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Protective Effects of Patterned Electrical Stimulation on the Deafened Auditory System

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ABSTRACT

It is well known from morphological studies that auditory deprivation, especially deprivation at an early age, results in progressive degeneration in both the auditory periphery and the central auditory system. Much less is known, however, about the functional consequences of auditory deprivation on the capacity to encode and process electrical signals in the central auditory system.

A previous study (Snyder et al. 1990) examined electrically evoked auditory brain stem response (EABR) thresholds and minimum thresholds in the inferior colliculus (IC) of neonatally deafened cats, studied as adults after durations of deafness <1.5 years (SD group). EABR thresholds were only slightly higher in SD animals than in controls. In contrast, IC minimum thresholds were much lower in SD animals than in control animals, resulting in a significant difference between EABR and IC thresholds. However, the average width of spatial tuning curves (STC) measured 6 dB above minimum threshold in the SD group was not different from controls. In another study, we reported data from three cats that were neonatally deafened and studied as adults after prolonged periods of deafness (>2.5 years, LD group). These animals showed a significant *decrease* in temporal resolution as compared to normal control cats that were acutely deafened as adults (Snyder et al., 1995), but threshold data were not reported. To further explore the functional consequences of neonatal auditory deprivation on signal processing in the central auditory system, this Quarterly Progress Report presents additional data from neonatally deafened animals in the SD group and comparisons to data from the LD group, which now includes several additional subjects.

EABR thresholds are about 4.4 dB higher than minimum IC pulse thresholds (0.2 ms/phase), *independent* of the duration of deafness and spiral ganglion survival, suggesting that higher stimulus levels are necessary to obtain *synchronized* neural activity sufficient to elicit coherent EABR activity. However, some characteristic differences were observed as a function of duration of deafness. Specifically, LD animals had EABR and minimum IC sine (100 Hz) thresholds that were significantly higher than thresholds measured both in control animals and in SD animals. The cochleotopic representation of signals in the IC was maintained in both groups of neonatally deafened animals, even after very prolonged periods of deafness. However, the spatial selectivity for electrical signals in the IC was significantly degraded in LD animals.

The results suggest that prolonged auditory deprivation initiated at birth can significantly alter the representation and processing of intracochlear electrical signals in the central auditory system. However, the reported changes are related to *severe* degenerative changes in the auditory periphery (SGC density ~8% of normal). In contrast, response thresholds and signal representation in animals with moderate peripheral pathology (SGC density ~43% of normal) are within the range of normal variability.

INTRODUCTION

Clinical studies have shown particularly poor speech discrimination performance in prelingually deafened subjects who receive a cochlear implant (CI) as adults. It is not clear at present to what extent these results are due to peripheral pathology or to functional changes in the central auditory system.

Numerous morphological studies (conducted both in human tissues post-mortem and in experimental animals) have shown that auditory deprivation, especially deprivation at an early age, results in progressive degeneration in both the auditory periphery, i.e. reduction in spiral ganglion cell (SGC) density, and the central auditory system. Much less is known, however, about the functional consequences of auditory deprivation upon the capacity to encode and process electrical signals in the central auditory system.

To study the functional consequences of early auditory deprivation and neural degeneration on signal processing, an animal model of congenital deafness has been developed. In a previous study (Snyder et al. 1990), we compared electrically evoked auditory brain stem response (EABR) thresholds and minimum thresholds in the inferior colliculus (IC) in a group of 6 neonatally deafened cats, studied as adults with durations of deafness <1.5 years (SD group). EABR thresholds were only slightly higher in the SD group as compared to the controls. In contrast, IC minimum thresholds to sinusoidal stimuli in SD animals (27 μA) were much lower than those for the control animals (41 μA), resulting in a large difference between EABR and IC thresholds for the SD group. However, the average width of spatial tuning curves (STC) measured 6 dB above minimum threshold in SD animals was not different from that recorded in the control animals. In another study, we reported data from three cats that were neonatally deafened and studied as adults after prolonged periods of deafness >2.5 years (LD group). These LD animals showed a significant *decrease* in temporal resolution (maximum following frequency) as compared to normal control cats that were acutely deafened as adults (Snyder et al., 1995), but threshold data were not reported.

In the present investigation, the previous work is extended by additional analyses of data from neonatally deafened animals in the SD group and comparison to data from the LD group, which has now been extended to include several additional subjects. Electrically evoked auditory brainstem response (EABR) thresholds and neuron response thresholds in the inferior colliculus (IC) are compared in the two groups. Threshold distributions across the isofrequency gradient of the IC were analyzed to investigate the cochleotopic representation and spatial selectivity of electrical intracochlear signals and again compared in the two groups. Electrophysiological data also were analyzed with regard to spiral ganglion cell (SGC) density and were compared to data from acutely deafened adult animals with prior normal auditory experience (controls).

METHODS

Table 1 documents the histories of the neonatally deafened animals included in this report. Results were obtained from five SD animals (duration of deafness ranging from 6 to 14 months) and eleven LD animals (duration of deafness 30 to 86 months). Twelve acutely deafened adult cats with prior normal auditory experience served as controls.

Animals were deafened by the systemic administration of aminoglycosides beginning immediately after birth. Profound hearing loss (>108 dB SPL) was confirmed by auditory brainstem responses (ABR) testing to clicks. All animals were implanted with a scala tympani electrode array in the left cochlea. Implants consisted of four ball-shaped electrode contacts (≈300 mm in diameter) designated 1 through 4 from apical to basal cochlear locations. The electrodes were arranged as two bipolar offset-radial pairs (apical pair 1,2; basal pair 3,4) with 1 mm separation between electrodes comprising a pair and 3 mm between the two pairs. A percutaneous connector allowed direct electrical connection to the electrodes.

Table 1. HISTORIES OF EXPERIMENTAL ANIMALS

Cat #	Age at Surgery (Months)	Age @ Initial Stimulation (Months)	Duration of Stimulation (Weeks)	Age at Sacrifice (Months)	SGC-Survival (% Normal)
SD animals (deaf <1.5 yr)					
K11	8	NA	NA	8	NA
K26	13	NA	NA	14	23.5
K30	2.5	NA	NA	7	NA
K44	4	NA	NA	6	64.4
K46	9	NA	NA	9	40.3
LD animals (deaf >2.5 yr)					
K03	30.5	NA	NA	31	13.1
K16	44	NA	NA	44	10.7
K24	30	NA	NA	30	7.2
K33	51	NA	NA	51	5.1
K51	76.5	NA	NA	78	4.9
K73	37.5	NA	NA	38	18.3
K111	11	NA	NA	38	NA
CH611	77	78	33	50	3.1
CH618	52	52	34	60	NA
CH539	65	65	14	69	NA
K56	82	84	4	86	5.1

In final electrophysiological experiments, EABR thresholds for biphasic pulses (0.2 ms/phase, 20 pps) were determined. The IC contralateral to the implant was surgically exposed under barbiturate anesthesia. Using tungsten microelectrodes, multi- or single neuron thresholds for pulses (0.2 ms/phase; 2-5 pps) and sines (3 cycles of 100 Hz) were determined at 100 μm intervals along electrode tracts oriented perpendicular to the isofrequency laminae of the IC (Snyder et al., 1990; Vollmer et al., 1999; Leake et al., in press). The stimulation system was calibrated to a reference level of 0 dB=1.0 μA peak to peak.

Thresholds were plotted as a function of IC depth to generate spatial tuning curves (STC; Fig. 1) for several penetrations in each animal. Three different physiological measures will be reported here: 1) Minimum neural thresholds in the central nucleus of the IC were determined and compared with EABR thresholds. 2) The locations of minimum thresholds (BL; best location) were defined and compared for the apical and basal electrode pairs. 3) The STC widths for sines were measured at 6 dB above minimum threshold. In addition, SGC density was determined as described previously (Leake et al. 1991).

Because chronic electrical stimulation *per se* does not appear to affect threshold measures, the data for stimulated and unstimulated LD animals will be combined in the analysis of thresholds. However, since chronic stimulation can effect STC width (Snyder et al. 1990, Leake et al., in press), results for stimulated and unstimulated animals have been analyzed separately. Only STC widths from unstimulated LD animals will be reported in this QPR.

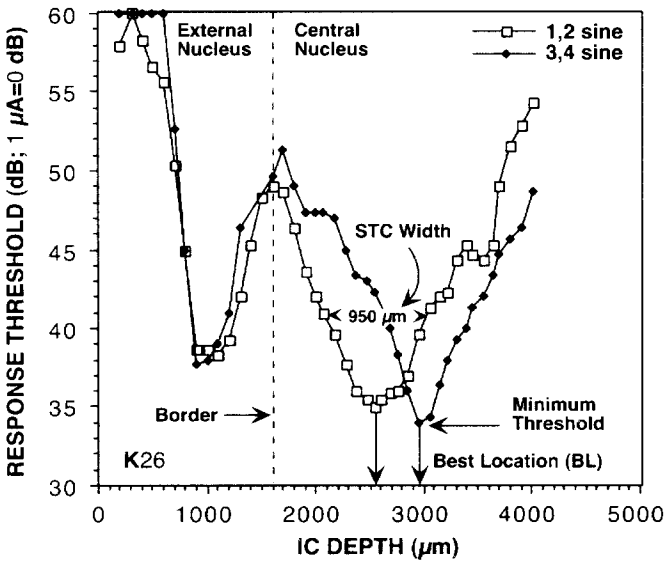

Figure 1. Spatial tuning curves for sine thresholds for stimulation of the apical electrode pair 1,2 (open symbols) and basal electrode pair 3,4 (closed symbols) plotted as a function of IC depth. Best location (BL) for each electrode pair is a relative measure of the cochleotopic gradient in the central nucleus of the IC. High threshold region indicates border between external and central IC nucleus. STC width measured 6 dB above minimum sine threshold for electrode pair 1,2.

RESULTS

1. RESPONSE THRESHOLDS IN THE LONG DEAFENED AUDITORY SYSTEM

EABR thresholds for pulses (0.2 ms/phase) are systematically higher than IC thresholds for sines (5 ms/phase) in all three experimental groups (Fig. 2), largely due to the shorter phase duration of the pulses. The differences between the two threshold measures for the control, SD and LD group are 14.9 dB, 16.5 dB and 15.7 dB, respectively. However, both average EABR threshold and mean minimum IC sine threshold in LD animals (49 dB and 34 dB, respectively) are significantly higher ($P<0.05$) than those in control animals (39 dB and 24 dB) and in SD animals (41 dB and 25 dB). This finding suggests that the long duration of deafness and/or the severe SGC loss in the LD group results in elevated response thresholds.

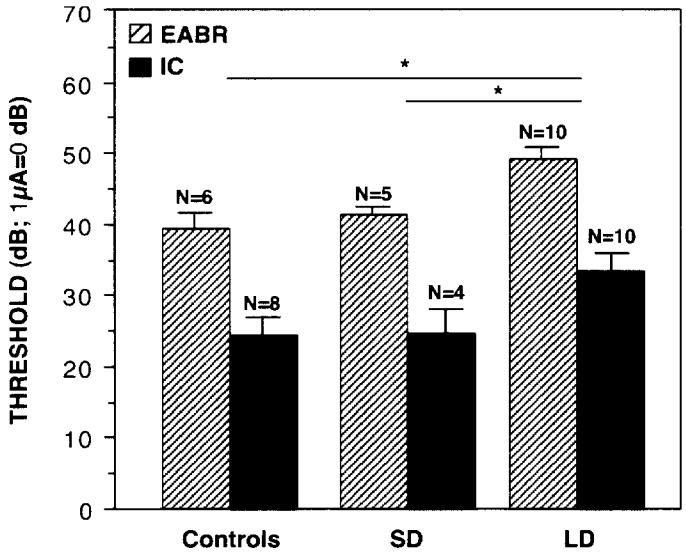

Figure 2. Average EABR thresholds to pulsed stimuli (0.2 ms/ph) and minimum thresholds in the IC to sines (5 ms/phase) for the 3 experimental groups. Statistical significance (* indicates $P<0.05$) refers to both threshold measures. N=number of animals.

In the SD group, the mean SGC density (averaged for all cochlear sectors) is 43% of normal, (range, 24-64%). In LD animals, this value is 8% of normal (range, 5-18%). Figure 3 shows EABR thresholds as a function of duration of deafness (A) and SGC-density (B). EABR thresholds are strongly correlated with duration of deafness (R=0.76), with thresholds increasing with the duration of deafness (Fig. 3A). Because increasing duration of deafness is known to be related to progressive SGC loss, it is not surprising that EABR thresholds are also correlated with SGC density (R=0.72). Thus, decreasing SGC density results in elevated EABR thresholds (Fig. 3B). However, the range of EABR thresholds among the acutely deafened control animals is relatively large (shaded areas in Figs. 3A, B), presumably due to the influence of other factors (e.g. intracochlear electrode location). Thus, relatively long durations of deafness (≥48 months; dashed line Fig. 3A) and a relatively severe reduction in SGC density (≤8% of normal) as seen in the LD group are necessary to affect EABR thresholds above normal variability. The same observation holds true for minimum IC sine thresholds (not illustrated).

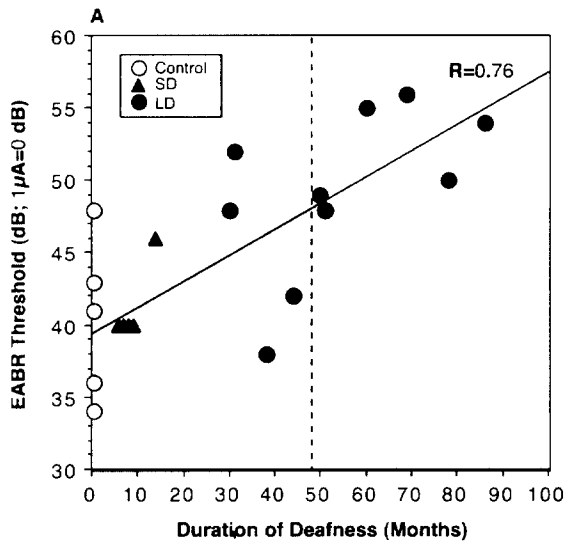

Figure 3A. EABR thresholds are shown as a function of the duration of deafness. Linear regression line is plotted. Grey area marks the range of variability in EABR thresholds among a group of normal cats. Dashed line indicates the duration of deafness resulting in EABR thresholds that exceed the range of normal variability (shaded area).

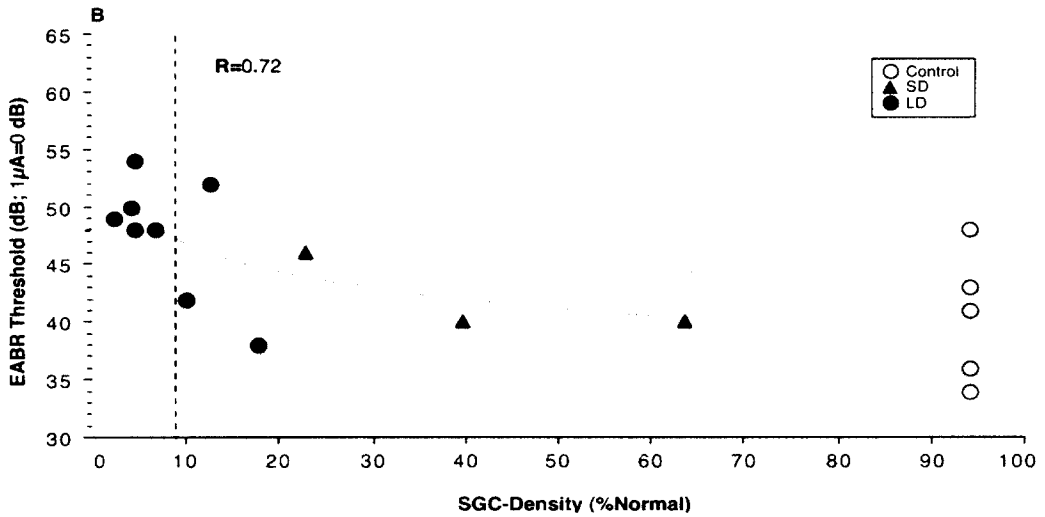

Figure 3B. EABR thresholds are plotted as a function of SGC-density. Logarithmic regression line is shown. Grey area marks the range of normal variability of EABR thresholds. Dashed line indicates the SGC-density resulting in EABR thresholds that exceed the range of normal variability (shaded area).

A comparison between EABR thresholds and minimum IC thresholds for the same *pulse* signal (0.2 ms/phase) shows that both thresholds are strongly correlated (R=0.95) (Fig. 4). EABR thresholds are almost always higher than minimum IC thresholds, and this difference is similar across all experimental groups. The mean threshold difference is 4.4 dB. Thus, EABR thresholds systematically underestimate the sensitivity of the central auditory system to electrical stimulation as compared to IC minimum neural thresholds (Beitel et al. 2000), independent of the duration of deafness or SGC survival. One possible explanation for the difference between the two threshold measures is that higher stimulus levels are necessary to obtain *synchronized* neural activity sufficient to elicit coherent EABR activity.

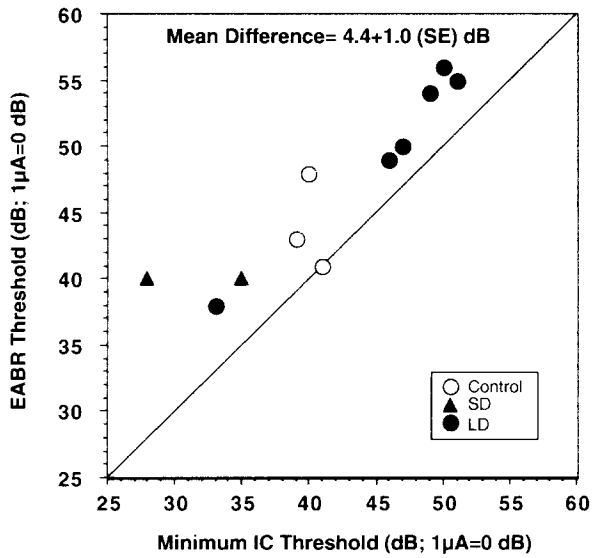

Figure 4. EABR thresholds (biphasic pulses, 0.2 ms/phase, 20 pps) are plotted against minimum IC pulse thresholds (biphasic pulses, 0.2 ms/phase, 2-10 pps) in the same animals. The mean threshold difference accounts for all experimental animals. Diagonal line indicates identical EABR and IC thresholds.

2. SPATIAL REPRESENTATION OF ELECTRICAL SIGNALS IN THE IC

The location of minimum threshold (BL) is dependent upon the cochleotopic frequency gradient in the IC (Fig. 1). That is, increasing depth across the central nucleus of the IC corresponds to increasingly higher characteristic frequency and to more basal intracochlear electrode locations in implanted animals (Snyder et al. 1990). The difference in BL between the apical electrode pair 1,2 and the basal pair 3,4 is a relative measure of this cochleotopic gradient. When the BLs for electrode pair 1,2 are compared to BLs for electrode pair 3,4 for different recording penetrations, results for the two congenitally deafened groups are not different from those for the controls (Fig. 5). Across all groups most of the BLs for pair 3,4 (43 of 53) are located deeper in the IC than the BLs for pair 1,2. These data suggest that the fundamental tonotopic organization of the IC is maintained in long deafened animals.

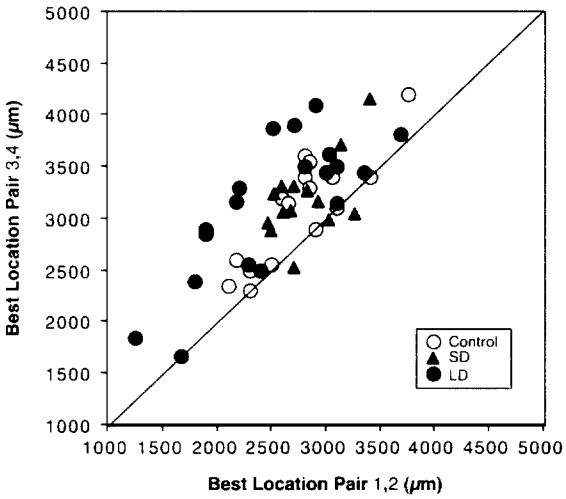

Figure 5. Tonotopic organization for apical electrode pair 1,2 and basal electrode pair 3,4 in the central nucleus of the IC. Best location (BL) for pair 3,4 is plotted against BL for pair 1,2. Diagonal line indicates identical BL for both electrode pairs.

When measured at a given intensity above minimum threshold, the STC width provides a quantitative estimate of the spread of excitation across the IC frequency domain or the spatial selectivity of specific electrode positions in the cochlea (Fig. 1). Figure 6 summarizes the average STC widths measured in the 3 experimental groups at 6 dB above minimum threshold for sinusoidal stimulation delivered to the apical electrode pair 1,2. The SD group has a mean STC width that is similar to control animals (866 μm and 909 μm, respectively). In contrast, the LD group demonstrates a broader average area of excitation (1378 μm). This increase in STC width is statistically significant, although there is substantial individual variability among subjects in each of the experimental groups. This finding suggest that a severe reduction in SGC survival and/or prolonged duration of deafness as modeled in the LD group leads to a degradation in spatial selectivity of electrical signals.

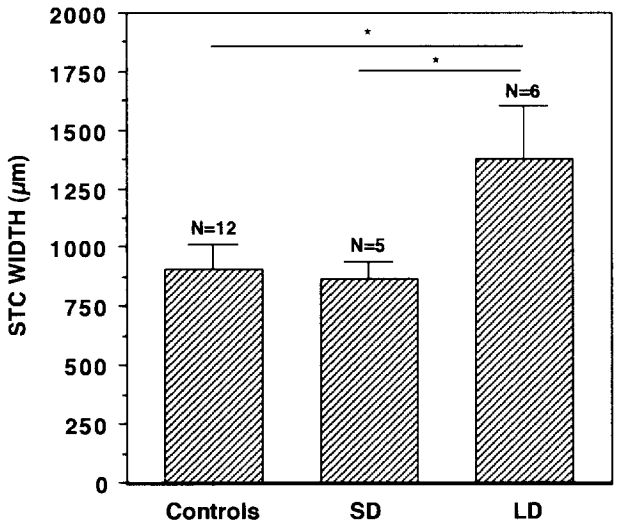

Figure 6. Average STC widths for electrode pair 1,2 in the 3 experimental groups. Error bars show standard error. (* indicates P<0.05). N=Number of animals.

Figure 7 shows STC widths as a function of duration of deafness (A) and as a function of SGC density (B). The data suggest that STC width increases with both duration of deafness and with increasing loss of spiral ganglion cells. However, the range of normal variability is quite large, and the correlation coefficient in Fig. 7B (R=0.44) is small. It is only for a small number of animals, with durations of deafness longer than ~48 months or SGC-densities of less than ~6% of normal, that the STC widths exceed the normal variability. These data indicate the importance of factors other than peripheral pathology (e.g., precise position of intracochlear electrode contacts relative to neural structures, formation of fibrotic encapsulation of the intracochlear electrode, etc.) which can influence the selectivity of electrical stimulation.

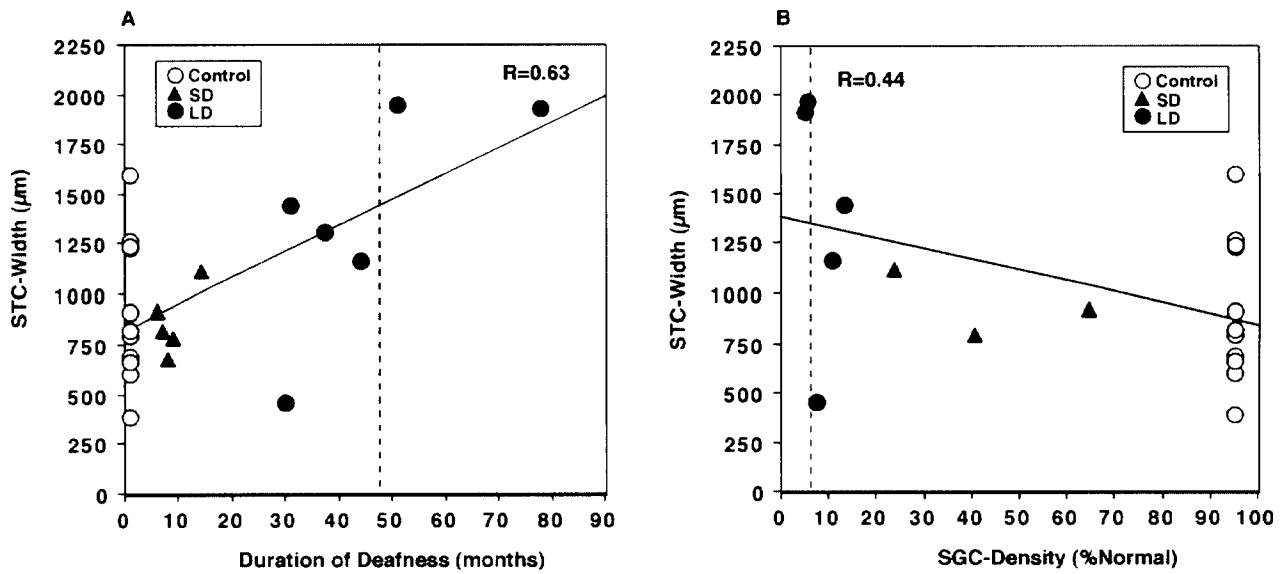

Figure 7. STC width measured at 6 dB above minimum IC sine threshold for pair 1,2 is plotted against duration of deafness (A) and SGC density (B). Regression lines are shown in each graph. Shaded area indicates range of STC widths in normal subjects. Dashed lines mark duration of deafness (A) or SGC-density (B) associated with STC widths exceeding the range of normal variability.

SUMMARY AND CONCLUSIONS

Electrically evoked auditory brainstem response (EABR) thresholds and minimum neural thresholds in the inferior colliculus (IC) were estimated in animals that were neonatally deafened and studied after durations of deafness varying from 6 to 86 months. Results were compared with data from control animals that were deafened as adults and studied immediately. EABR thresholds were always about 4.4 dB higher than minimum IC pulse thresholds (0.2 ms/phase), *independent* of the duration of deafness and spiral ganglion survival. The latter result suggests that higher stimulus levels are necessary to obtain *synchronized* neural activity sufficient to elicit coherent EABR activity. However, characteristic differences also were observed as a function of duration of deafness. Specifically, LD animals that were studied after prolonged deafness (>2.5 yr.) had EABR and minimum IC sine (100 Hz) thresholds that were significantly higher than thresholds measured both in control animals and in SD animals (deafened <1.5 yr.)

The cochleotopic representation of signals in the IC was maintained in both groups of neonatally deafened animals, even after very prolonged periods of deafness. However, the spatial selectivity for electrical signals in the IC was significantly degraded in LD animals.

The results suggest that prolonged auditory deprivation beginning at an early age can significantly alter the representation and processing of intracochlear electrical signals in the central auditory system. Similar changes may contribute to the outcome in speech discrimination performance in prelingually deafened adult CI users. However, the reported changes (increased thresholds and degradation of spatial selectivity) are related to *severe* degenerative changes in the auditory periphery (SGC density ~8% of normal). In contrast, response thresholds and signal representation in animals with moderate peripheral pathology (SGC density ~43% of normal) are within the range of normal variability. Further studies are required to investigate to what extent anatomical and functional changes in the central auditory system (e.g. central demyelination, synaptic processes) influence signal processing and whether the reported changes can be modified or reversed by chronic intracochlear stimulation.

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Work Planned for the Next Quarter

1) Two neonatally deafened animals that are part of the GM1 ganglioside series will be studied in terminal acute electrophysiological studies during the next quarter.

2) Two additional neonatally deafened animals in the GM1 ganglioside/2-channel stimulation group will continue chronic electrical stimulation throughout the next quarter. (One of these subjects is receiving ***simultaneous*** 2- channel stimulation with the analog processor; the second is receiving ***alternating*** AM pulsatile 2- channel stimulation.)

3) Evaluation of cochlear nucleus data will be completed in animals from the first GM1-treatment group, whose spiral ganglion data were reported in the previous QPR. Our working hypothesis is that GM-1 administered in the period after neonatal deafening and prior to cochlear implantation will ameliorate the degenerative effects of neonatal deafening seen in the CN and further increase effects of electrical stimulation.