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:


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).


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).


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).


**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 (Cincinnati, Ohio). Copies of the abstracts submitted for the meetings will be sent to NASA-Ames as a supplement to this report.

Attachments
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An apparatus suitable for producing motion sickness in laboratory animals and constructed at this university is herein described. The apparatus is a modified version of that previously described by Fox and Daunt (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 through the up and down motion of the device's steel arm, or to both rotational and see-saw motion simultaneously (Cross-coupled). The apparatus is presently being used in our laboratory to study the neuropharmacologic 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).
BRAIN BIOGENIC AMINES AND METABOLITES IN RATS EXPOSED TO CROSS-COUPLED MOTION DURING THE DARK PHASE OF A LIGHT-DARK CYCLE.

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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).
BRAIN BIOGENIC AMINES AND METABOLITES IN RATS SUBJECTED TO CROSS-COUPLED MOTION. J.O. Owaseyo, 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
2. Brain
3. Motion
4. Rats
CONTRIBUTION OF MEDIAL VESTIBULOSPINAL NEURONS (VSNs) TO SPATIAL TRANSFORMATION IN THE VESTIBULO-COLLIC REFLEX (VCR). J. L. Perlmutter, T. Yamamoto, J. E. Baker, B.W. Canoll, 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 and 11 decerebrate cats, head movements were identified by their responses to electrical stimulation of the labyrinth and descending MLF. The direction of rotation producing maximal activation (MAD) was determined for each subject. Alert and decerebrate cat data were similar (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 of canal inputs, 25% had MAD aligned with the ipsilateral posterior (18), anterior (1) or horizontal (0) canal. Another 46% received convergent input from orthogonal canal(s) that shifted their MAD >10° from that of the primary ipsilateral input canal (9°), horizontal canal (23°), vertical canal (horizontal canal, 14% all 3 canals). 28% of VNSs responded as if their primary input were from contralateral canal(s). Low frequency responses of several cells suggested additional weak otolith input. In alert can, tonic eye position sensitivity was higher in 2nd order VSNs. In cat, V3-2nd and 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. EY06435, EY07342

ANALGESIC AND D-ERGOTAMINE RESPONSES TO NOTION-SICKNESS IN MONOSODIUM GLUTAMATE-TREATED RATS. A.C. Scaliet, S. Wilson, R.L. Hostetler*, V. Henry, Jr., A. Andrews, and C.A. Walker*. Mail. Ctr. for Toxicol. Res., Jefferson, AR 72079-9002 and Univ. of Arkansas. Pine Bluff, Pine Bluff AR 72711. Drugs, x-irradiation, and motion-sickness produce motor 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 models, we measured analgesia (55°C hotplate) before and after 10 minutes of cross-coupled acceleration as well as NE levels. We also evaluated the effects of the AP (and other circuimventricular organs, CVOs) produced by neonatal MSG treatment. Motion-sickness produced a brief (10 sec) increase in AP NE which was greater in MSG-treated than control rats (25% vs 16%, p<0.01). These results identify analgesia as a useful endpoint for motion-sickness, suggest that NE 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 2G-5.

RESPONSE PROPERTIES OF VESTIBULAR NEURONS PROJECTING TO UPPER CERVICAL SPINAL CORD. J. Watanabe, R.H. Schor, V.J. Wilson, Y. Tazaka, B.J. Tatemoto, Rockefeller Univ., New York, NY 10021 and Univ. Pittsburgh, Pittsburgh, PA 15213. Different spatial types (e.g. roll vs pitch) evoke neck responses, vestibulocerebellar reflexes, which have different temporal properties (Baker et al., 1985). Furthermore, the dynamics of the reflex suggest that input from the ipsilateral vertical semicircular canal (VSNs) is at least 200 ms delayed from VSNs are identified by their responses to horizontal input from the contralateral vertical canal in 27/46 auditory cats. In the lateral, medial, and posterior human neck projections were observed to be activated from the contralateral anterior canal. These responses were initiated by the ipsilateral horizontal canal, but were also activated by the contralateral horizontal canal. The direction of rotation eliciting a response was consistent with a linear sum of inputs from both horizontal canals. These results suggest that the cervical cord is capable of detecting the spatial orientation of the head and that this information is used to enhance the perceived motion of objects in space. Two subjects were tested with the test apparatus rotated in 45° increments from 0° to 180°. The motion sickness responses were observed to be unaffected by the rotation of the apparatus. The motion sickness responses were observed to be unaffected by the rotation of the apparatus.

MOTION SICKNESS AND MOTOR STRATEGY. D.G. Watt, L. Novè*, T. Fass* and A.V. Smith*. Aerospace Medical Research Unit, McGill University, Montreal, Canada H3G 1V6. 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 26 weeks. Each session required a different pattern of eye, head and body movements and was repeated for 30 minutes with each pattern lasting 15 minutes. All experiments caused dizziness, postural instability and oscillations which could develop if the subject was distracted during the repetitive movement, but more often appeared when normal activity resumed. Vestibular-elicited, the greatest changes tending to occur in those subjects who become 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)