., the average number of driven spikes per stimulus pulse, normalized for the number of stimulus trains, is plotted for each stimulus repetition rate in Fig. 2B.

Neurons with \( F_{\text{max}} < 10 \) pps were excluded from the analysis. First spike latencies of responses to pulse trains at 20 pps were measured for each single neuron. Latencies <4.5 ms were excluded from the analysis to ensure that neither responses from afferent fibers nor stimulus artifact contaminated the results.

Based on the STCs, the locations of single neurons were assigned to either ICX or ICC. \( F_{\text{max}} \) and first spike latencies were analyzed separately for the two nuclei (Vollmer et al. 1999). Neurons from penetrations in which STCs were incomplete and did not allow a clear definition of the border between the two nuclei for either pulsatile or sinusoidal stimulation were assigned as ICX or ICC neurons if their recording locations fell into the nonoverlapping depth range of either nucleus calculated for the given animal group. For example, in control animals the recording depths for ICX neurons ranged from 300 to 1,880 \( \mu \text{m} \), and for ICC neurons the range was 1,355–5,500 \( \mu \text{m} \). Therefore neurons from incomplete STCs were included as ICX neurons if their recording depth was <1,354 \( \mu \text{m} \) and included as ICC neurons if their recording location was >1,881 \( \mu \text{m} \). Neurons that did not meet these criteria were excluded from the analysis (see RESULTS) (Vollmer et al. 1999).

Cochlear histology

After completion of the electrophysiological experiment, the cochlea of all long-deafened animals were preserved for histology. The methods for the preparation of cochlear specimens were identical to those described by Leake et al. (1999) and will be described here only briefly. The cochlea were perfused, decalcified and embedded in LX resin. Semithin sections (1–2 \( \mu \text{m} \)) were stained with toluidin-blue to assess the presence or condition of the organ of corti and the survival of auditory nerve fibers. OC, organ of Corti; ScT, scala tympani; RC, Rosenthal’s canal.

**FIG. 2.** A: poststimulus time histograms (PSTHs) for responses from a single neuron to pulse trains of increasing frequencies. Stimulus frequency (pps), vector strength (VS), and significance of phase locking \((P)\) are shown for each histogram. Binwidth = 670 \( \mu \text{s} \). \( F_{\text{max}} \) was defined as the highest frequency to which the neuron followed in a synchronized manner \((P < 0.01, \text{Raleigh-test; Mardia 1972})\). B: entrainment (driven spike rate per stimulus) is plotted as a function of pulse repetition rate (pps). The curve indicates low-pass filtering.
TEMPORAL RESOLUTION IN LONG-DEAFENED AUDITORY SYSTEM

A

B

C

D

100 μm

100 μm
RESULTS

SGC survival

Figure 3A illustrates the organ of corti of a normal hearing cat. In contrast, Fig. 3B shows an example of the severe degeneration of the organ of corti observed in the long-term deafened animals included in this study. Histological examination revealed that there were no surviving inner or outer hair cells in any of the LDU or LDS animals. Further, cochleae from control animals (Fig. 3A) demonstrated a severe loss of SGC and myelinated nerve fibers when compared with cochleae from control animals (Fig. 3C).

Figure 4A shows the morphometric SGC data for the six LDU and the five LDS animals. The volume ratios (densities) of the SGC somata are averaged for the 10% sectors of the spiral ganglion from the cochlear base to the apex (normalized for basilar membrane length of each individual cochlea). All SGC densities reported in this study refer to the implanted left cochlea in each animal. The data in each group are expressed as percent of normal SGC density as described previously (Leake and Hradek 1988). Severe degeneration was observed throughout the cochlea, and the mean SGC density was <14% of normal for each of the sectors in both long-deafened groups. Figure 4B displays the SGC density averaged across all cochlear sectors. The mean SGC density in the LDU group was reduced to 7.9% of normal, whereas in the LDS group the mean SGC density was reduced to only 3.1% of normal. This difference was statistically significant (Student’s t-test; P < 0.01).

Somewhat greater survival in the LDU group was seen in the 70–80% (13.7% of normal) and the 80–90% (13.2% of normal) sectors. However, these results are mainly due to the data from a single animal (K73) that had an average SGC density of 44 and 39% of normal in these sectors, respectively, and an overall SGC density of 18.3% (see Table 1). It is possible that this animal had, at an early state of deafness, some residual apical hair cells and perhaps even some low-frequency residual hearing that was missed with our standard ABR thresholds measures. When the SGC data from K73 were excluded from the analysis, the distribution of SGC densities across all cochlear sectors for the LDU group became relatively flat, and the overall SGC density was reduced to 5.9% of normal. However, the difference in overall SGC density between the LDU and LDS animals remained significant (P < 0.001).

Table 1 summarizes the density of SGC (as percent of normal) averaged across all cochlear sectors for the individual cats. The data indicate that degeneration of the spiral ganglion was very severe in all 11 animals.

Maximum following frequencies (F_max)

The responses of 659 single neurons to pulse trains of increasing frequencies were recorded in control, LDU and LDS animals. F_max was estimated for 261 neurons in control animals, for 164 neurons in LDU animals, and for 215 neurons in LDS animals. As assessed by the STC for each recording penetration (e.g., Fig. 1), ~15% of all neurons (n = 97) were located in the ICX, and ~78% of all neurons (n = 499) were located in the ICC.

Approximately 7% of all neurons (n = 44) could not be assigned to either ICX or ICC and were therefore excluded from the analyses. Because STC widths tend to be very broad and dynamic ranges very small in long-deafened animals...
(Vollmer et al. 2000), a clear W-shape of the STCs often could not be identified, and boundaries between ICX and ICC were difficult to determine. Thus the number of neurons that could not be assigned to either ICX or ICC was somewhat larger in both LDU (9.8%, \( n = 16 \) neurons) and LDS animals (9.8%, \( n = 21 \) neurons) compared with unassigned neurons in the control group (2.7%, \( n = 7 \) neurons).

Quantitative distributions of \( F_{\text{max}} \). Figure 5 illustrates the distributions of \( F_{\text{max}} \) values and the median \( F_{\text{max}} \) for all IC neurons that were assigned to either ICX (■) or ICC (□) in the three experimental groups. Across the three groups of cats, >99% of all ICC neurons had \( F_{\text{max}} < 300 \) pps. Generally, \( F_{\text{max}} \) values for IC neurons in each group covered a fairly broad range of frequencies, but the distributions of \( F_{\text{max}} \) for ICC neurons always extended to higher frequencies than that of ICX neurons. For ICC neurons, however, the distributions differed markedly for the three groups. The distribution of ICC neurons in LDU cats peaks at the lowest \( F_{\text{max}} \) (60–80 pps, median \( F_{\text{max}} = 70 \) pps; Fig. 5B), the distribution of the control group peaks at an intermediate \( F_{\text{max}} \) (80–100 pps, median = 95 pps; Fig. 5A), and the distribution of the LDS cats peaks at the highest \( F_{\text{max}} \) (120–140 pps, median = 135 pps; Fig. 5C).

Because \( F_{\text{max}} \) values were usually not normally distributed, the central tendency of each distribution is best expressed by the median \( F_{\text{max}} \). Figure 6 summarizes the median \( F_{\text{max}} \) and the variability (quartile deviation, \( Q \)) of all single-neuron data for the three groups of cats and presents statistical comparisons (Mann-Whitney \( U \) tests). Results are shown separately for ICX (left) and ICC (right). In the ICX, there were no significant differences in \( F_{\text{max}} \) among the three groups (\( P > 0.01 \)). In the controls and the LDS animals, the median \( F_{\text{max}} \) of ICX neurons was significantly lower than the median \( F_{\text{max}} \) of neurons in the ICC. In fact, the median \( F_{\text{max}} \) in the ICX was less than half that recorded in the ICC in both these groups. Controls had a median \( F_{\text{max}} \) of 45 pps in the ICX versus 95 pps in the ICC, and LDS animals had a median \( F_{\text{max}} \) of 60 pps in the ICX versus 135 pps in the ICC. In contrast, there was no significant difference in median \( F_{\text{max}} \) between ICX and ICC in the LDU animals (47 pps for ICX neurons vs. 70 pps for ICC neurons).

Statistical comparisons of the data for ICC neurons show that \( F_{\text{max}} \) values for the three experimental groups were all significantly different from one another. LDU cats exhibited the poorest temporal resolution, the control group had an intermediate median \( F_{\text{max}} \), and the LDS cats demonstrated significantly higher \( F_{\text{max}} \) than both the LDU and control groups.

Topographic distribution of \( F_{\text{max}} \). Previous studies have suggested that ICX neurons have a weak tonotopic organization with characteristic frequencies (CFs) tending to decrease with increasing recording depth (Aitkin et al. 1975). In contrast, the ICC has a clear tonotopic gradient from low to high CFs with increasing recording depth (Brown et al. 1997; Merzenich and Reid 1974; Snyder et al. 1990). To determine if there is a correlation between the frequency-following capability of IC neurons and the tonotopic gradients in the nuclei, it was necessary to first exclude the possibility of a confounding relationship between temporal resolution and the locations of minimum ICC thresholds (best location; BL) for each stimulating electrode pair. Analyses showed that temporal resolution did not vary systematically relative to BL. Instead, the distributions of both \( F_{\text{max}} \) and latencies as a function of depth relative to BL were relatively flat for all three groups of animals. Thus inter-animal or -electrode differences in BLs did not influence the analysis of temporal resolution versus recording depth when normalized to the ICX/ICC border.
We then analyzed the spatial distributions of $F_{\text{max}}$ along IC depth for all neurons assigned to either ICX or ICC in the three groups (Fig. 7). The recording depths are not normalized to the border between ICX and ICC in these plots. Instead, the actual recording depths noted during the experiment are shown. Neurons from STCs that allowed a clear identification as either ICX or ICC neurons and neurons that were assigned to either nucleus based on criteria described in METHODS are shown separately. As mentioned in the preceding text, the relatively flat STCs and the severely reduced dynamic ranges in the long-deafened animals (Vollmer et al. 2000) made it particularly difficult to determine the boundaries between ICX and ICC. As a result, the number of identified ICX and ICC neurons is markedly reduced in these animals. However, Fig. 7 documents that the assigned neurons fall within the range of identified neurons for both ICX and ICC in each group of animals. Although we cannot exclude the possibility of a misassignment of individual neurons, Fig. 7 shows that misassignments would be limited to a few neurons located close to the border between ICX and ICC and would not influence the overall outcome of our topographic analysis.

In the LDU group, there is no overlap between the depth ranges for ICX and ICC neurons, probably due to the limited numbers of ICX neurons recorded ($n = 14$). In the control and LDS animals, there is substantial overlap in depths for ICX and ICC neurons. This overlap is due to variability in the location of the border between the two nuclei (600–3,300 μm across subjects).

If temporal resolution of IC neurons and the tonotopy in the IC are correlated, $F_{\text{max}}$ should decrease with recording depth (decreasing CF) in the ICX and should increase with recording depth (increasing CF) in the ICC. Consequently, the linear regression lines for $F_{\text{max}}$ in the ICX should have negative slopes with increasing IC depth, and those in the ICC should have positive slopes.

In fact, with the exception of the ICC in control animals, all the slopes of the regression lines for $F_{\text{max}}$ in the ICX and ICC are positive (Fig. 7). However, all correlation coefficients for both nuclei data are relatively small (ICX: all $R < 0.45$, ICC: all $R < 0.16$), and with the exception of the ICX data in the LDS groups, none of the correlations are statistically significant. If the exceptional regression analysis was repeated with the depths of the recording locations normalized to the border in a more limited set of ICX neurons (raw data from Fig. 8C),
groups. In the three groups of cats, neurons in the ICC exhibited a relatively broad range of $F_{\text{max}}$ at any given recording depth with the exceptions of the sparcely sampled superficial and deepest recording locations.

To determine whether a relationship exists between $F_{\text{max}}$ and defined areas in the IC, Fig. 8 summarizes the median $F_{\text{max}}$ for specific depth ranges along the CF gradient in each experimental group. In this analysis, the recording depths have been normalized to the border between ICX and ICC. Neurons were excluded from this analysis if the exact recording depth relative to the border could not be determined precisely, thereby reducing the number of neurons and changing the median $F_{\text{max}}$ in Fig. 8 (see METHODS). The horizontal lines in Fig. 8A indicate the median $F_{\text{max}}$ for the ICX (50 pps) and ICC neurons (100 pps) in the control animals and are reproduced for comparison in Fig. 8, B and C. The --- indicate the border between the two nuclei.

Plotted in this manner, there is no apparent relationship between $F_{\text{max}}$ and IC depth (i.e., CF gradient) for ICX neurons. In the ICC of control animals (Fig. 8A) neurons show a broad maximum in $F_{\text{max}}$ around the center of the ICC, whereas temporal resolution decreases at the more superficial (dorsolateral) and deep (ventromedial) recording locations. In the ICC of LDU animals (Fig. 8B), the median $F_{\text{max}}$ values exhibit a broad decline throughout the nucleus, and at all depth sectors the values are equal to or smaller than the median $F_{\text{max}}$ for controls. In contrast, ICC neurons from LDS animals (Fig. 8C) show a broad increase in $F_{\text{max}}$ across the entire ICC compared with control animals. These results indicate that the regions of increased $F_{\text{max}}$ after high-frequency stimulation are not correlated with the tonotopic gradient in the ICC.

First spike response latencies

Onset latencies for single neurons were recorded as a second measure of temporal resolution. Of the 645 neurons for which latency values were obtained, 270 were recorded in control animals, 159 in LDU animals, and 216 in LDS animals. A total of 100 neurons (15.5% of all neurons) were located in the ICX, 501 neurons (77.7%) were located in the ICC, and 44 neurons (6.8%) could not be assigned to either ICX or ICC and were excluded from the analyses.

Quantitative distributions of first spike latencies. In Fig. 9 the distributions of first-spike latencies in the three groups are shown separately for the ICX (●) and the ICC (□). Values and arrows indicate the median latencies for each nucleus. Generally, latencies of ICC neurons are clearly distributed toward shorter latencies compared with ICX neurons. In LDU animals (Fig. 9B), the majority of latencies are shifted toward longer latencies (7–10 ms, median 8.0 ms), whereas most latencies in LDS animals (Fig. 9C) are shorter (5–7 ms, median 6.4 ms) than those recorded in the controls and LDU animals. The median first spike latency data for ICX and ICC neurons and statistical comparisons (Mann-Whitney $U$ test) are summarized in Fig. 10. In control animals (Fig. 9A), most latencies are between 5 and 8 ms (median 6.9 ms). In LDU animals (Fig. 9B), the majority of latencies are shifted toward longer latencies (7–10 ms, median 8.0 ms), whereas most latencies in LDS animals (Fig. 9C) are shorter (5–7 ms, median 6.4 ms) than those recorded in the controls and LDU animals.
In the ICC, responses recorded from LDU animals have significantly longer median latencies [8.0 ± 0.9 (Q) ms; \( P < 0.01 \)] than those from both the control group [6.9 ± 0.8 (Q) ms] and the LDS group [6.4 ± 0.8 (Q) ms]. The difference in latencies between the LDS and control animals is not significant.

**Topographic distribution of latencies.** The spatial distributions of onset latencies along IC depth are shown in Fig. 11. The data are identified as ICX (■ and ○) and ICC (■ and □) neurons. Neurons from STCs with a well-defined border that allowed a definite identification as either ICX or ICC neurons, and those neurons that were assigned to either nucleus by the criteria described in METHODS are identified separately. Because both \( F_{\text{max}} \) and latencies were determined for the majority of neurons, the ranges of recording locations in the two nuclei and the regions of overlap between ICX and ICC neurons in each group are virtually identical to those reported for the spatial distributions of \( F_{\text{max}} \) (see Fig. 7).

With the exception of depths >5,000 μm, where only a small number of neuronal responses could be recorded, a relatively broad range of latencies occurs at any recording location throughout the IC in each group of animals (Fig. 11). However, neurons in the ICC are distributed toward shorter latencies that comprise a narrower range of latencies than those in the ICX.

The slopes of the linear regression lines in both ICX and ICC of all three groups are negative. However, all correlation coefficients are very small (all \( R < 0.33 \)), and with the exception of those for the ICX and ICC in LDS animals the correlations are not statistically significant. When the regression analysis was repeated for neurons from STCs with a well-defined border and with the depth normalized to the border (raw data from Fig. 12C), the correlation between \( F_{\text{max}} \) and both ICX and ICC depths in LDS animals is no longer significant.

To better examine and illustrate a possible relationship between changes or differences in latency and the CF gradient in the IC, the median latencies are plotted for identified ranges of depth normalized to the border between ICX and ICC in Fig. 12.
Median latencies from control and LDS animals (Fig. 11, A and C, respectively), show relatively flat distributions across the IC with a slight tendency for the shortest latencies to be located around the center of the ICC. Median latencies in the LDU animals decrease progressively with increasing ICC depth (Fig. 12B). However, the number of ICC neurons per depth range is very limited in these animals, and no neurons were recorded at the deepest ICC locations (>3 mm re border) where control animals usually show a tendency for an increase in latencies.

FIG. 11. Distributions of first spike response latencies along IC depth for ICX (●, ○) and ICC neurons (■, □) for groups A–C. ● and ■, neurons for which the exact borders between ICX and ICC could be identified (ident.); ○ and □, neurons for which the exact borders could not be determined (ass.). Linear regression lines and correlation coefficients (R) are shown for all ICX and ICC neurons. n, numbers of neurons.

FIG. 12. Distributions of median latencies for identified depth ranges in the IC for groups A–C. —, the median latency for ICX (left) and ICC (right) neurons in control animals and are repeated in B and C. - - -, borders between ICX and ICC, which are assigned a depth value of 0 to normalize data across subjects. Number of latencies measured at each depth range is given in the bars. Median latencies (MDN) are shown separately for the ICX and ICC in each graph. n, number of neurons for each IC subnucleus. Error bars = SE.
With the exception of the median latencies at depths of 2.5–3 mm \( n = 3 \), the median latencies in the LDU group are longer throughout the entire IC as compared with both control and LDS animals.

The results indicate that first spike latencies in control and LDS animals are not systematically correlated with the tonotopic gradient of either nucleus, and similar to the changes in \( F_{\text{max}} \), changes in latencies occurred relatively uniformly across the entire ICC.

**Correlation between \( F_{\text{max}} \) and response latencies**

Langner and colleagues (1987) reported in normal hearing cats a significant correlation between the onset latencies of IC neurons and their best modulation frequencies (BMF; modulation frequency that evokes the strongest neuronal response) in response to amplitude modulated (AM) tones.

Despite different stimulus conditions (acoustic vs. electric) and different criteria used for the determination of temporal resolution (BMF vs. \( F_{\text{max}} \)), similar estimates of temporal resolution of IC neurons have been reported previously for both acoustic, AM-evoked responses and electrically evoked responses to unmodulated pulse trains (Snyder et al. 1995; Vollmer et al. 1999). Among the similarities are the temporal patterns of IC responses (PSTHs), the latency distribution, and the range and distribution of the frequency following capabilities of IC neurons (\( F_{\text{max}} \) and BMF).

Figure 13 shows the relationship between and the covariation of onset latencies and \( F_{\text{max}} \) for ICX and ICC neurons in the three groups of animals. To produce the curves in Fig. 13, the equation used by Langner and colleagues was corrected for the instantaneous onset of electrical pulses and the lack of cochlear delays in electrical stimulation [onset latency = \((5.1 \pm 0.9)\) ms + \((1.2 \pm 0.2) / CF + 0.16 \pm 0.03\) \( / F_{\text{max}} \)] (cf. Snyder et al. 1995). The two curves in each panel encompass the lowest and the highest first spike latencies predicted by the modified equation. The majority of both ICX and ICC neurons from each experimental group have latencies within the predicted range of latencies for given \( F_{\text{max}} \) marked by the two curves. The closest agreement between latencies predicted by the modified equation and the observed data are found for neurons from LDS animals. Generally, the correlations in Fig. 13 show a decrease in latencies with increasing \( F_{\text{max}} \), suggesting an inverse correlation between \( F_{\text{max}} \) and onset latencies in response to electrical stimulation of the auditory nerve.

**DISCUSSION**

**Cochlear histology**

The SGC density in both unstimulated and chronically stimulated long-deafened cats was severely diminished as compared with normal. LDU animals had an average SGC density of \(~8\%\) of normal, and LDS animals an average of \(~3\%\) of normal. This difference in SGC density between the two groups of long-deafened animals was statistically significant. Previous studies have shown that SGC degeneration continues progressively for many years after aminoglycoside-induced hair cell loss (Hardie and Shepherd 1999; Leake and Hradek 1988; Leake and Rebscher 2004; Shepherd and Javel 1997; Xu et al. 1993). Thus the overall lower SGC survival in the LDS animals may be explained on the basis of the older age at study (68.8 mo) in these animals as compared with the LDU animals (duration of deafness = age at study: 46.5 mo).
Effects of long-term deafness and chronic electrical stimulation on temporal resolution

CENTRAL NUCLEUS OF THE IC (ICC). Long-term auditory deprivation and chronic electrical stimulation greatly affected temporal resolution in the ICC of long-deafened animals.

Long-term auditory deprivation. Long-term deafness per se (LDU cats) resulted in a significant decrease in temporal resolution of ICC neurons (i.e., lower $F_{\text{max}}$ and longer latencies) as compared with control subjects. A previous study (Snyder et al. 1995) of neonatally deafened, unstimulated adult animals also reported a lower mean $F_{\text{max}}$ value (86 pps) as compared with normal control cats (93 pps), but this difference in $F_{\text{max}}$ did not achieve statistical significance. The mean age at study of these animals was 41.7 mo (unpublished data) and was, therefore only slightly lower than that of the LDU animals included in the present study. Because Snyder and colleagues did not distinguish between responses from ICX and ICC neurons, it seems likely that inclusion of ICX neurons with low temporal resolution in the analysis masked the differences in $F_{\text{max}}$ between the unstimulated and control animals.

Shepherd and colleagues (1999) also reported a reduction in the temporal resolution of ICC neurons (lower $F_{\text{max}}$ and longer latencies) in neonatally bilaterally deafened, unstimulated animals when compared with control animals. It should be noted, however, that the two animals studied had substantially shorter durations of deafness (12 and 13 mo) compared with the LDU animals in the present study (mean: 46.5 mo), suggesting that the negative effects of auditory deprivation on temporal resolution of ICC neurons may occur earlier than the prolonged durations of deafness reported in the present study.

Shepherd and colleagues (1999) also reported an even greater increase in latency for ICC neurons in a single long-deafened (deafened as juvenile), unstimulated animal. However, given the limited data available, no conclusion can be drawn about the exact time course of functional changes caused by auditory deprivation.

Overall, however, previous work (Shepherd et al. 1999; Snyder et al. 1995) and the present study agree that auditory deprivation clearly reduces temporal resolution of neurons in the ICC.

Chronic electrical stimulation. In a previous study, we reported that chronic electrical stimulation delivered in the developing auditory system caused significant functional changes in the IC. Specifically, in neonatally deafened animals that were implanted ~6–8 wk after birth and chronically stimulated for several months with high-frequency pulsatile signals, neurons in the ICC had significantly higher temporal resolution than neurons recorded from control animals (Vollmer et al. 1999). The present study extends these findings by examining stimulation effects in the mature, long deafened auditory system and demonstrates that the introduction of chronic high-frequency stimulation even after long periods of complete auditory deprivation results in a significant increase in temporal resolution of ICC neurons. In fact, the increase in temporal resolution observed in LDS animals is virtually identical to that previously reported for the neonatally deafened, early stimulated animals (Vollmer et al. 1999).

Moreover, similar to the previous findings in early-stimulated animals, the increase in $F_{\text{max}}$ after chronic high-frequency stimulation of LDS animals was not only significantly higher than in LDU animals but also higher than in control animals. These findings are remarkable because the prolonged periods of neonatal deafness in the LDS animals resulted in severe degeneration of the spiral ganglion and auditory nerve fibers. Initially we wondered if the severe peripheral pathology observed in long-term deafness would reduce or eliminate any benefit for temporal resolution of chronic electrical stimulation of the cochlea. However, the data reported here clearly indicate that the long-deafened, mature auditory system is highly capable of plastic changes and substantial functional recovery including the potential to reverse at least one aspect of functional degradation (temporal resolution) observed after prolonged periods of auditory deprivation.

In fact, the LDS animal with the shortest period of chronic stimulation (7 wk; K56) demonstrated an increase in median $F_{\text{max}}$ of ICC neurons that exceeded that of control animals and reached the second highest $F_{\text{max}}$ value (142 pps) in the group of LDS animals. These data suggest that despite severe peripheral pathology, even short periods of chronic stimulation are sufficient to induce marked changes in temporal resolution in the long-deafened auditory system. However, the present study was not designed to systematically investigate the exact time course of functional changes after chronic stimulation.

Consistent with increased temporal resolution of ICC neurons in neonatally deafened animals that were exposed to chronic electrical stimulation either during development or as adults, clinical studies also have shown evidence of improved temporal processing with device use even in prelingually deafened adult cochlear implant subjects (Busby et al. 1991). Presumably, peripheral pathology is not the limiting factor for functional plasticity in the long-deafened central auditory system.

TOPOGRAPHIC DISTRIBUTION OF TEMPORAL RESOLUTION VERSUS RECORDING LOCATION. The normalization of the recording depth to the border between ICX and ICC allows a more exact investigation and interpretation of the relationship between different neuronal response properties and their recording location in the IC (i.e., inferred relative CF). Because of the large variability in the location of the border between ICX and ICC, these relationships or correlations can otherwise easily be masked or distorted.

Temporal resolution was not systematically correlated with the tonotopic gradient in the ICC in any of the investigated groups. That is, increasing depth in the ICC does not correspond to increasingly higher temporal resolution. Instead, temporal resolution of ICC neurons was relatively evenly distributed across each of the nuclei and, in the control and LDS animals, showed only a broad maximum around the center of the nucleus with a decrease in temporal resolution toward both more dorsolateral (superficial) and more ventromedial (deep) regions. Long-term deafness resulted in a broad decrease in temporal resolution across the entire ICC, and chronic electrical stimulation resulted in an increase of temporal resolution in neurons throughout the ICC. There was no evidence of a preferential or selective effect on neurons in any particular CF region of the ICC, regardless of whether the animals had a history of complete auditory deprivation or chronic electrical stimulation.

These results support findings reported in earlier studies from our laboratory of responses to electrical stimulation in
control and neonatally deafened, early stimulated animals (Vollmer et al. 1999). Further, they are also consistent with earlier studies using acoustic stimulation by Langner and colleagues (1987), who described a relatively weak correlation between onset latency and CF in normal hearing cats. Shirane and Harrison (1991) described a small but significant relationship between latency and electrode depth in the IC of two normal control chinchillas. However, the lack of differentiation between ICX and ICC neurons may be responsible for this apparent correlation.

In contrast, Shepherd and colleagues (1999) reported an orderly decrease in latency of ICX neurons from ~25 to 10 ms with increasing recording depth in control, bi- and unilaterally deaf animals but not in their long-deafened animal in which neurons could not be recorded in IC depths <2,500 μm. We also saw a weak tendency for ICX latencies to decrease with increasing depth in our three groups of animals. However, the significance of this finding is unclear because the tonotopic gradient of the ICX is from high to low frequencies. Therefore if temporal resolution is related to CF, we would expect latency to increase with lower CFs (i.e., increasing depth), not to decrease.

**Mechanisms.** The specific mechanisms underlying the described changes in temporal resolution of ICC neurons after long-term deafness and after chronic electrical stimulation of the long-deafened auditory system are not known. Among possible explanations for the decreased frequency following ability of ICC neurons after long-term auditory deprivation are changes in the balance of excitatory and inhibitory influences on IC neurons (Raggio and Schreiner 1999; Schreiner and Raggio 1996), a weakening of individual excitatory synapses (Kotak and Sanes 1997), a decrease in excitatory neurotransmitter release (Vale and Sanes 2002), and a decrease in synaptic density in the IC of neonatally deafened cats (Hardie et al. 1998). Moreover, the loss of myelin observed after long-term deafness may lead to an increase in membrane capacitance (Koles and Rasminsky 1972; Tasaki 1955) that could reduce the efficiency of a neuron in responding to electrical stimuli and increase the likelihood of conduction block. Also associated with the loss of myelin and partial neural degeneration are prolonged refractory periods and an increased vulnerability of the propagating spike (Cragg and Thomas 1964; Felts et al. 1997; Koles and Rasminsky 1972; McDonald and Sears 1970; Shepherd and Javel 1997; Smith and McDonald 1999; Tasaki 1955). These changes result not only in an increase in response latency and jitter but in a general reduction in conduction and synaptic efficacy of afferent connections along the ascending central auditory system. This reduced efficacy of pathway and synaptic transmission may contribute to lower temporal resolution particularly in neurons in the ICC that receives mainly input from afferent auditory neurons. In contrast, neurons in the ICX receive major inputs from the somatosensory system (e.g., Aitkin 1986) and, therefore, may be less affected by auditory deprivation than ICC neurons.

The present study shows that chronic electrical activation of the cochlea in LDS animals not only reverses the described functional degradation and restores the temporal resolving capacity to a “normal” level, but also significantly increases the $F_{\text{max}}$ of ICC neurons above the level of control animals. These findings suggest that neural remodeling or auditory plasticity can occur despite extensive structural and functional degeneration of the auditory nerve and the central auditory system. The specific underlying functional and/or structural modifications in afferent projections are unknown. Changes may occur prior to and/or at the level of the IC (e.g., Eysel et al. 1981; Kaas 1996; Keller et al. 1990) and may include local Hebbian-type synaptic processes (Cruishank and Weinberger 1996; Diamond et al. 1993), changes in the synaptic organization or strength of existing afferent connections (e.g., modification in synaptic size or relocation of synapses to more effective sites on the target neuron), sprouting of new afferents that results in increased synaptic density, and/or alterations in membrane properties. Each of these mechanisms could lead to an increase in synaptic efficacy, higher synchrony in the neuronal excitation pattern and, thus, to an increase in the temporal resolution of IC neurons. Moreover, together with previously reported results from neonatally deafened, early stimulated animals, the present findings suggest that higher-frequency electrical stimulation may be more effective in modulating the inhibitory and excitatory mechanisms in the ICC than lower-frequency stimulation or normal acoustic stimulation (Vollmer et al. 1999).

Based on these hypotheses, the broad increase in temporal resolution observed across the entire ICC after chronic stimulation (LDS animals) could be related to a relatively broad spread of current into the modiolus. In long-deafened animals, the severe reduction of peripheral auditory nerve processes and SGC may provide a particularly low impedance pathway for the current to spread into the modiolus (Frijns 1995) and to excite auditory nerve fibers over a very broad range of CFs. Also, the broader STC widths and reduced dynamic ranges observed in these animals would lead to broader current spread at a given suprathreshold level compared with a subject with narrower STC widths and larger dynamic ranges. Given the assumption that high-frequency stimulation is especially effective in modulating the efficacy of afferent stimulation prior to and/or at the level of the ICC (Vollmer et al. 1999), the particularly broad current spread of suprathreshold electrical pulsatile stimuli in long-deafened animals (Vollmer et al. 2000) may explain the broad increase in temporal resolution of single neurons across most of the ICC.

**EXTERNAL NUCLEUS OF THE IC (ICX)** The present study provides the first report characterizing driven activity and temporal resolution in the ICX of long-deafened cats. There were no significant differences in the temporal resolution (median $F_{\text{max}}$ and first spike latencies) of ICX neurons among the three groups of animals. These observations are consistent with previous data from neonatally deafened animals that received chronic electrical stimulation immediately after deafening at an early age (Vollmer et al. 1999). Those animals also did not show any differences in the $F_{\text{max}}$ of ICX neurons. Moreover, ICX data from all groups in the present study are very similar to previously reported data from ICX neurons in those early-stimulated animals. Together these findings suggest that the temporal resolution of neurons in the ICX is not affected by the stimulation history or auditory experience (e.g., the temporal parameters of stimulation) (Vollmer et al. 1999), by the duration of deafness, or by the age at onset of stimulation.

One explanation for the absence of plastic changes in the temporal response properties of ICX neurons after long-duration deafness and chronic electrical stimulation is the strong...
somatosensory input to the ICX (e.g., Aitkin 1986). This input may maintain or dominate the frequency following capabilities of ICX neurons and make them less sensitive to auditory deprivation or changes in auditory inputs. Another possible explanation is that the ICX, in contrast to the ICC, receives major descending projections from both the primary and non-primary auditory cortices (e.g., Andersen et al. 1980; Coleman and Clerici 1987; Faye-Lund 1985; Gonzalez-Hernandez et al. 1987; Kudo and Nakamura 1988; Oliver and Huerta 1992; Willard and Martin 1983). Because mean $F_{\text{max}}$ of auditory cortical neurons is about an order of magnitude lower than that for neurons in the IC (Schreiner and Raggio 1996), corticofugal input may dominate the temporal resolution of ICX neurons and prevent or counteract the influence of chronic (high-frequency) auditory stimulation on functional changes.

ICX VERSUS ICC. Previous results from control animals and neonatally deafened animals that received chronic electrical stimulation during development have shown characteristic differences in the temporal resolution of electrical signals between neurons in the ICX and ICC (Shepherd et al. 1999; Snyder et al. 1991; Vollmer et al. 1999). Specifically, neurons in the ICC had significantly higher temporal resolution (i.e., higher $F_{\text{max}}$ and shorter latencies) than those in the ICX. In the present study, ICC neurons in LDU animals exhibited higher temporal resolution as compared with ICX neurons. However, in the LDU animals, no significant difference was observed in temporal resolution between ICX and ICC ($P > 0.01$). This lack of difference was in part due to the low $F_{\text{max}}$ values determined for neurons in the ICC (median $F_{\text{max}} = 70$pps), but it should be noted that the smaller number of neurons recorded ($n = 14$) and the large variance in $F_{\text{max}}$ in the ICX of this group might also have contributed to this result.

COVARIATION BETWEEN $F_{\text{MAX}}$ AND RESPONSE LATENCIES. A negative correlation between first spike latencies and $F_{\text{max}}$ has been described earlier in acoustical studies with normal hearing cats (Langner et al. 1987) and in electrical studies of both control and neonatally deafened, early stimulated animals (Shepherd et al. 1999; Snyder et al. 1995; Vollmer et al. 1999). In the present study, we have documented a negative correlation between first spike latency and frequency following capability of IC neurons in LDU and LDS animals. These findings are consistent with our suggestion that long-term auditory deprivation results in a reduction in synaptic efficacy in the central auditory system and thus in a general reduction in temporal processing capabilities (lower $F_{\text{max}}$ and longer latencies), whereas chronic electrical, higher frequency stimulation results in an increase in synaptic strength and therefore in improved temporal resolution (higher $F_{\text{max}}$ and shorter latencies). The negative correlation between latency and frequency following is also in agreement with the suggestion that this co-variation may be based on the existence of intrinsic neuronal mechanisms in the temporal processing of periodic signals in central auditory neurons (Langner and Schreiner 1988; Langner et al. 1987; Schreiner and Langner 1988) that are not affected by either long-term deafness or chronic electrical stimulation.

Conclusion

Overall, the results indicate that auditory experience can profoundly alter the functional status of the long-deafened, adult auditory system and emphasize the importance of neuronal plasticity in the modulation of temporal resolution in the deaf central auditory system.

Furthermore, the results have important clinical implications. Clinical studies with long-term, prelingually deafened adult cochlear implant users have demonstrated a reduced ability to resolve temporal patterns of electrical signals including poor gap detection and a reduced ability to perceive different rates of stimulation compared with postlingually deaf adults or prelingually deaf subjects with short durations of deafness prior to implantation (Busby et al. 1991–1993). However, there is also evidence that prelingually deafened subjects implanted as adults show gradual improvement in their temporal resolution skills. The improvements in prelingually deaf adult cochlear implant subjects may reflect enhanced temporal resolution in the central auditory system with increasing auditory experience and device use.

Acknowledgments

We thank Dr. Charlotte M. Moore for help in the data collection, E. Dwan for the daily maintenance of the animals, and M. Fong for electrical engineering.

Grants

This work was supported by Neural Prosthesis Program Contract N01-DC-3-1006 and Deutsche Forschungsgemeinschaft Vo 640/1–1.

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