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FINAL TECHNICAL REPORT
NASA-AMES AGREEMENT NO. NAG 2-427

INSTITUTION: University of Arkansas at Pine Bluff
Pine Bluff, Arkansas 71601

TITLE OF INVESTIGATION: The Neurochemical and Neuropharmacological Basis of Motion Sickness

TYPE OF REPORT: Final Technical Report

NASA GRANT NUMBER: NAG 2-427

PRINCIPAL INVESTIGATOR: Dr. C.A. Walker

The NASA Technical Officer for this grant is Nancy G. Daunton, NASA-Ames Research Center, Moffett Field, California 94035.

THE NEUROCHEMICAL AND NEUROPHARMACOLOGICAL BASIS OF MOTION SICKNESS

FINAL TECHNICAL REPORT
NASA GRANT #NAG 2-427
PI: Dr. C.A. Walker

A. SCIENTIFIC PRESENTATIONS

The following presentations at scientific meetings have been made on the results obtained from the above named research project funded by NASA:

1. Walker, C.A., Lickteig, D.L., Tei, B.E. and Owasoyo, J.O. (1988). A New Modified Apparatus for Inducing Motion Sickness in Laboratory Animals. Proceedings, 59th Annual Meeting, Aerospace Medical Association, New Orlean, L.A.

ABSTRACT

An apparatus suitable for producing motion sickness in laboratory animals and constructed at the university is herein described. The apparatus is a modified version of that previously described by Fox and Daunton (1982).

It consists of a 66-inch steel arm anchored at the center to a wooden platform and attached to a motor that makes the arm move in a see-saw fashion. At each end of the steel arm is mounted an aluminum disc that can be rotated by a motorized device. Detachable cages are mounted on each disc for animal holding. The animal can then be exposed to rotational motion by rotation of the aluminum disc, or to see-saw motion simultaneously (Cross-

coupled). The apparatus is presently being used in our laboratory to study the neuropharmacological basis of motion sickness in the rat. The device can be adapted for use with other animal species by modifying the cage mounted on the aluminum discs (supported by NASA grant # NAG 2-427).

2. Owasoyo, J.O., Tei, B.E., Lickteig, D.L., Newport, G. and Walker, C.A. (1989). Brain Biogenic Amines and Metabolites in Rats exposed to Cross-coupled Motion during the Dark Phase of a Light-Dark Cycle. Proceedings, 19th International Conference, International Society for Chronobiology, Washington, D.C.

ABSTRACT

Travel by land, sea or air sometimes results in motion sickness in man. It is therefore of interest to study brain neurochemical changes that accompany exposure to motion. The purpose of this study was to determine brain dopamine (DA), dopac (DC), 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) in animals exposed to cross-coupled motion. Adult, male Fisher 344 rats were used in this study. Control and sham animals (n=6) as well as animals (n=6) subjected for 20 minutes during the dark phase of a light-dark cycle to cross-coupled motion were sacrificed by decapitation at 30, 60 and 120 minutes after exposure to motion. The brain was removed and dissected into cortex, medulla and cerebellum for HPLC analysis of biogenic amines and metabolites. Exposure to motion resulted in a significant decrease in the DA level accompanied by an increase in the DC level of the cortex and medulla as well as an increase

in 5-HIAA level in these brain areas. No change in the level of biogenic amines or metabolites was observed for the cerebellum. These findings suggest an involvement of brain biogenic amines in the effect of motion. A similar study is being conducted in animals exposed to motion during the light phase of a light-dark cycle (Supported by NASA grant #NAG 2-427).

3. Owasoyo, J.O., Akmal, M.M. and Walker, C.A. (1989). Brain Biogenic Amines and Metabolites in Rats Subjected to Cross-coupled Motion. Society for Neuroscience Abstracts 15:1225.

ABSTRACT

It is of wide interest to better understand physiologic factors that contribute to motion sickness in man. Therefore, the purpose of this study was to examine brain neurochemical changes that may accompany motion sickness by determining brain dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC), 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5HIAA) in rats subjected to cross-coupled motion. Adult, male, Fischer 344 rats were used in this study. Control and sham animals, as well as animals (n=6) subjected for 20 minutes to cross-coupled motion were sacrificed at 30, 60 and 120 minutes after exposure to motion. The brain was removed and dissected into cortex, medulla and cerebellum for HPLC analysis of DA, DOPAC, 5-HT and 5-HIAA. Exposure to motion resulted in a significant increase in the DOPAC and 5-HIAA levels as well as an increase in the 5-HT concentration of the cortex and medulla. No change in the levels of biogenic amines or

metabolite was observed in the cerebellum. These findings suggest that biogenic amine levels in the cortex and medulla may be involved in the effect of cross-coupled motion (Performed at NCTR and supported by NASA grant #NAG 2-427).

4. Scallett, A.C., Wilson, S., Rountree, R.L., Henry Jr., W., Andrews, A. and Walker, C.A. (1989). Analgesic and B-Endorphin (BE) Responses to Motion-Sickness in Monosodium Glutamate-treated Rats. Society for Neuroscience Abstracts 15: 516.

ABSTRACT

Drugs, x-irradiation, and motion-sickness produce emetic responses and/or taste aversions. Area postrema (AP) lesions attenuate x-irradiation and drug-induced, but enhance motion-sickness-induced taste aversions in rats. To develop other indices of motion-sickness, we measured analgesia (55°C hotplate) before and after 30 minutes of cross-coupled acceleration as well as BE levels. We also evaluated animals with lesions of the AP (and other circumventricular organs, CVOs) produced by neonatal MSG treatment. Motion-sickness produced a brief (< 30 minute) increase in analgesic latency which was greater in MSG-treated than control rats (105% vs 51%, $p < 0.01$). MSG-treated rats showed the expected decrease in hypothalamic BE (51%, $p < 0.01$), but in correspondence to the analgesic effects, motion-sickness produced a further and larger relative drop of hypothalamic BE in MSG than control rats (52% vs 16%, $p < 0.01$). These results identify analgesia as a useful endpoint for motion-sickness,

suggest that BE may mediate certain motion-sickness responses, and confirm that CVO lesions enhance rather than block such responses. Supported by U.S.A. FDA and NASA Grant NAG 2-427.

B. FUTURE PRESENTATIONS

The final aspect of this project which involves determination of brain acetylcholine/choline levels in control rats and in rats subjected to cross-coupled motion during the light and dark phase of a light-dark cycle has been completed. Acetylcholine/choline was assayed simultaneously in brain samples using an HPLC method with electrochemical detection developed by Bioanalytical systems (BAS), West Lafayette, Indiana. The data is presently being analyzed and will be prepared for presentation at the 1991 meetings of the Society for Neuroscience (New Orleans, LA) and Aerospace Medical Association (Cincinatti, Ohio).
Copies of the abstracts submitted for the meetings will be sent to NASA-Ames as a supplement to this report.

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Dr. J.O. Owasoyo
Dept. of Biology
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Pine Bluff, AR 71601
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A NEW MODIFIED APPARATUS FOR INDUCING MOTION SICKNES IN LABORATORY ANIMALS.

C.A. Walker, D.L. Lickteig, B.F Tei and J.O. Owasoyo,. The UAPB Research Cente University of Arkansas at Pine Bluff, Pine Bluff Arkansas 71601.

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BRAIN BIOGENIC AMINES AND METABOLITES IN RATS EXPOSED TO CROSS-COUPLED MOTION DURING THE DARK PHASE OF A LIGHT-DARK CYCLE.

J. O. Owasoyo, B. E. Tei, D. L. Lickteig, G. Newport* and C. A. Walker

University of Arkansas at Pine Bluff, Pine Bluff, AR 71601 and National Center for Toxicological Research*, Jefferson, AR 72079

Travel by land, sea or air sometimes results in motion sickness in man. It is therefore of interest to study brain neurochemical changes that accompany exposure to motion. The purpose of this study was to determine brain dopamine (DA), dopac (DC), 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) in animals exposed to cross-coupled motion. Adult, male, Fisher 344 rats were used in this study. Control and sham animals (n=6) as well as animals (n=6) subjected for 20 min. during the dark phase of a light-dark cycle to cross-coupled motion were sacrificed by decapitation at 30, 60 and 120 min. after exposure to motion. The brain was removed and dissected into cortex, medulla and cerebellum for HPLC analysis of biogenic amines and metabolites. Exposure to motion resulted in a significant decrease in the DA level accompanied by an increase in the DC level of the cortex and medulla as well as an increase in 5-HIAA level in these brain areas. No change in the level of biogenic amines or metabolites was observed for the cerebellum.

These findings suggest an involvement of brain biogenic amines in the effect of motion. A similar study is being conducted in animals exposed to motion during the light phase of a light-dark cycle (Supported by NASA grant #NAG 2-427).

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Joseph Olu Owasoyo, Ph.D.

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BRAIN BIOGENIC AMINES AND METABOLITES IN RATS SUBJECTED TO CROSS-COUPLED MOTION. J.O. Owasoyo, M.M. Akmal and C.A. Walker. UAPB Research Center, University of Arkansas at Pine Bluff, Pine Bluff, AR 71601.

It is of wide interest to better understand physiologic factors that contribute to motion sickness in man. Therefore, the purpose of this study was to examine brain neurochemical changes that may accompany motion sickness by determining brain dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC), 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) in rats subjected to cross-coupled motion. Adult, male, Fischer 344 rats were used in this study. Control and sham animals, as well as animals (n=6) subjected for 20 min to cross-coupled motion were sacrificed at 30, 60 and 120 min after exposure to motion. The brain was removed and dissected into cortex, medulla and cerebellum for HPLC analysis of DA, DOPAC, 5-HT and 5-HIAA. Exposure to motion resulted in a significant increase in the DOPAC and 5-HIAA levels as well as an increase in the 5-HT concentration of the cortex and medulla. No change in the levels of biogenic amines or metabolite was observed in the cerebellum. These findings suggest that biogenic amine levels in the cortex and medulla may be involved in the effect of cross-coupled motion (Performed at NCTR and supported by NASA grant #NAG 2-427).

KEY WORDS: (see instructions pg. 4)

1. Biogenic Amines
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211.19

SOME VESTIBULOSPINAL NEURONS ALSO STAIN WITH ASPARTATE-LIKE IMMUNOREACTIVITY. G.A. Kevetter and A.R. Coffey*. Dept. Otolaryngology and Anatomy and Neuroscience. Univ. TX Med. Branch, Galveston, TX 77550.

In an effort to further characterize vestibulospinal pathways in the gerbil, immunocytochemistry was combined with retrograde identification of neurons. Small injections of 20% horseradish peroxidase (HRP) were made into the C5-C6 cord of anesthetized gerbils. Sections were reacted with nickel acetate-diaminobenzadine, giving a black reaction product. Sections were incubated in polyclonal antisera to aspartate (1:200 or 1:500, Chemicon) for 24 hours. They were then incubated in biotinylated anti-rabbit, followed by avidin-biotin-peroxidase complex, and finally reacted with diaminobenzidine to give a brown reaction product. Brown cells, stained with aspartate-like immunoreactivity (ASP-lir), were located in all four major vestibular nuclei. These included small and medium cells in the medial (MVN) and descending (DVN) vestibular nuclei and medium and large ASP-lir cells in the lateral (LVN) and ventromedial (VMVN) nuclei. In MVN, more cells were stained for ASP-lir caudally than rostrally. After the small injections of HRP into the cervical cord most cells were labeled in the caudal two-thirds of MVN and the adjacent DVN. Double-labeled cells (containing both the black particulate reaction product from retrogradely-transported HRP and also the diffuse brown reaction product from ASP-lir staining) were located in MVN, especially along the border with DVN. (Supported in part by BNS-NSF-84-18559).

211.20

CONTRIBUTION OF MEDIAL VESTIBULOSPINAL NEURONS (VSNs) TO SPATIAL TRANSFORMATION IN THE VESTIBULO-COLLIC REFLEX (VCR). S.J. Perlmutter, Y. Iwamoto, J.F. Baker, B.W. Peterson, Northwestern Univ. Med. School, Chicago, IL USA

We are investigating the neural substrates of spatial motor patterns of the VCR by recording VSN and neck muscle EMG activity. In 2 alert and 11 decerebrate cats (heads fixed), 2nd and higher order VSNs were identified by their responses to electrical stimulation of the labyrinth and descending MLF. The direction of rotation producing maximal activation (MAD) was determined from 0.5 Hz rotations in many vertical and horizontal planes. Connections of VSNs to neck motoneurons are being studied with spike-triggered averaging and cross-correlations.

Alert and decerebrate cat data were similar and combined (79 VSNs). Type II responses were more common in higher order than 2nd-order cells. Four VSNs exhibited complex behavior suggesting otolith input. Of 74 neurons with responses consistent with a linear sum of canal inputs, 25% had MADs aligned with the ipsilateral posterior (18), anterior (1) or horizontal (0) canal. Another 46% received convergent input from orthogonal canal(s) that shifted their MADs >10° from that of the primary ipsilateral input canal (9% vertical-vertical canal, 23% vertical-horizontal canal, 14% all 3 canals). 28% of VSNs responded as if their primary input were from contralateral canal(s). Low frequency responses of several cells suggested additional weak otolith input.

In alert cats, tonic eye position sensitivity was clear in 7/30 2nd-order VSNs. In 1 cat, 3/9 2nd- and 0/4 higher-order cells had axon collaterals identified by ascending MLF stimulation.

Significant spatial transformation of vestibular signals occurs on VSNs, even at the 2nd-order level. VSNs had more convergent input than VOR relay neurons reported last year. EY06485, EY07342

211.21

RESPONSE PROPERTIES OF VESTIBULAR NEURONS PROJECTING TO UPPER CERVICAL SPINAL CORD. S. Nonaka*, R.H. Schor, V.J. Wilson, Y. Yamagata*, B.J. Yates. Rockefeller Univ., New York, NY 10021 and Univ. Pittsburgh, Pittsburgh, PA 15213.

Different spatial tilts (e.g. roll vs pitch) evoke neck responses (vestibulocollic reflex) which have different temporal properties (Baker et al., 1985). Furthermore, the dynamics of the reflex suggest that it receives important input from irregular vestibular afferents (Bilotto et al., 1982). We examined the response properties of neurons in the lateral, medial, and descending vestibular nuclei of decerebrate cats which could be antidromically activated from mid-C1, but not from C5. The tilt direction evoking maximal modulation, and the response dynamics of these neck-projecting neurons, were examined using planar and rotating (wobble) sinusoidal tilts (0.02 to 2 Hz). The response properties of this neck population resemble those of vestibular neurons in an earlier study whose projection was not identified (Kasper et al., 1988); a larger fraction of the neck sub-population has advanced phase (> 90° at 1 Hz), suggesting a contribution from irregular afferents. Most neurons projecting to the neck exhibited the same temporal response to varying spatial stimuli. Some neurons exhibiting spatio-temporal convergence (Baker et al., 1984) were observed, but apparently too few to account for vestibulocollic reflex behavior; this behavior may be due to convergence of inputs with different spatial and temporal properties at other levels of the reflex pathway. (Supported by NIH grants NS02619, NS24930, NS08506).

211.22

OCULAR COUNTERROLLING IN PARABOLIC FLIGHT: PREDICTIVE TEST OF SPACE MOTION SICKNESS? S.G. Diamond and C.H. Markham, Dept Neurology, UCLA Sch Medicine, Los Angeles, CA 90024.

An earlier study examined 4 subjects who had symmetric ocular counterrolling (OCR) in ground-based 1G testing. During parabolas flown on a NASA KC-135 aircraft, 3 of the 4 had no eye torsion while upright in 0G or 1.8G. Tilted, they had no OCR at 0G, and more OCR at 1.8G than at 1G. None of these 3 became sick during flight.

The fourth subject had leftward eye torsion at 0G in upright and tilted positions. This bias was also seen at 1.8G, where he had less OCR than at 1G when tilted to the side inducing rightward OCR. He did become sick in flight.

These results suggested that asymmetry of the otolith system may be well compensated in the usual 1G environment on earth, but that exposure to unaccustomed gravitational states may unmask this compensation. The sudden asymmetric vestibular responses thus stimulated may be the cause of the unique motion sickness observed in space flight.

To test this hypothesis, 7 subjects with symmetric OCR in 1G underwent testing on the KC-135 for 20 parabolas to examine the correlation of asymmetric OCR in non-1G states with space motion sickness. Three subjects were former astronauts; some had been sick in space and others not. The OCR test attempted to ascertain blind which were which. Two subjects were prospective astronauts; the test attempted to predict their motion sickness in space. The remaining subjects were drawn from the NASA subject pool.

211.23

MOTION SICKNESS AND MOTOR STRATEGY. D.G.D. Watt, I. Nevo*, T. Yang* and A.V. Smith*. Aerospace Medical Research Unit, McGill University, Montreal, Canada H3G 1Y6.

Motion sickness occurs frequently in altered gravity environments such as orbital or parabolic flight. Under these conditions, coordination of eye, head and body movements is often unusual, with the eyes and head rotating with the torso when reorienting to a new target. Are these inappropriate motor strategies a cause of motion sickness?

10-17 subjects took part in each of 12 experiments over 24 weeks. Each session required a different pattern of eye, head and body coordination to be repeated for 30 minutes (e.g. sweep gaze back and forth between targets located 130 degrees to either side of straight ahead, at 0.7 Hz). A questionnaire and 5 vestibular tests were administered before and repeatedly after the rhythmical movement.

All experiments caused dizziness, postural instability and oscillopsia. Motion sickness could develop if the subject was distracted during the repetitive movement, but more often appeared when normal activity resumed. Vestibular responses were decreased, the greatest changes tending to occur in those subjects who became motion sick.

These results suggest that some (perhaps many) forms of motion sickness are associated with transiently altered vestibular function resulting from inappropriate motor strategies. The signs and symptoms may serve as a warning against these counter-productive strategies. Thus, "motion sickness" might be better labelled Dysadaptation Syndrome. (Supported by Medical Research Council of Canada)

[redacted]

ANALGESIC AND B-ENDORPHIN (BE) RESPONSES TO MOTION-SICKNESS IN MONOSODIUM GLUTAMATE-TREATED RATS. A.C. Scallet, S. Wilson*, R. L. Rountree*, W. Henry, Jr.*, A. Andrews*, and C.A. Walker[1], Natl. Ctr. for Toxicol. Res., Jefferson, AR 72079-9502 and [1]Univ. of Arkansas-Pine Bluff, Pine Bluff AR 71601.

Drugs, x-irradiation, and motion-sickness produce emetic responses and/or taste aversions. Area postrema (AP) lesions attenuate x-irradiation and drug-induced, but enhance motion-sickness-induced taste aversions in rats. To develop other indices of motion-sickness, we measured analgesia (55°C hotplate) before and after 30 minutes of cross-coupled acceleration as well as BE levels. We also evaluated animals with lesions of the AP (and other circumventricular organs, CVOs) produced by neonatal MSG treatment. Motion-sickness produced a brief (<30 min) increase in analgesic latency which was greater in MSG-treated than control rats (105% vs 51%, $p<0.01$). MSG-treated rats showed the expected decrease in hypothalamic BE (51%, $p<0.01$), but in correspondence to the analgesic effects, motion-sickness produced a further and larger relative drop of hypothalamic BE in MSG than control rats (52% vs 16%, $p<0.01$). These results identify analgesia as a useful endpoint for motion-sickness, suggest that BE may mediate certain motion-sickness responses, and confirm that CVO lesions enhance rather than block such responses. Supported by U.S.A. FDA and NASA Grant NAG 2-427.