6th Quarterly Progress Report

January 1 through March 31, 2005

Neural Prosthesis Program Contract #N01-DC-3-1006

Protective and Plastic Effects of Patterned Electrical Stimulation on the Deafened Auditory System

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ABSTRACT

Previous studies conducted by our group have demonstrated that electrical stimulation from a cochlear implant elicits significant trophic effects on spiral ganglion cell survival in neonatally deafened cats (Leake et al., 1999, 2000). In this Quarterly Progress Report, we present initial results from a new study designed to investigate the possible role of the developmental "critical periods" in the stimulation-induced alterations in the cochlea and central auditory system. Specifically, we examined cats deafened at 30 days of age, after a brief period of normal auditory experience and compared results to previous results in neonatally deafened animals.

In this new experimental model of early-acquired hearing loss, animals were deafened at 30 days of age using the same deafening protocol as for neonatally deafened animals. Profound hearing losses occurred by 48-56 days of age. Unilateral electrical stimulation with bipolar electrodes and temporally challenging signals (325pps/60Hz AM) was initiated immediately after deafening and continued over periods of 28-30 weeks. To investigate whether this initial period of normal auditory function provided additional benefits for the trophic effects of subsequent cochlear implant stimulation, data from this group were compared with a group of neonatally deafened animals carefully matched to the 30 day group for age at implantation and duration of stimulation.

Preliminary control data from animals deafened at 30 days of age (n=3) and studied at 7-8 weeks age (time of implantation of subjects undergoing chronic stimualtion) showed that spiral ganglion cell (SGC) degeneration was at least as severe (62% or normal) as that seen in a matched group of neonatally deafened animals (67% of normal). This suggests the possibility of an accelerated time course of degeneration in the 30-day deafened group. Preliminary data in implanted/stimulated 30 day deafened animals (n=3) demonstrated a significant (more than 20%) increase in SGC survival in the stimulated ears as compared to the deafened control side, indicating that electrical stimulation significantly enhanced SGC survival in this group. In fact, 91% of the SGC that were present *when stimulation was initiated* were maintained over the prolonged stimulation period in the 30 day deafened group, as compared to only 78% maintained in the age-matched neonatally deafened group. On the other hand, these preliminary data did *not* demonstrate a significant difference in final SGC survival between the 30-day deafened and the neonatally deafened groups at the end of the experiment. Although auditory pathways are still immature at 30 days of age, deafening in this older group was initiated after the development of adult-like spontaneous activity in the auditory nerve and adult-like auditory brainstem responses, in contrast to the neonatally deafened group. Thus, these preliminary results did not provide compelling evidence for a developmental critical period at least during the first postnatal month. Delaying the onset of deafness by more than 30 days and initiating stimulation immediately thereafter did not provide additional benefit for SGC survival over the long term. It should be noted, however, that there was a trend toward higher maintenance of SGC in the 30 day deafened group; it will be of interest to see if this trend achieves statistical significance with a larger number of subjects in subsequent experiments.

In addition during this last quarter, several members of our group attended the annual midwinter meeting of the Association for Research in Otolaryngology to present findings of this Contract research. Six abstracts are appended to this QPR.

INTRODUCTION

The cat auditory system undergoes extensive maturation during the first few weeks of life. Kittens are unresponsive to sound at birth. Spontaneous activity can be recorded at about 7 days postnatal (P) and almost adult-like ABR-thresholds have been reported by about 21 days postnatal (Walsh and Romand, 1992; Fig. 1a). In many previous studies conducted by our group, animals were deafened by ototoxic drug (neomycin) injections initiated immediately after birth and thus these animals never experienced any normal hearing (Fig.1b).

There is substantial evidence from many animal studies that normal auditory input early in life is essential both for normal anatomical maturation and for development of normal adult-like function (Blatchley et al., 1983; Eggermont et al., 1986; Rubel et al., 1984; Rubens et al., 1980; Russell et al., 1995). In order to evaluate the possible role of such a developmental critical period in the effects of electrical stimulation seen in neonatally deafened animals, we have initiated a new experimental series in which neomycin administration is delayed until animals are 30 days of age. This allows us to study the consequences of electrical stimulation of SGC without interfering with the major developmental effects taking place in the auditory system during the first postnatal month (Fig.1c). The initial goal was to evaluate whether this brief period of normal auditory experience would affect either SGC vulnerability to the ototoxic drug and/or influence the subsequent trophic effects of chronic electrical stimulation delivered by a cochlear implant on spiral ganglion neuronal survival.

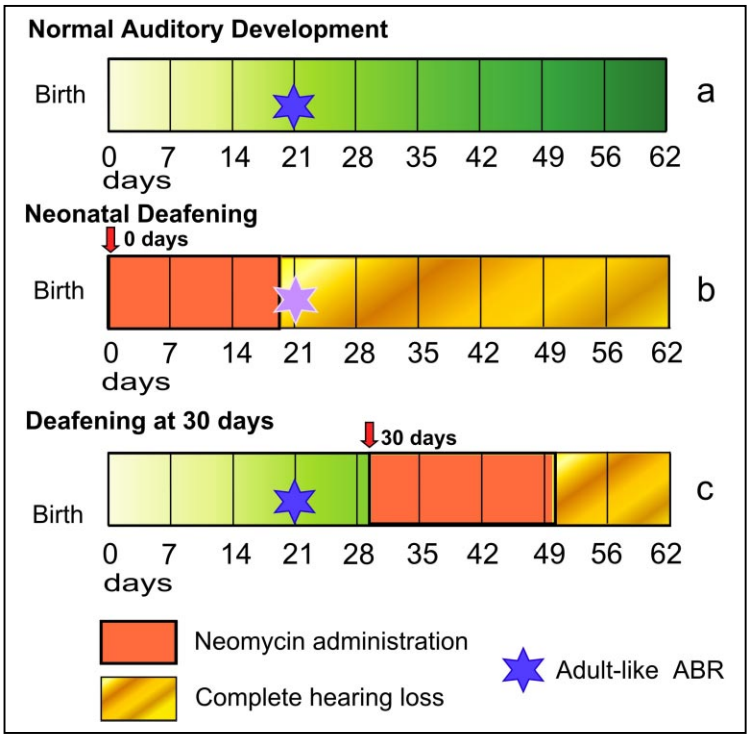

Figure 1.
Illustration of the two different deaf animal models presented in this report for studying the effects of electrical stimulation on spiral ganglion cell survival.

METHODS

Experimental data from six animals deafened by the new protocol are included in this report. Ototoxic drug administration was initiated at 30 days of age using a protocol identical to that employed for neonatal deafening in prior studies. Specifically, daily subcutaneous injections of neomycin sulfate (60mg/kg) were administered for 16 days, and in 2-3 day increments thereafter, until a profound hearing loss was confirmed by the absence of click-evoked auditory brainstem responses at 105 dB SPL. Three of the animals (K186, K187, K188) comprised a control group that were studied at 8 weeks of age in order to evaluate the consequences of the ototoxic drug when administered in older animals and to estimate spiral ganglion survival at the time that animals to be chronically stimulated undergo cochlear implant surgery. The other three animals (K146, K149, K151) were implanted unilaterally at the age of 8-9 weeks with an intracochlear electrode containing two pairs of stimulating contacts, activated as two bipolar stimulation "channels." The animals received temporally challenging chronic electrical stimulation for 4 hours per day, for an average for 29 weeks. The stimulus consisted of a continuous train of charge-balanced biphasic pulses (200 μsec/phase) delivered at a carrier rate of 325 pps and amplitude modulated with a sinusoidal envelope of 60 Hz (100% modulation depth). EABR thresholds were assessed every two weeks for each bipolar channel, and the stimulus intensity for each channel was set at 2 dB above EABR threshold for a single 200μsec/phase pulse delivered on that channel. Table 1 shows the individual deafening and stimulation histories for each cat.

Animals	Neomycin (days)	Age at initial stim. or age at study (weeks)	Period of stimulation (weeks)	Stim. Freq.	Administration of GM1
K146	18	7	30	325/60	-
K149	19	8	29	325/60	GM1
K151	26	8	28	325/60	GM1
Average	**21**	**7.7**	**29**	**-**	-
K186	20	8	-	-	-
K187	22	9	-	-	-
K188	23	8	-	-	-
Average	**21.7**	**8.7**	**-**	**-**	**-**

Table 1. Duration of deafness and stimulation histories are shown for cats deafened at 30 days of age. The cats that received chronic stimulation from a cochlear implant were stimulated with biphasic pulses (200 μsec/phase) delivered at a carrier rate of 325 pps and sinusoidally amplitude modulated at 60 Hz.

Two animals in the stimulated group received ganglioside GM1 until time of implantation. Due to the absence of any significant effect of GM1, the data in this preliminary analysis are combined for animals deafened at 30 days with and without GM1 treatment.

To investigate whether the initial brief period of normal auditory function in animals deafened at 30 days of age provided additional benefits for SGC survival, the data from the two 30-day deafened groups were compared with data from neonatally deafened animals. The subjects were carefully selected from prior studies to match the time of implantation, duration of stimulation and age at study of the new 30-day deafened experimental subjects. In addition, 3 of the 5 neonatally deafened, chronically stimulated subjects also received GM1 ganglioside, to match the 30-day deafened chronic stimulation group, in which 2 of the 3 subjects received GM1.

Group	Number of animals	Neomycin (days)	Age at initial stimulation or sacrifice, (weeks)	Period of stimulation (weeks)	Age at study (weeks)	GM1 treatment, % of group
Deafened at 30 days, stimulated	3	21	7.7	29	36	66%
Deafened at 30 days, control	3	21.7	8.7	-	8.7	-
Neonatally deafened, stimulated	5	19	7.4	29	36	60%
Neonatally deafened, control	4	18.5	8.5	-	8.5	-

Table 2. Duration of ototoxic drug administration and stimulation histories are shown for the two experimental groups cats deafened at 30 days of age and for the comparison neonatally deafened groups.

After completion of the terminal acute electrophysiological experiments (data will be presented later) animals were euthanized humanely by an overdose of barbiturate. Cochlear and transcardiac perfusions were performed with histological fixative containing 2.5% paraformaldehyde and 1.5% glutaraldehyde in 0.1M phosphate buffer. Temporal bones and brain were removed and examined using previously described methods (Leake et al., 1999). Briefly, specimens were postfixed in osmium tetroxide, dissected, decalcified briefly (≈72 hours) and embedded in LX^{TM} epoxy resin. After reconstruction in surface preparations, the length of the basilar membrane was measured and blocks taken at ≈2mm intervals along the basilar membrane were sectioned (1.5 μm thickness) at 50 μm intervals. Spiral ganglion cell survival was estimated using a point-counting method and expressed as percentage of normal for every 10%-sector of the cochlea in each animal. Since cell size can influence cell density in the point-counting method, the cell areas of 25 spiral ganglion cells with clear nuclei at three cochlear locations were measured in the stimulated ears in the two deafened/stimulated groups, in regions where SGC survival was similar.

RESULTS

I. Control group, animals studied at 8 weeks of age.

Data from control animals, studied at about 8 weeks of age (the time when the other animals received a cochlear implant and began chronic stimulation) showed significant spiral ganglion cell loss. This finding is noteworthy, considering that the animals were deafened after the onset of hearing and studied only 2-3 weeks after completion of the ototoxic drug treatment. Spiral ganglion cell data for the three individual subjects are shown in Figure 1.

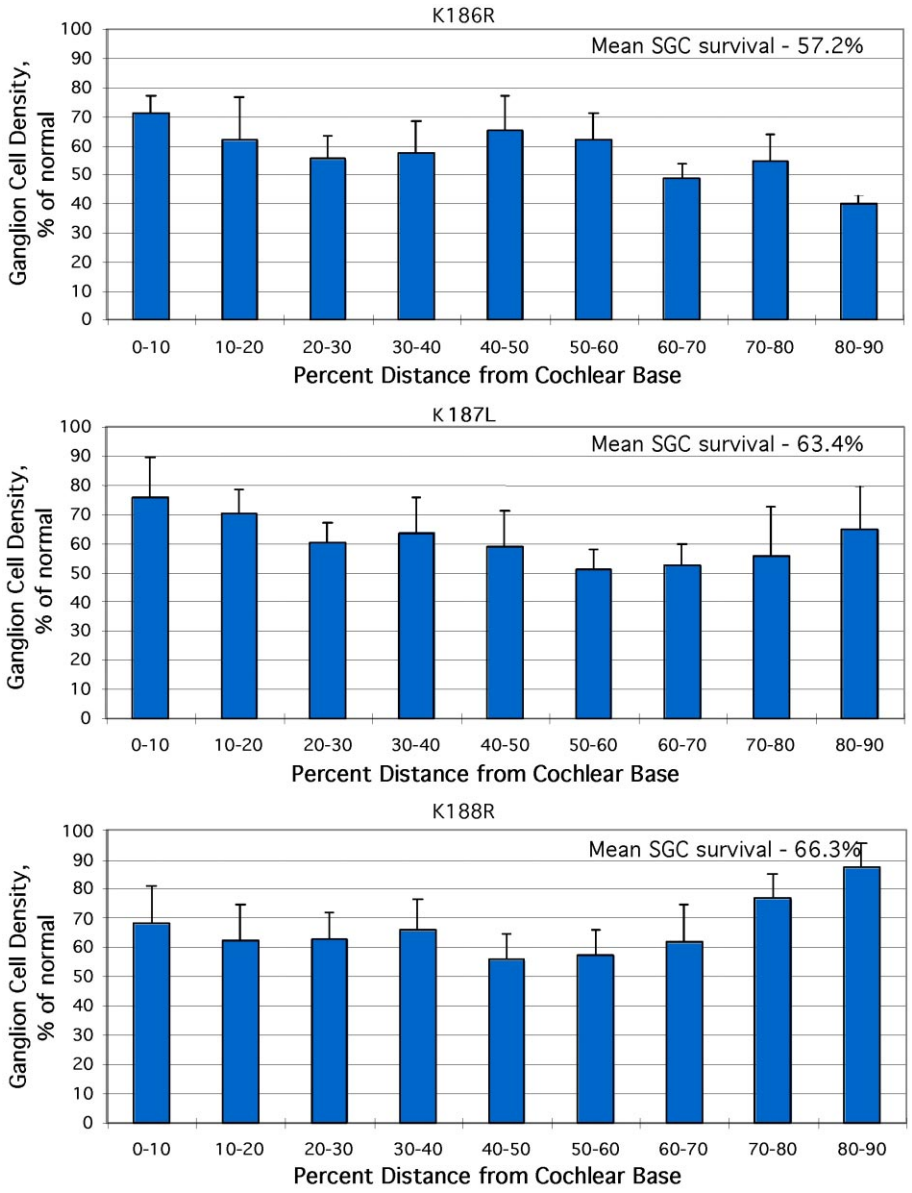

Figure 2.
Spiral ganglion survival is shown for three cats deafened at 30 days of age and studied of 8-9 weeks of age, the time when other subjects received a cochlear implant and chronic stimulation was initiated.

Error bars indicate standard deviation of the mean.
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Figure 3A presents the mean SGC data for the group of 3 animals deafened at 30 days of age. Spiral ganglion cell density was 61.7% of normal when averaged over all sectors of the cochlea. This value was actually slightly *lower* than the neuronal density recorded in the comparison group of neonatally deafened animals studied at the same age (Fig. 3B), although the difference did not achieve statistical significance with the small number of subjects studied to date.

Another interesting finding in these control groups of neonatally and 30-day deafened subjects was an apparent difference in the extent of SGC loss observed in different sectors of the cochlea. We have previously reported neonatally deafened animals exhibit a consistent pattern of SGC survival that is higher in the basal and apical sectors of the cochlea, with more marked loss of the neurons in the middle regions (Leake et al., 1997). That effect is very consistent and is also observed after several months of deafness and even in long-term deafened animals. In contrast, only one of the 30-day deafened animals showed increased survival in the apical part of the cochlea, and in the averaged data from the 3 subjects the extent of cell degeneration was relatively uniform throughout the cochlea, as illustrated in Figure 3.

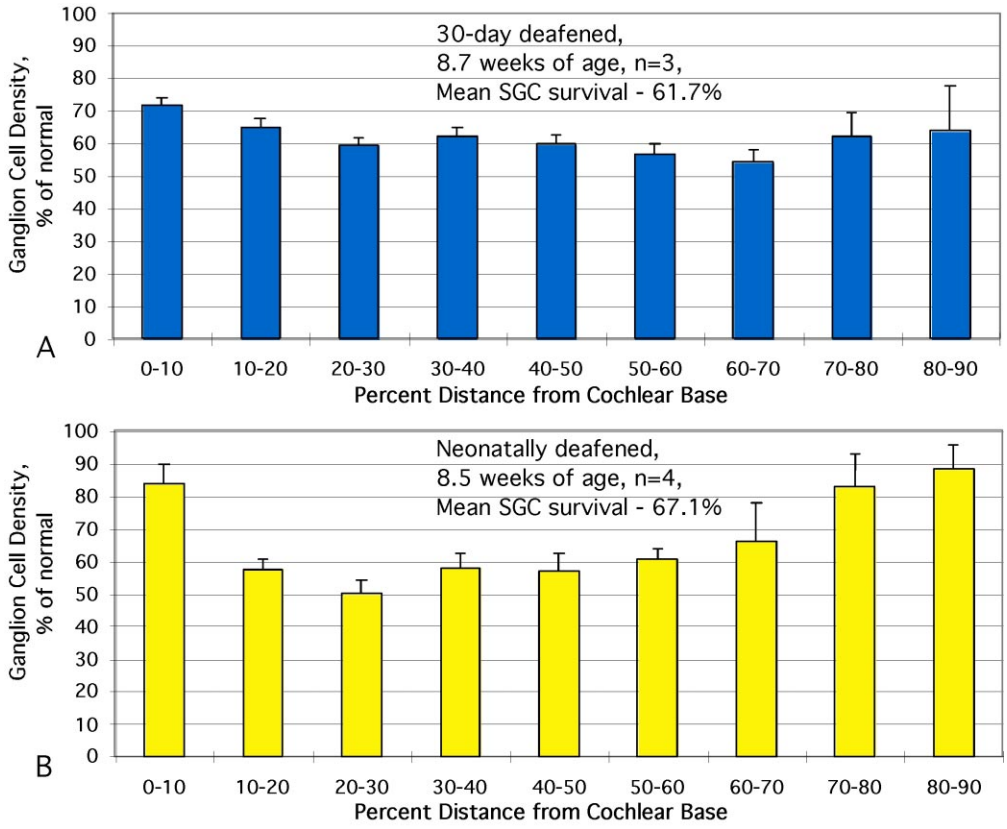


Figure 3. Spiral ganglion neuronal survival in animals deafened at 30 days of age (A) and neonatally deafened animals (B) was studied at 8-9 weeks of age. Overall survival was not significantly different in the two groups, and was actually slightly lower in the 30-day deafened group despite the period of normal hearing and shorter duration of deafness in this group. However, the distribution of remaining SGC was different in the 2 groups. Because maturation of the cochlea occurs sequentially from base to apex, later maturation of the apical region could account for its decreased vulnerability to neomycin administration in the neonatally deafened animals.

II. Chronically stimulated animals.

To date, three cats deafened at 30 days of age have completed the chronic stimulation protocol, with an average of 29 weeks of electrical stimulation. Spiral ganglion cell densities in the stimulated cochleae for each animal were compared with the neuronal densities from the same cochlear region in the contralateral cochleae. The data indicate that chronic electrical stimulation in these animals induced a marked increase in SGC survival in the implanted ears. Figure 5 shows representative histological sections illustrating the increased spiral ganglion cell density in Rosenthal's canal in the stimulated cochlea (left) and the more severe degeneration of spiral ganglion neurons observed in the contralateral cochlea (right). Figure 6 presents the quantitative analyses of the SGC data for the 3 individual 30-day deafened subjects, showing that about 20% more of the normal cell density was maintained in the stimulated cochleae over prolonged periods of stimulation of about 7 months.

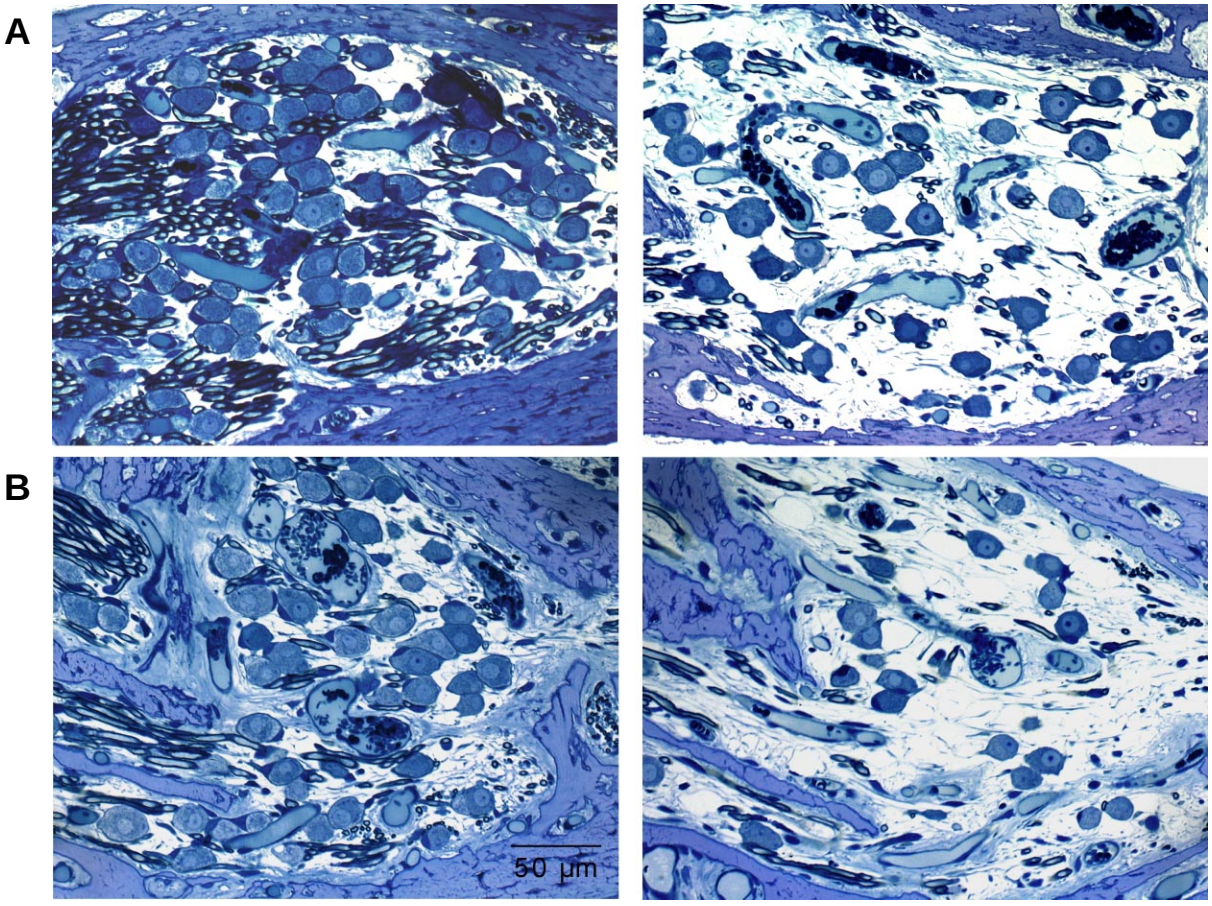


Figure 4. Histological sections illustrating increased SGC survival in stimulated cochleae versus control deafened ears in animals deafened at 30 days of age. A. Sections taken 3 mm from the base at 10-20% cochlear distance showing SGC survival of 65% of normal in the stimulated ear (on the left) and 30% of normal in the deafened control ear (on the right). B. Sections taken 7 mm from the base, 30-40% cochlear distance, with 50% of normal (left) and 25% of normal (right).

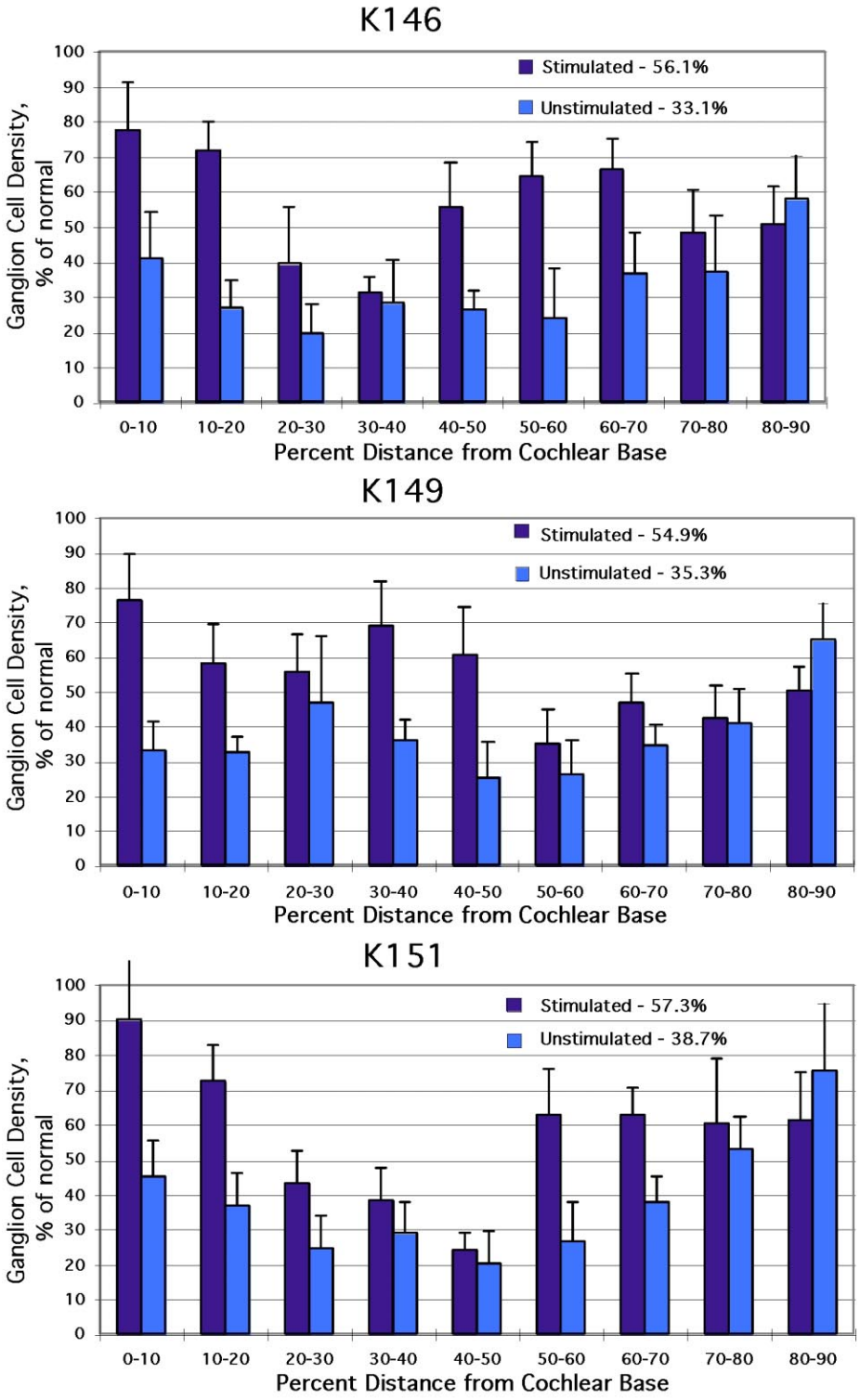


Figure 5. Spiral ganglion survival in three 30-day deafened cats following chronic electrical stimulation for periods of 28-30 weeks, showing maintenance of about 20% higher SGC density in the stimulated cochleae.

Figure 6A shows the pooled data for this initial group of three 30-day deafened animals. Overall SGC survival for these animals was 56.1% of normal. In order to compare the effects of electrical stimulation in the two different models of deafness we used data from previous studies conducted in neonatally deafened cats. For this comparison group we selected subjects that were closely matched to the 30-day deafened group. Specifically, the number of neomycin injections required to induce profound herring loss was similar, cochlear implantation occurred at the same age, and animals in both groups were stimulated for equivalent periods with similar temporally challenging stimuli. In this matched comparison group of neonatally deafened subjects, the overall survival in the stimulated cochleae was 52.3% of normal. This was about 18% higher than the cell density in the unstimulated, deafened control side (Fig. 6B). Thus, electrical stimulation delivered by a cochlear implant over several months clearly resulted in highly significant increases in neuronal survival in both experimental groups regardless of the deafening protocol. However, although the absolute value recorded in the 30-day deafened group was slightly higher than that in the neonatally deafened group, this difference did not achieve statistical significance.

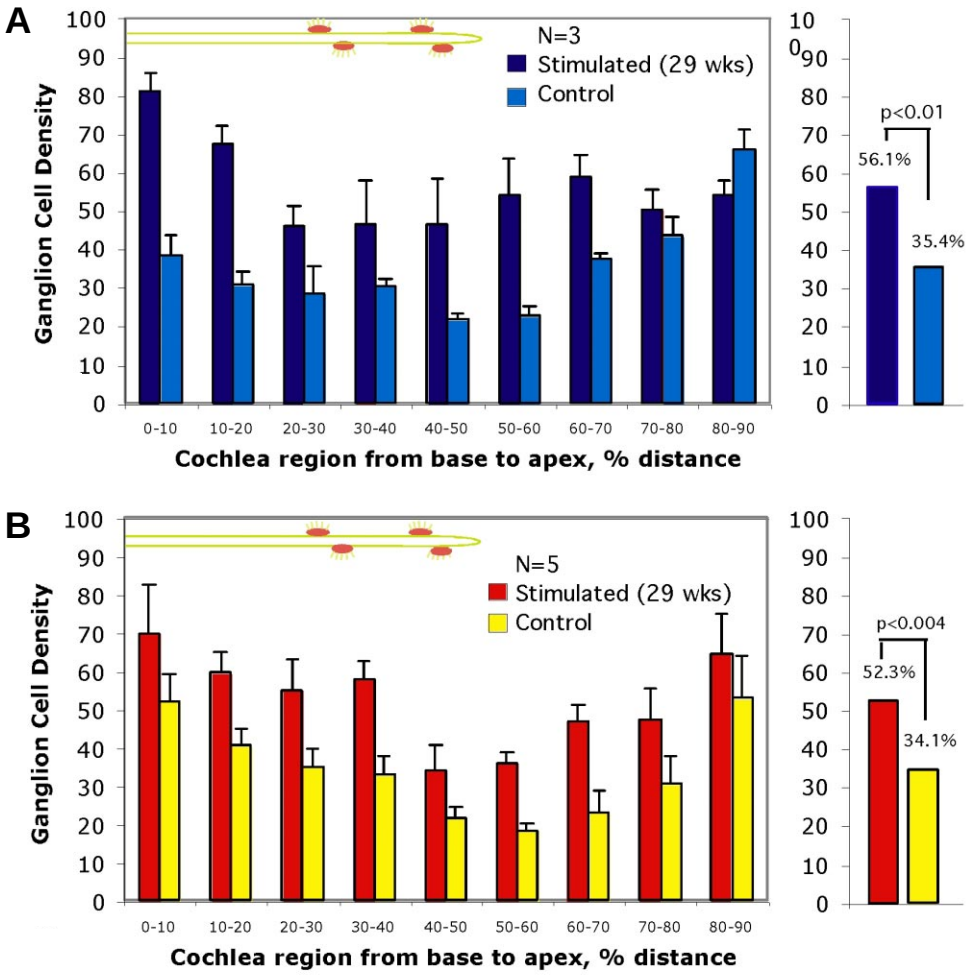


Figure 6.
SGC survival is compared in animals deafened at 30 days of age (A) and in a matched group of animals deafened immediately after birth (B).

In both groups, the stimulated cochleae showed significantly higher survival than the unstimulated control ears.

Although a slightly higher absolute SGC value was observed in the 30-day deafened/stimulated group, there was no *significant* difference between these two groups, which model early-acquired and congenital profound hearing loss.

Thus, as in the control groups studied at 7-8 weeks of age, postponement of neomycin administration up to 30 days of age did not appear to provide additional benefit for spiral ganglion cell survival after a prolonged period of chronic electrical stimulation, at least in this small initial study group. There was no significant difference between SGC densities in stimulated ears of the 30-day deafened and neonatally deafened groups of animals.

SGC soma size also could affect our measurement of cell density in the point-counting method used in our studies and this potentially could obscure differences between the 2 groups. To address this issue, SGC soma size was measured in a subset of the cochlear regions examined. The data demonstrated that there was no difference in cell size between the stimulated ears in the two deafened groups (Fig. 7).

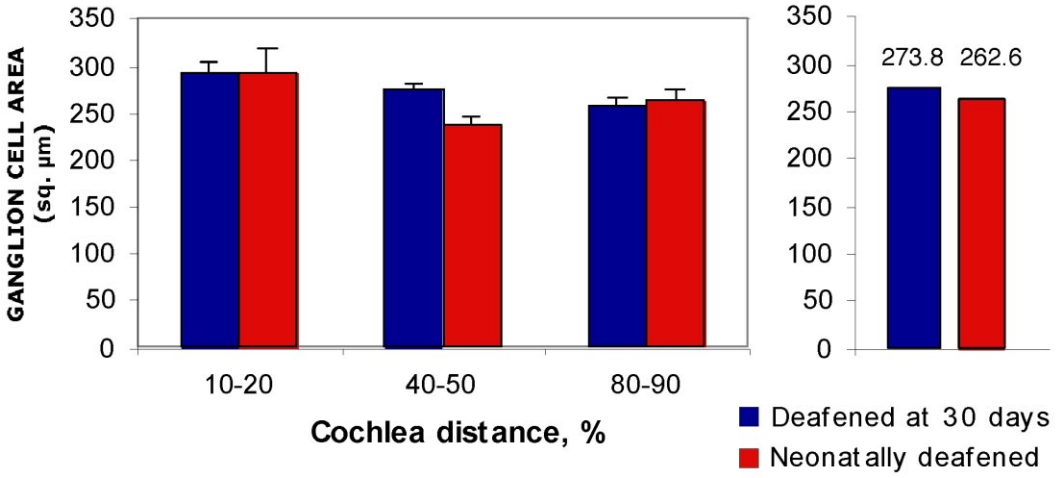
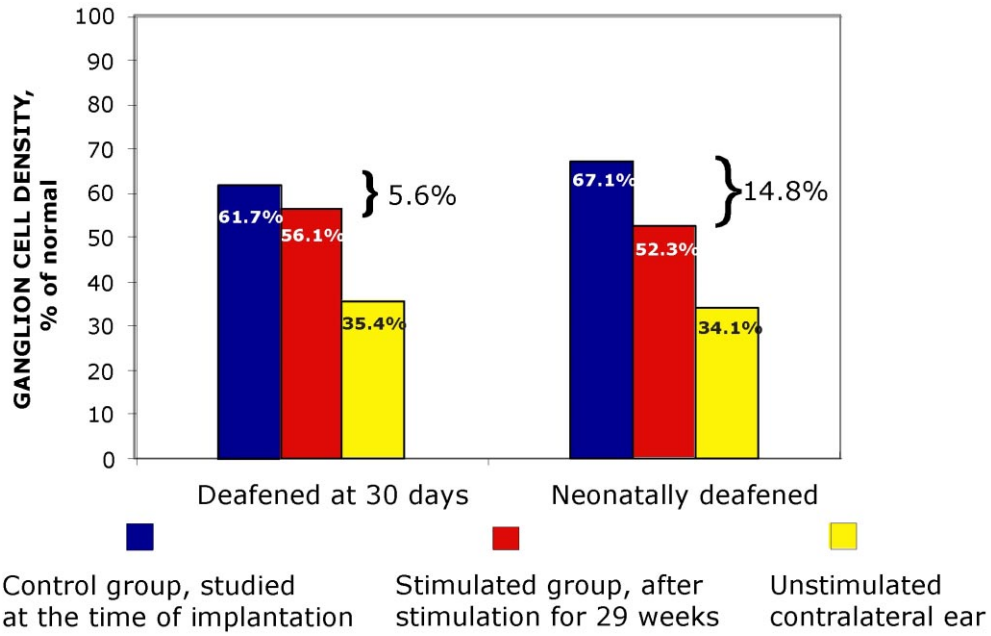


Figure 7. Ganglion cell size in the stimulated cochleae in cats deafened neonatally and at 30 days. Although the cell size appears to be slightly lower for neonatally deafened animals in the 40-50% sector of the cochleae, the mean values are not significantly different in the two groups.

In a final analysis of these data, we have also compared the SGC survival in control animals (at the time of implantation) and after several months of electrical stimulation in the two respective animal models (Fig. 7). In the 30-day deafened cats the mean SGC survival (averaged for all cochlear sectors) decreased by 5.6% over the 29 weeks of stimulation (from 61.7% of normal to 56.1%). This suggests that electrical stimulation maintained about 91% of neurons present at the time of implantation.

In contrast, mean SGC survival in the neonatally deafened animals dropped from an initial average of 67.1% of normal to a final mean of 52%. Thus, only 78% of the initial surviving population of cells was maintained over the subsequent stimulation period in the earlier-deafened group. This finding is likely due to the fact that for the 30-day deafened subjects electrical stimulation was initiated very soon after the deafening protocol was completed. That is, since ototoxic drug treatment was initiated at 30 days of age and continued for about 20 days, these animals were already 50 days old when the profound hearing loss occurred, and they were implanted and stimulation was initiated quite soon after this, at the age of 7-8 weeks.

Figure 7



SUMMARY AND CONCLUSIONS

In both experimental groups SGC survival was already significantly compromised at the time of implantation and initial electrical stimulation. In animals deafened at birth SGC survival was 67% of normal by the time their littermates were implanted at about 8 weeks of age. In the 30-day deafened subjects, SGC density had dropped to 62% at 8 weeks of age, despite the fact that these animals had adult-like hearing thresholds when ototoxic drug administration was initiated, and they were studied only about 2 weeks after profound hearing loss occurred. Although not statistically significant in these preliminary data, this trend toward lower survival in the 30-day deafened group is noteworthy, as it may point toward an accelerated time course of primary afferent degeneration in this animal model of early-acquired hearing loss and the possibility of a sensitive period for auditory deprivation after a brief initial period of normal auditory experience.

In addition, neuronal survival in the animals deafened at 30 days was noted to be more uniform throughout the cochlea and did not show the pattern of better survival at the base and apex that was observed in neonatally deafened animals. This suggests that different cochlear regions may vary in their vulnerability to ototoxic drug damage because they mature at different times. For example, neural survival may be better in the apical cochlea in neonatally deafened animals since that region is known to mature later. Immature features along the cochlea such as close proximity of the tectorial membrane to the organ of Corti, closed tunnel of Corti, low rates of synaptic activity, etc. may reduce the effective exposure to the ototoxic drug during the initial days of drug administration in this animal model of congenital deafness.

Electrical stimulation delivered by a cochlear implant over several months significantly enhanced spiral ganglion cell survival – both in neonatally deafened animals and in animals deafened at 30 days of age. The neonatally deafened group showed maintenance of about 18% higher cell density in the stimulated ears, and the 30-day deafened group showed an increase of about 20%. There was, however, no significant difference in SGC survival in the stimulated ears of the 30 day deafened group (modeling early acquired deafness), as compared to the neonatally deafened group (modeling congenital deafness), although additional data are required due to the limited number of subjects studied to data.

On the other hand, it is interesting that the further reduction in SGC survival that occurred between control group studied at 8 weeks of age and the stimulated group studied at 9 months of age was less for animals deafened at 30 days (6%) than for neonatally deafened subjects (15%). That is, although the 30-day group had lower initial SGC survival at the time of implantation, a greater percentage of the neurons in the 30-day group (91%) were maintained over the several months of electrical stimulation as compared to the in the neonatally deafened group (78%). From these findings we infer that initiating electrical stimulation shortly after onset of deafness may provide additional benefit in spiral ganglion survival.

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WORK PLANNED FOR NEXT QUARTER

1) Ongoing data analyses of spiral ganglion survival, cochlear nuclear morphology and projections as well as electrophysiological data will continue in subjects that have been studied in terminal experiments during the last year. This includes several subjects in which the anti-apoptotic drug desmethyldeprenyl (DES) was administered in deafened neonates both prior to implantation and continuing throughout the chronic stimulation period, and one additional stimulated subject that was deafened at 30 days of age.

2) Two additional subjects will be deafened at 30 days of age, rather than neonatally. One subject will be euthanized as a control at 8 weeks of age. The other will be implanted unilaterally at the same age and will undergo chronic daily 2-channel intracochlear electrical stimulation in this new experimental series designed to evaluate the potential critical period effects of a short period of normal hearing early in life. Chronic stimulation will continue in one other 30-day deafened subject implanted last quarter and in a second subject that is a neonatally deafened, single channel stimulation subject.

3) Studies of the human cochlea will continue, with analyses directed toward employing the Greenwood frequency/place function for the organ of Corti to derive a more accurate frequency map for electrical stimulation of the spiral ganglion with a cochlear implant.

4) Several abstracts will be submitted for the 2005 Conference on Implantable Auditory Prostheses. Also, Dr. Leake will travel to the University of Melbourne in Australia during the next quarter to visit the group working under Dr. Robert Shepherd's NIH Contract with the same title as this contract. The purpose of this visit is to spend several days in detailed discussions and review of technical aspects of chronic electrical stimulation studies in cats being conducted at both sites and to examine possible factors that may underlie disparities in results obtained by our two groups. (*N.B. Support for this trip will be provided by the Sullivan Endowment fund at UCSF, and no funds will be requested from this Contract.)

Abstract **993**, Date **1:00 pm, Wednesday, February 23, 2005**
Session **T15: Cochlear Implant Physiology**

Degradation in Topographic Specificity (Frequency Resolution) of Spiral Ganglion Projections to the Cochlear Nucleus After Neonatal Deafening is Not Reversed by Chronic Electrical Stimulation

**Patricia A. Leake, Russell Snyder, Gary T. Hradek, Leila Chair, Ben H. Bonham*

Previously, we studied the development of spiral ganglion (SG) projections to the cochlear nucleus (CN), using the neuronal tracer NeurobiotinTM</sup> to label small sectors of the SG representing a narrow frequency range. SG projections in normal pre-term kittens showed clear tonotopic organization at 60 days gestation, several days before auditory nerve spontaneous activity emerges and long before hearing onset. But when normalized for CN size, projections in AVCN, PVCN and DCN were 53, 36 and 32% broader, respectively, in neonates than in adult cats. Thus, significant refinement of these pathways occurs in early postnatal life.

This study examined SG projections in 5 adult cats that were deafened neonatally by ototoxic drug administration. At 6-8 weeks of age, animals received a unilateral cochlear implant that delivered electrical stimuli on 2 bipolar channels for 14-34 weeks. Preliminary data show that the basic tonotopic order of SG projections was intact in these deaf animals, but when normalized for the smaller size of the CN, projections were significantly broader than in controls. Laminae in AVCN, PVCN and DCN were all 30-45% broader than normal. Further, there was no significant difference between projections in the stimulated vs. unstimulated CN in the deaf cats. However, it must be noted that selectivity of stimulation, assessed by threshold vs. depth functions in the inferior colliculus, varied widely among subjects.

Our findings suggest that normal auditory experience may be essential for precise refinement of the SG to CN projections. In early-deafened animals the tonotopic order is established and preserved into adulthood, but topographic specificity (inferred frequency resolution) of the primary afferent input to the central auditory system is significantly degraded. Moreover, electrical stimulation from an implant was not sufficient to induce normal refinement of this pathway.

Supported by NIDCD Grant RO1DC000160 and Contract N01-DC-3-1006.

Abstract **1092**, Date **1:00 pm, Wednesday, February 23, 2005**
Session **T8: Inner Ear Anatomy and Physiology 3**

A Frequency-Position Function for the Human Spiral Ganglion

**Divya Sridhar, Olga A. Stakhovskaya, Patricia A. Leake*

Characteristic frequencies for cochlear implant (CI) electrode stimulation sites are currently estimated based on the Greenwood frequency-position equation for the organ of Corti (OC). However, contemporary perimodiolar CI designs target the spiral ganglion (SG), and there is evidence that represented frequency in the SG may be significantly offset from that on the OC. The goal of this study was to derive a frequency-position function for the SG. Surface preparations of osmium-stained cadaveric cochleae (n=) fixed <14 hours postmortem were examined; the OC and SG were measured, and radial fiber trajectories were traced to define a series of frequency-matched coordinates. Mean OC length was 32.1±2.38 mm; mean SG length was 13.96±0.82 mm; mean SG/OC ratio was 0.42±0.02. Frequency-matched points, expressed as percentage of total SG vs. OC length, demonstrated a consistent intersubject correlation that was best fit by a cubic function, which permits derivation of SG frequency by substitution into GreenwoodÕs equation. Data also included the first estimates of SG critical band width and its variance as a function of position along the cochlea; unlike that of the OC, SG critical band width decreases from base to apex. Thus, if CI electrodes are spaced evenly, frequency resolution of stimulation decreases in lower frequencies. The longitudinal position of CI electrodes in the cochlea can be correlated with pitch perception for each electrode as well as with threshold, growth of loudness, and speech intelligibility. As subjects with greater residual hearing and better SG survival receive implants and advances in CI design permit more spatially precise stimulation, and accurate frequency map for the SG provides a basis for matching subjects speech processor maps to the appropriate frequencies of CI stimulation sites, potentially increasing clinical benefits. (Research supported by Doris Duke Clinical Research Fellowship to D.S. and NIDCD Contract #N01-DC-3-1006)

Abstract **540**, Date **8:00 am - 11:20 am, Monday, February 21, 2005**
Session **: F: The Brain's View of the Cochlear Implant**

Patterns of Excitation in the Inferior Colliculus Produced by Intracochlear Electrical Stimulation in Cats and Guinea Pigs: Models of Cochlear Implant Stimulation

**Russell Snyder, Ben H. Bonham, Steve Rebscher, Patricia A. Leake*

Contemporary human cochlear implants (CIs) use intracochlear electrodes with several electrical contacts to activate the auditory nerve array. The contacts of these devices are distributed along the cochlear spiral, and activation of each pair of contacts (consisting of an active and one or more return contacts) is thought to excite a restricted, unique and tonotopically appropriate population of auditory nerve fibers. Psychophysical and clinical studies indicate that these devices allow open-set speech reception in many users. Our studies seek to understand mechanisms that underlie this performance by focusing on the many factors that influence the spatial (spectral) and temporal distribution of neural activity evoked across the tonotopic organization of the central nucleus of the inferior colliculus. Among these factors are: the orientation and separation of the active and return contacts in a pair, the mode of stimulation (monopolar, bipolar and tripolar), the rate and amplitude of the electrical pulses, the recent activation history of the neuronal populations (forward masking), and the number of populations activated at any one time (simultaneous masking with two-channel stimulation). We will review the results of our multichannel intracochlear electrical stimulation experiments in deaf animal models. These models are designed to accurately reflect CI stimulation in humans. We will compare the patterns of activation produced by electrical stimulation with those evoked by acoustic stimuli in these animal models.

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Abstract **221**, Date **1:00 pm, Wednesday, February 23, 2005**
Session **T15: Cochlear Implant Physiology**

Forward Masking in Cat Inferior Colliculus Using Combined Electric and Acoustic Stimulation of the Cochlea

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Combined electric and acoustic stimulation (EAS) has been applied successfully to cochlear implant users with residual low frequency hearing. Using a forward masking paradigm, we examined the spectro-spatial interactions of EAS on inferior colliculus (IC) neurons. Anesthetized normal hearing cats were implanted with a scala tympani electrode array. An earphone was sealed to the auditory meatus for acoustic stimulation. Neural activity was recorded simultaneously at 16 sites along the tonotopic gradient of the central nucleus of the IC. A 20-ms electric probe was preceded by a 50-ms acoustic masker. Probe and masker were systematically varied in intensity and frequency. At low intensities, electric probe frequencies >1 kHz evoked activity at primary IC locations that corresponded to the probe frequency. This activity was masked when the electric probe was preceded by acoustic stimuli at the same frequency. At higher intensities, the electric probe evoked additional activity at a secondary IC location corresponding to the cochlear site of the stimulating electrode. This activity was masked by acoustic frequencies that corresponded to the same cochlear site. Strength of masking was generally increased by increasing masker intensity. Similar masking effects occurred when the electric probe was replaced by an acoustic probe (two-tone masking) at either the frequency of the electric probe or a frequency corresponding to the cochlear site of electrical stimulation. The results indicate that EAS produces complex spatial interactions in the central auditory system. The extent of these interactions is dependent on the intensities and spectral characteristics of both electric and acoustic stimulus components. The results also suggest that electric stimulation evokes low-threshold acoustic-like electrophonic responses as well as high-threshold direct activation of the auditory nerve.

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Session **T15: Cochlear Implant Physiology**

Effect of Electrical Stimulation on Spiral Ganglion Survival in Animals with Early-Acquired Hearing Loss

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Previously, we reported that electrical stimulation from a cochlear implant (CI) has significant trophic effects on spiral ganglion cell (SGC) survival in neonatally deafened cats. In this study we explored developmental critical period(s) by examining a different deaf animal model. Kittens were deafened at 30 days of age by ototoxic drug administration identical to that used in neonates. Profound hearing losses occurred by 48-56 days of age. Unilateral electrical stimulation with bipolar electrodes and temporally challenging signals (325pps) was initiated immediately after deafening and continued over periods of 35-3 weeks to match stimulation in neonatally deafened animals. Two subjects deafened at 30 days and half of the neonatally deafened group also received GM1 ganglioside, but due to the absence of any significant effect of GM1, the data were combined for animals with and without GM1 treatment.

Animals deafened at 30 days of age (n=3) demonstrated a highly significant increase (more than 20%) in SGC survival in the stimulated ears as compared to the deafened control side, suggesting that electrical stimulation significantly enhanced SGC survival in this group. At the same time, these preliminary data did not show a significant difference in SGC survival between the 30-day deafened and neonatally deafened groups. Although auditory pathways are still immature at 30 days of age, deafening in this older group was initiated after the development of adult-like spontaneous activity in the auditory nerve and adult-like auditory brainstem responses, in contrast to the neonatally deafened group. Thus, these interesting results did not provide evidence for a developmental critical period at least during the first postnatal month. Delaying the onset of deafness by more than 30 days and initiating stimulation immediately thereafter did not provide additional benefit for SGC survival over the long term. *Supported by NIDCD Grant #RO1 DC000160 and Contract #N01-DC-3-1006.*

Abstract **790**, Date **1:00 pm, Wednesday, February 23, 2005**
Session **T15: Cochlear Implant Physiology**

The Effect of Post-Implant Cochlear Fibrosis on Residual Hearing

**Chul-Hee Choi, Ross E. Tonini, Patricia A. Leake, Daniel C. Chelius, John S. Oghalai*

Intracochlear scarring is one of well-described sequelae of cochlear implantation. We developed a mathematical model of passive cochlear mechanics to predict the impact that this might have upon residual acoustical hearing after implantation. The cochlea was modeled using lumped impedance terms for scala vestibuli (SV), scala tympani (ST), and the cochlear partition (CP). The damping of ST and CP was increased in the basal one half of the cochlea to simulate the effect of scar tissue. We found that increasing the damping of the ST predominantly reduced basilar membrane vibrations in the apex of the cochlea, while increasing the damping of the CP predominantly reduced basilar membrane vibrations in the base of the cochlea. We also measured changes in residual hearing after cochlear implantation by comparing the pre-operative to post-operative auditory steady-state evoked responses in 12 children. The average loss after implantation ranged from 3-10 dB across the frequency range. According to our model, ST damping must not have increased more than 100 times normal and CP damping must not have increased more than 10 times normal. As long as intracochlear scarring continues to occur with cochlear implantation, there will be limitations on the hearing preservation. Supported by NIH grants: NIDCD DC05131 and National Organization for Hearing Research Foundation