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"Investigation of Otolith Responses Using Ground Based Vestibular Research Facility"

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I. ABSTRACT

During the tenure of this grant, experiments were conducted at the University of Michigan, the University of Texas Medical Branch (UTMB) and at the Vestibular Research Facility (VRF), Ames Research Center, Moffett Field, CA. The general goal of this research was to examine tilt sensitivity of horizontal semicircular canal afferents using the unique capabilities of the VRF at the Ames Research Center. During the tenure of this grant the VRF was being activated and the investigators that participated in this grant contributed toward that development and field testing of the VRF. Computer programs were written, developed and tested which controlled the short axis centrifuge at the VRF, acquired action potentials and produced data reduction analyses including histograms and gain and phase calculations. The principal investigators also interacted with the staff at the VRF to develop a pre-amplifier for the acquisition of action potentials. Finally, the investigators of this grant gathered data both at the VRF and at UTMB which has been used to contribute toward our understanding of the tilt sensitivity of semicircular canal afferents in the unanesthetized gerbil preparation. The experience in software development and in hardware development gained during the period of this grant contributed directly to the success of a meaningful neurophysiological space flight experiment (COSMOS 2044 - September, 1989).

II. OBJECTIVES

The objectives stated in the initial award of this grant were to: 1) Develop techniques during ground based studies that would lead to meaningful neurophysiological space flight experiments; 2) investigate the sensitivity of the semicircular canals to linear acceleration as a possible contributing factor to space motion sickness; 3) develop the experiment capabilities in the ground based VRF and 4) investigate the physiological and anatomical factors related to the sensitivity of semicircular canals to linear acceleration. To achieve the latter goal, sub-goals were formed in which the purpose was: 1) To investigate the frequency response to tilt sensitive horizontal canal afferents to dynamic linear acceleration and compare responses to otolith primary afferents using translation and counter-rotation and 2) compare the frequency responses in objective one, with two types of vestibular nuclei neurons: a) Those that respond to static head tilt and b) those that respond to head tilt in angular acceleration.

III. ACCOMPLISHMENTS

Technical Accomplishments

A pre-amplifier was developed with unique characteristics. The characteristics of this pre-amplifier included a negative capacity compensation circuit that could be remotely controlled from outside the animal specimen container of the VRF. The amplifier also contained provisions for the remote passage of a square wave pulse to calculate the impedance of the microelectrode. This amplifier was tested and used to acquire single unit neuronal data during studies at the VRF. The amplifier included a lithium battery power supply as well as a 60 Hz notch filter. These features enhanced the capability of this amplifier.

A series of computer programs were developed and tested at both the VRF and UTMB. The programs that were written at the VRF consisted of a suite of programs that were used to power both the main centrifuge axis as well as the counter rotation axis on the periphery of the centrifuge. These programs were modified to power the single axis of a Contravez #823 rate table at UTMB.

Experimental Accomplishments

During the time period between 1982-1989 progress was made on technical developments as indicated above. During 1985 the UTMB team consisting of Drs. Correia, Dickman and Perachio spent a total of four and half months on site at the VRF to obtain data using the counter rotation mode of the VRF centrifuge. During those studies, responses were obtained from 26 primary afferents that were exposed to a full experimental protocol. Additionally, data was gathered from 30 to 40 units where only a portion of the protocol was completed. Of the 26 full protocol units, 15 were identified as lateral canal afferents, seven as anterior canal afferents and four as otolith afferents. Analysis of these data indicated that about one half of the lateral canal afferents did modulate their firing frequency in response to dynamic linear acceleration produced by counter rotation and centrifugation. Yet the modulated responses were not consistently time locked to the stimulus and the response gains were low. In these units, response modulation appeared to be time locked for only a few cycles and would drift over the next few cycles. However, three of the 15 lateral canal afferents did respond systematically to dynamic linear acceleration by consistently modulating with respect to the sinusoidal stimulus. Further analysis revealed that these three units were sensitive to static tilts of 45 degrees pitch (nose up) while the other lateral canal afferents did not appear to respond to static tilt. In contrast, analysis of the four otolith afferent units revealed a systematic modulated response as expected. Therefore, in the gerbil, these data indicated that the tilt sensitivity observed by Perachio and Correia (1983), of horizontal canal afferents was not generalizable to a dynamic linear acceleration stimulus where the resultant vector rotated through the animal's head. Because of concerns about the quality of the stimulus produced by the VRF centrifuge, studies were conducted at UTMB during the time period 1986-1987 to further investigate horizontal canal tilt sensitivity and characterize polarization vectors of otolith afferents. After several initial pilot studies, it was decided to investigate the responses of horizontal canal afferents to small angle pitch tilts at several low frequencies in the gerbil. Tilt sensitive horizontal canal afferents were identified according to their response to angular head accelerations. Horizontal canal afferent responses to static pitch tilts of 0, ±10 and ±20 degrees about the inter-aural axis were recorded first to determine tilt sensitivity. Tilt sensitive afferents were then stimulated with sinusoidal pitch oscillations at ±10 degrees at 0.01, 0.05, 0.075 and 0.1 Hz. Otolith afferents were identified by their lack of response to angular head acceleration. Otolith afferent responses to small angle pitch and roll rotations (±15 and ±25 degrees) about the inter-aural axis were then recorded at two frequencies (0.05 and 0.10 Hz). Sensitivity and polarization vectors were determined by methods described by Peterka (1981). The results of these analysis were as follows:

1) Tilt Sensitive Horizontal Canal Afferents: Approximately 50 tilt sensitive HCAs were evaluated with all units showing a systematic modulation of response to sinusoidal tilts. Most units showed a systematic response at the lower frequencies, i.e., 0.01 and

0.05, but not at the higher frequencies, i.e., 0.075 and 0.10 Hz. However, a few units continued to respond well at all frequencies. Gain and phase values were calculated (re nose down position) using cross spectral Fourier techniques. Bode plots of gain and phase values were calculated. At 0.01 Hz, the mean (±SEM) gain for regularly firing afferents (CV < 0.1, n = 14) was 0.37 (±0.06) imp/sec/deg and mean phase lead (re nose down position) of 8.6 (±6.2) degrees. Irregular neurons (CV > 0.10, n = 26) showed a greater mean phase lead of 17.3 (±3.3) degrees and mean gain of 0.52 (±0.07) imp/sec/deg. At. 0.05 Hz, the mean response of regular (n = 14) and irregular (n = 26) units produced a phase lag of 31.3 (±3.1) degrees and 17.1 (±2.7) degrees and a mean gain of 0.37 (±0.05) and 0.68 (±0.11) imp/sec/deg, respectively. Responses from 11 units were collected at 0.075 and 0.10 Hz. However, due to the lack of response for some fibers at these frequencies no mean gain and phase values could be determined. It appears from the data collected, that most tilt sensitive HCAs have a bandwidth that does not extend beyond 0.10 Hz. Perhaps this is the reason why only a few of the HCA tilt-sensitive units, stimulated with counter-rotation at the VRF in 1985, were shown to systematically modulate. With the VRF protocol, the stimulus frequencies were 0.125 and 0.395 Hz which may have been outside the frequency response bandwidth for most HCA tilt - sensitive units. With the 1985 VRF data, 20% (3 of 15) of the HCA units were shown to systematically modulate to 0.125 Hz counter-rotation. Only eight UTMB protocol - units were examined at 0.75 and 0.10 Hz and three of these units still had high gains at 0.10 Hz.

2) Otolith Afferent Polarization Vectors: Twenty one otolith afferents were examined, with sensitivity and polarization vector values determined. For these units, the sensitivity values ranged widely, with a mean (±SEM) sensitivity of 42.13 (±6.03) spikes/sec/g. This sensitivity value is quite similar to that reported for primates (Fernandez and Goldberg, 1976) and cats (Loe et al.,1973). This project addressed the sensitivity and polarization vector origination for rodent otolith afferents in gerbils (*Meriones Unguiculatus*). The calculated mean (±SEM) resting discharge rate (response rate when the polarization vector is aligned perpendicular to gravity) was 51.73 (±7.36) spikes/sec, which is slightly lower than the resting discharge rate reported for the monkey. Like Peterka (1981), we adopted the following coordinate reference system: +z is directed out the top of the head; +y is directed out the back of the head; and +x is directed out the left ear. The calculated polarization vectors generally aligned into two groups when projected on to the coronal head plane. Thirty-three percent of the units had polarization vectors located between 0-30 degrees above the ipsilateral ear. Another 38% of the units had polarization vectors located between 0 - ±30 degrees off the z-axis. When projected on to the horizontal plane, the polarization vectors were also generally aligned into two groups. Thirty percent of the units had polarization vectors located between 0-60 degrees away from the animal's -y-axis (nose) toward the ipsilateral ear. Another 30% of the units had polarization vectors located between 0-30 degrees behind the ipsilateral ear toward the back of the animal's head (+y-axis). Thus, it appears that the rodent otolith afferent sensitivities and polarization vectors may be similar to those reported for primates and cats.

Recently (Dickman et al., 1991) studies have been carried out investigating the tuning characteristics of otolith afferents. Historically, it has been assumed that otolith afferents have a preferred direction of sensitivity, the so called "polarization vector" and at other directions away from this vector, the response gain falls off as a cosine function. Angelaki et al. (1991) studied vestibular nuclei neurons in the gerbil and determined that for some neurons the tuning was quite broad. That is, there were other directions of sensitivity which were nearly equal to that of the polarization vector. Dickman et al., (1991) studies vestibular afferent fibers. While they identified some fibers that were somewhat broadly tuned, typically most of the afferent fibers had small tuning breadth. The difference between the sharpness of spatial tuning found for vestibular primary afferents in the vestibular afferents, as compared to vestibular nuclear neurons in the same animal indicates that convergence of fibers on to the vestibular nuclei neurons from different afferents may contribute to the breadth of tuning. Other factors that contribute to the this increase breadth of tuning in vestibular nuclei neurons are under investigation.

IV. SUMMARY

The first goal of this grant was to develop techniques and conduct studies that would lead to a meaningful flight experiment. During the course of the grant a suite of computer programs were developed that were used to drive the centrifuge at the VRF and a programmable rotator at UTMB. These programs proved to be the fore runner of a subsequent set of programs that were used to acquire and analyze data in conjunction with the Cosmos 2044 space experiment. Moreover, during the course of this grant a pre-amplifier was developed. This pre-amplifier serves at the prototype model for a multiplexing amplifier that will be used to acquire neural responses in flight on the Cosmos 1992 space experiment. These two accomplishments met one of the goals of this grant. A second goal was to develop the experiment capabilities of the ground based vestibular research facility centrifuge. The UTMB and University of Michigan team worked closely with engineers at the VRF to make the VRF centrifuge a functional neurophysiological instrument. Problems such as grounding and interference were eliminated. Electrophysiological signals were obtained using a remotely controlled micromanipulator and these neurophysiological signals were processed on line using a suite of computer programs developed during the course of this grant. Therefore, the second goal was met. The final goal was to examine the sensitivity of semicircular canals to linear acceleration. These experiments were to be conducted as follow ups to the initial observations by Perachio and Correia (1983), that a certain percentage of horizontal semicircular canal afferents demonstrated tilt sensitivity. To this end, studies were conducted using counter rotation on the VRF centrifuge and pitch rotations about an earth horizontal axis. The results from the first set of experiments were ambiguous and therefore have not been published. The second set of experiments have been published in abstract form and are currently being submitted for publication. This publication is entitled "Response Properties of Gerbil Otolith Afferent Fibers to Small Angle Pitch and Roll Tilts" by Dickman, Angelaki and Correia (*in preparation*). These sets of studies also served as fore runner experiments for experiments that were conducted in conjunction with Cosmos flight 2044. The Cosmos 2044 results produced more straight forward findings. We observed in those experiments that in the rhesus monkey, using stereotaxic location of the vestibular nerve and metal microelectrodes, the presence of semicircular canal tilt sensitivity was not present generally and when it was present, did not seem to be affected following 14 days of microgravity. Those results are in the process of being prepared for publication. The question of tilt sensitivity of horizontal canal afferents continues to be controversial. The *experementia cruciae* have not been conducted.

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VI. PUBLICATIONS, ABSTRACTS AND PRESENTATIONS

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DEPARTMENT OF HEALTH AND HUMAN SERVICES **FINAL INVENTION STATEMENT AND CERTIFICATION** (FOR GRANT OR AWARD)	DHHS GRANT OR AWARD NO. NAG 2-186

A. We hereby certify that, to the best of our knowledge and belief, all inventions are listed below which were conceived and/or first actually reduced to practice during the course of work under the above-referenced DHHS grant or award for the period 7/2/82 (original effective date) through 6/30/89 (date of termination).

B. INVENTIONS (Note: If no inventions have been made under the grant or award, insert the word "NONE" under Title below.)

NAME OF INVENTOR	TITLE OF INVENTION	DATE REPORTED TO DHHS
Manning J. Correia, Ph.D.	None	N/A

(Use continuation sheet if necessary)

C. FIRST SIGNATURE — The person responsible for the grant or award is required to sign (in ink). Sign in the block opposite the applicable type of grant or award.

TYPE OF GRANT OR AWARD	WHO MUST SIGN (title)	SIGNATURE
Research Grant	Principal Investigator or Project Director	M Correia
Health Services Grant	Director	
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D. SECOND SIGNATURE — This block **must** be signed by an official authorized to sign on behalf of the institution.

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