11th Quarterly Progress Report

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

Submitted by:

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SUMMARY OF WORK COMPLETED DURING THE PAST QUARTER.

1) Work has continued on our new pilot experimental series evaluating the effects the neurotrophin brain derived neurotrophic factor (BDNF), delivered directly to the cochea via an osmotic pump, combined with electrical stimulation (ES) via a cochlear implant. Three subjects have now been implanted with our new UCSF feline cochlear implant incorporating a drug delivery cannula. (See QPR #9, October 1 – December 30, 2005 for a full description of this device).
    a. SG data analysis was completed for the first animal in this series, a neonatally deafened animal that was implanted at 4 weeks of age and studied after 6 weeks of BDNF and ES. At the time of sacrifice, the BDNF cannula was observed to have become separated from the Intracochlear electrode near the round window. Additional tests were performed on the BDNF electrodes and modifications were implemented to rectify this problem.
    b. Two additional subjects that had been deafened at 30 days of age during the previous quarter underwent cochlear implantation at 7 weeks of age, with the modified BDNF cochlear implants. Chronic electrical stimulation on 2 bipolar channels was implemented via the CII™ processor (Advanced Bionics Corp).
    c. The initial small BDNF pumps were replaced after 2 weeks with larger pumps capable of drug delivery for 30 days. One animal was sacrificed for study after 6 weeks of combined BDNF and ES. Histological data evaluating the cochleae have been completed and results look very promising. Data collected include a comparison of our standard morphometric method which evaluates SG density and cell counts using the "nucleator" serial section morphometric method that allows accurate quantification of surviving SG cell number, as well as evaluation of cell size.
    d. In the third BDNF animal, the osmotic pump was successfully replaced a total of 4 times with no problems, and BDNF delivery combined with ES was continued over a total period of 15 weeks. This animal will be studied early in the next quarter a brief terminal acute electrophysiological experiment recording from the inferior colliculus to characterize the activation of the central auditory system with the chronically applied ES.

2) Ongoing chronic electrical stimulation continued in another 30-day deafened cat that is scheduled to continue stimulation for a duration of 6 months. This subject damaged the external connector after 4 months of ES, but it was successfully repaired late this quarter. This animal is the last in the experimental series in which

the effects of a short but potentially fundamentally significant period of normal hearing early in life ("critical" or "sensitive" period) are being evaluated by comparing effects of deafness and chronic stimulation in neonatally deafened vs 30-day deafened animals. Data being collected in this series will document both SG survival and alterations in the cochlear nucleus.

3) The main component of this Quarterly Report is a full-length manuscript that has been prepared for submission to the Journal of Research in Otolaryngology, and entitled: *"Frequency Map for the Human Cochlear Spiral Ganglion: Implication for Cochlear Implants."* This research was done primarily by a postdoctoral fellow working under this Contract research, Dr. Olga Stakhovskaya, who was collaborating with Dr. Leake and with a Doris Duke Clinical Research Fellow, Dr. Divya Sridhar, on this project. The goals of this study were to derive an accurate frequency-position function for the human SG and to explore the implications of the differences between SG and OC frequency maps with respect to the design and surgical insertion of CI. The data obtained provide a mathematical function for relating represented frequency along the OC to that of the SG. In addition, the findings suggest that a relatively simple metric (basal coil diameter) may allow prediction of cochlear size and OC/SG length in pre-operative images and thus may allow estimation of the insertion depth required to reach specific angles of rotation and frequencies. This is a potentially important finding because deeper CI electrode insertions are correlated with increased incidence/extent of trauma to the cochlea. Finally, results suggest that OC and SG frequencies expressed as a function of rotation angle from the round window are fairly constant across subjects. The data presented in this manuscript should provide a basis for more accurate frequency estimates for implanted CI electrodes.

Due to possible copyright infringement issues, the completed manuscript is being submitted to the NIH Project Officer as an appendix, and we are requesting that it not be posted on the NIH website. The abstract is included below, and interested individuals may contact the investigators for a preprint.

4) During this past quarter the Principal Investigator attended the 9th International Conference on Cochlear Implants, a very large European clinical meeting with (1500 registrants) in Vienna, Austria, and delivered two podium presentations: "Insights on Auditory Prosthesis Design from Animal Models" and "Estimating Frequencies for Cochlear Implant Electrodes." (Abstracts appended).

On this same trip, Dr. Leake gave an invited presentation at a satellite workshop, the "2nd Williams Workshop on Tissue Engineering the Auditory Nerve" organized by Dr. Rick Altschuler.

5) Finally, during the past quarter we hosted a 2-day site visit by Dr. Roger Miller, the NIDCD Project Officer for this Contract. During his visit, Dr. Miller met with the investigators and staff working on this contract and reviewed the progress on various projects and plans for the future during several powerpoint presentations and laboratory demonstrations.

WORK PLANNED FOR THE NEXT QUARTER.

1) Ongoing daily chronic electrical stimulation combined with BDNF infusion will continue in the third cat in this series. In this animal the BDNF pump was changed successfully a total of 4 times and BDNF delivery coupled with ES was continued for a total period of 15 weeks. This animal will be studied early next quarter in a brief terminal acute electrophysiological experiment recording from the inferior colliculus. Data collection will focus on spatial tuning curves to both electrical pulse and sinusoidal stimuli (multichannel probe recording), and 2-channel interaction studies to characterize the activation of the central auditory system with the chronically applied ES. Cochlear and cochlear nucleus specimens will be prepared for histological analyses.

2) Three additional animals are being, or will be, deafened during the upcoming quarter as additional subjects for the BDNF pilot series. Littermate pairs of animals will be deafened, and implanted at the same time and will begin BDNF infusion/ES together. One animal of each pair will be studied after 3 months and the second subject will have the osmotic pump removed at 3 month and will continue ES after withdrawal of BDNF for an additional 3-month period. This protocol is designed to evaluate the long-term effects of an initial limited period of neurotrophin infusion followed by ES alone.

3) The final 30-day deafened subject will be studied a terminal acute electrophysiological recording experiment and histological studies of the cochleae and cochlear nuclei will be undertaken.

4) As time and room in our chronic stimulation set-up permit, one additional normal-hearing control subject will be implanted and daily chronic electrical stimulation initiated using the Advanced Bionics CII BDCS processor.

5) The Principal Investigator will attend the NIH Neural Interfaces Workshop in Bethesda, Maryland August 21-23.

ABSTRACTS

Presentations at the 9th International Conference on Cochlear Implants:

Insights on Auditory Prosthesis Design from Animal Models

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Objectives: Studies in animals have shown significant neurotrophic effects of electrical stimulation via an implant in partially preventing degeneration after deafness. Several months of stimulation promotes increases of ≈20% in surviving spiral ganglion (SG) neurons, but survival is still far from normal. The objective of this work is to elucidate the factors that promote optimum anatomical and functional integrity of the auditory system after early deafness.
Methods: Cats deafened at birth or at 30 days of age model congenital and early acquired deafness. Anatomical changes in the SG and cochlear nucleus (CN) are examined and related to the functional consequences of electrical stimulation assessed in electrophysiological experiments recording neural responses in the inferior colliculus.
Results: Exogenous administration or modulation of neurotrophins promote neural survival, but must be for prolonged periods in conjunction with an implant for long-term efficacy. In contrast, cochlear trauma from electrode insertion causes marked neural degeneration in damaged regions. The cochleotopic organization of the SG to cochlear nucleus (CN) projections is intact even in neonatally deafened animals, but due to severe shrinkage of the CN, the spatial selectivity and inferred frequency resolution is significantly poorer than normal. Electrophysiological results also show that the fundamental tonotopic organization of the central auditory system develops normally even in subjects deafened at birth. With severe SG degeneration, stimulation from an implant can improve degraded temporal resolution, but does not reverse the marked reductions in spatial selectivity and dynamic range associated with severe pathology.
Conclusions: Results indicate that synchronized neural activity elicited by a cochlear implant exerts a powerful influence on the deafened auditory system during maturation. Central auditory processing may be profoundly altered by experience with electrical stimulation. Our findings emphasize the importance of initial fitting of an implant in the deafened, developing auditory system. In pediatric implants, it may be advantageous to introduce stimulation that emphasizes segregation and discrimination of inputs from individual channels. *(Research supported by NIDCD Contract N01-DC-3-1006)*

Estimating Frequencies for Cochlear Implant Electrodes

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Objectives: Greenwood's frequency-position equation is used to estimate frequencies for cochlear implant (CI) stimulation sites in temporal bone studies and in imaging studies of living CI recipients. The equation calculates frequency as percent of organ of Corti (OC) length, but there is often no accurate way to estimate OC length in such studies. Further, many CIs target the spiral ganglion (SG), and its map may be different from that of the OC. Our objective was to develop better methods for estimating cochlear-place frequency is such studies.
Methods: Cadaver cochleae (n=9) were fixed <24 hrs postmortem, stained with osmium tetroxide, microdissected, embedded in epoxy resin and examined in surface preparations. In digital images, the OC and SG were measured and radial nerve fibers were traced to define frequency-matched coordinates along the OC and SG in each specimen.
Results: Expressed as percent of length, the data sets were highly correlated and best fit by a cubic function, allowing derivation of SG frequency from Greenwood's equation. The mean OC length was 33.13 mm, but the mean length of the modiolar wall adjacent to the SG (optimum position of CI electrode) was only 15.49 mm. Both OC and SG lengths were correlated (r^2=0.78, 0.88 respectively; $p<0.005$) with cochlear size (basal coil diameter). Data also suggest that frequency vs. angular position is relatively constant, whereas insertion distance is correlated with cochlear size: At 450^o from the round window, mean OC frequency was 604 Hz with a range of only 0.4 octave; but insertion distance at 450^o varied from 20.9 to 24.8 mm.
Conclusions: These data should provide a means of estimating OC and SG length, and more accurate frequency-place maps in imaging studies, which sould in turn allow better matching of CI processor filter bands to stimulation sites. *(Research supported by NIDCD Contract N01-DC-3-1006)*