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Vestibular System and Neural Correlates of Motion Sickness
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SUMMARY

Initial studies re-examined the role of certain central nervous system structures in the production of vestibular-induced vomiting and vomiting in general. All experiments were conducted using cats. Vomiting and related prodromal activity were produced after ablation of the nodulus and uvula of the vestibulocerebellum by using sinusoidal electrical stimulation of the vestibular labyrinths of decerebrate animals to mimic natural vestibular stimulation. The nodulus and uvula, therefore, are not an essential part of the mechanism(s) by which vestibular input can activate brain stem structures responsible for vomiting. We were also unable to confirm the existence of an anatomically well defined brain stem "vomiting center" in other studies that used electrical microstimulation of the brain stem in an attempt to elicit vomiting.

Since these studies demonstrated that the essential role of various central structures in vestibular-induced vomiting is only poorly understood, efforts were re-directed to study the control of the effector muscles (diaphragm and abdominal muscles) that produce the pressure changes responsible for vomiting, with the goal of determining how this control mechanism is engaged during motion sickness. Experiments were conducted to localize the motoneurons that innervate the individual abdominal muscles and the portion of the diaphragm that surround the esophagus. In contrast to the rest of the diaphragm, the periesophageal region relaxes during expulsion, thereby facilitating rostral movement of gastric contents. In order to study the role of individual brain stem neurons in the control of the diaphragm and abdominal muscles during vomiting, a "fictive vomiting" preparation was developed using paralyzed, decerebrate animals. Fictive vomiting was defined by a characteristic pattern of co-activation of abdominal and phrenic nerves, elicited by emetic agents, that would be expected to produce vomiting in unparalyzed animals. A central question regarding respiratory muscle control during vomiting is whether these muscles are activated via the same brain stem pre-motor neurons that provide descending respiratory drive and/or by other descending input(s). This question was addressed in regard to expiratory neurons in the caudal ventral respiratory group (VRG). There is a large projection from these neurons to the thoracic and lumbar cord, from which the abdominal muscles receive their innervation; however, cross-correlation analysis indicated that there are few strong monosynaptic connections between these neurons and abdominal motoneurons. Some VRG expiratory neurons have the appropriate firing pattern during fictive vomiting to contribute to abdominal muscle control; however, other as yet unidentified inputs can also produce abdominal muscle activation during vomiting as was shown by severing the axons of VRG expiratory neurons.

In other experiments, we evaluated the use of a combination of pitch and roll motions to produce motion sickness in unrestrained cats. This stimulus combination can produce vomiting in only the most susceptible cats and is thus not as provocative a stimulus for cats as vertical linear acceleration, which has been used by other investigators.

INTRODUCTION

Initial studies re-investigated some of the work reported in the 1940-50s concerning the role of certain central nervous system structures in the production of vestibular-induced vomiting (motion sickness) and vomiting in general. It soon became obvious that this earlier work could not be confirmed (either by us or later by others) and that we were thus left with a poor understanding of how the central nervous system produces vomiting. I thus re-directed the focus of my work to concentrate on the neural control of the effector muscles (diaphragm and abdominal muscles) that produce the pressure changes responsible for vomiting, with the long-term goal of determining how this control mechanism is engaged when vomiting is produced during motion sickness. All of these studies used the cat.

The research projects are summarized below. The publication(s) containing the complete description of each project are listed by number, which corresponds to the number in the following List of Publications.

List of Publications Supported by NASA Award NAG 2-164

1. Miller AD, Wilson VJ. "Vomiting Center" reanalyzed: An electrical stimulation study. Brain Res. 270: 154-158, 1983.
2. Miller AD, Wilson VJ. Vestibular-induced vomiting after vestibulocerebellar lesions. Brain Behav. Evol. 23: 26-31, 1983.
3. Miller AD, Wilson VJ. Neurophysiological correlates of motion sickness: Role of vestibulocerebellum and "vomiting center" reanalyzed. In: Motion Sickness: Mechanisms, Prediction, Prevention and Treatment. AGARD Conference Proceedings No. 372., pp 21-1 - 21-5, 1984.
4. Miller AD, Ezure E, Suzuki I. Respiratory-spinal projections to cat's lumbar cord. Soc. Neurosci. Abstr. 10: 708, 1984.
5. Miller AD, Ezure E, Suzuki I. Control of abdominal muscles by brain stem respiratory neurons in the cat. J. Neurophysiol. 54: 155-167, 1985.
6. Miller AD, Suzuki I, Tan LK. Control of abdominal muscle activity during vomiting: Role of ventral respiratory group expiratory neurons. Soc. Neurosci. Abstr. 11: 25, 1985.
7. Tan LK, Miller AD. Motor innervation of cat's diaphragm: Relation to vomiting. Soc. Neurosci. Abstr. 11: 1155, 1985.
8. Tan LK, Miller AD. Innervation of periesophageal region of cat's diaphragm: implication for studies of control of vomiting. Neurosci. Lett. 68: 339-344, 1986.
9. Miller AD, Tan LK. Expiratory muscle control during vomiting: role of brain stem expiratory neurons. In: Respiratory Muscles and Their Neuromotor Control. Neurology & Neurobiology, Vol. 26 (Sieck, GC, Gandevia, SC, Cameron, WE, eds). Alan R. Liss, Inc., New York, 1987, 455-458.
10. Miller AD. Localization of motoneurons innervating individual abdominal muscles of the cat. J. Comp. Neurol. 256: 600-606, 1987.
11. Miller AD, Tan LK, Suzuki I. Control of abdominal and expiratory intercostal muscle activity during vomiting: role of ventral respiratory group expiratory neurons. J. Neurophysiol. 57: 1854-1866, 1987.
12. Miller AD. Mechanisms of respiratory muscle control during motion-induced vomiting. NASA Space Life Sciences Symposium: Three Decades of Life Science Research in Space, pp 101-102, 1987.
13. Miller AD, Tan LK. Possible role of brain stem respiratory neurons in mediating vomiting during space motion sickness. Aviat. Space Environ. Med. 58 (Suppl. A), 1987, in press.

SUMMARY OF INDIVIDUAL RESEARCH PROJECTS

(1) Development of stimulus conditions for producing motion sickness.

a) Alert cats. We evaluated the use of a combination of pitch and roll motions to produce motion sickness in unrestrained cats. The animals were placed inside a clear, ventilated, plexiglass box which was mounted on top of a hydraulically-driven tilt table. The table was driven using a sinusoidal waveform of 0.2-0.5 Hz, up to $\pm$ 20 degrees amplitude. Different stimuli were applied to the pitch and roll axes. One series of experiments was performed on three cats provided by Dr. Nancy Daunton (Ames Research Center, NASA, Moffett Field CA); these animals were known to be highly susceptible to vertical linear acceleration. On our apparatus, these cats exhibited episodes of prodromal symptoms including licking, swallowing, yawning, drowsiness, unusual postures, salivation, urination, and retching. Two cats reliably vomited within 20 minutes; the third vomited if pre-treated with naloxone (0.9 mg/kg s.c; cf. Crampton, Daunton, Pharmacol. Biochem. Behav. 19: 827-829, 1983).

An additional eighteen cats, selected at random from our animal colony, were tested using similar stimuli, without pre-treatment with naloxone. Although most of these animals exhibited various prodromal symptoms of motion sickness, none actually vomited during tests lasting up to one hour. The details of these tests are described in the Semiannual Progress Report, March - August, 1982.

In summary, although combinations of pitch and roll can produce motion-induced vomiting in highly susceptible cats, the incidence is so low that it would be desirable to use other motion stimuli for producing motion sickness in cats. Other investigators have found vertical linear acceleration to be more provocative (Suri, Crampton, Daunton, Aviat. Space Environ Med. 50: 614-618, 1979; Crampton, Lucot, Aviat. Space Environ. Med. 56: 462-465, 1985).

b) Decerebrate cats (publications 2 and 3). Natural vestibular stimulation can produce motion sickness in decerebrate animals (Bard et al., Fed. Proc. 6: 72, 1947; Miller, Schor, Tomko, unpublished observation). In order to study the central nervous system correlates of motion sickness in acute experiments, we developed an animal model whereby vomiting and related prodromal symptoms of motion sickness were produced by using sinusoidal electrical polarization of the labyrinths of decerebrate cats to mimic natural vestibular stimulation. Three out of 14 cats vomited; related prodromal symptoms were produced in 4 others. We used cats selected at random without regard to motion sickness susceptibility. It may be possible to obtain a higher incidence of vomiting and related symptoms in these decerebrate preparations by using animals that have previously been shown to be highly susceptible to motion sickness during chronic testing.

(2) Role of the vestibulocerebellum in vestibular-induced vomiting (publications 2 and 3).

Vomiting and related prodromal activity were produced after ablation of the nodulus and uvula in experiments using electrical stimulation of the vestibular labyrinths of decerebrate cats. In contrast to earlier widely held beliefs (Bard 1945, Wang and Chinn 1956), our results demonstrate that

the nodulus and uvula are not an essential part of the mechanism(s) by which vestibular input can activate the central structures responsible for vomiting.

(Since these studies were conducted, four other groups have shown that lesions of the area postrema, another brain stem structure previously thought to be indispensable for motion-induced vomiting, also do not prevent vomiting in response to motion.)

(3) The "vomiting center" reanalyzed using electrical stimulation of the brain stem (publications 1 and 3).

A knowledge of how vestibular input can produce vomiting is essential for our understanding of the basic mechanisms underlying motion sickness. We therefore sought to find a restricted anatomical localization of the so called medullary "vomiting center" (Borison and Wang 1949, 1951) in order to study its connections. In contrast to accepted views, vomiting proved unexpectedly difficult to produce by electrical stimulation of the brain stem of unanesthetized, decerebrate cats. Restricted localization of a "vomiting center", stimulation of which evoked readily reproducible results, could not be obtained. These results suggest that the structures that produce vomiting are distributed in the brain stem.

(4) Localization of motoneurons innervating individual abdominal muscles (publication 10).

Understanding the regulation of abdominal muscle activity is of major importance for understanding the control of vomiting. This study was the first systematic investigation devoted to establishing the locations of motoneurons innervating individual abdominal muscles, an important step for the study of abdominal muscle control. The motor pools of the individual abdominal muscles of the cat were localized using either intramuscular injections of horseradish peroxidase (HRP) to retrogradely label abdominal motoneurons or electrical microstimulation of the ventral horn at different segmental levels to produce localized twitches of the abdominal muscles. The segmental distribution of each motor pool was: rectus abdominis - T4-L3, external oblique - T6-L3, transverse abdominis - T9-L3, and internal oblique - T13-L3.

(5) Innervation of the periesophageal region of the diaphragm: implication for studies of control of vomiting (publications 7 and 8).

The diaphragm contracts during both the retching and expulsive phases of vomiting; however, the activity of the hiatal region around the esophagus is greatly reduced during expulsion, thereby facilitating rostral movement of gastric contents. The purpose of this study was to delineate this region of reduced activity and then to localize the portion of the phrenic motor pool that innervates it. Electromyographic (EMG) activity was recorded from different regions of the diaphragm during vomiting in cats. During expulsion, greatly reduced activity was obtained from electrodes placed up to about 3/4-1 cm away from the esophagus. HRP injected into this hiatal region labeled motoneurons throughout most of the rostral-caudal extent of the phrenic nucleus, with the exception of caudal C6 and rostral C7.

(6) Control of abdominal muscles by brain stem respiratory neurons (publications 4 and 5).

Brain stem respiratory neurons that project to the upper lumbar cord are likely to affect the activity of the abdominal muscles, which are innervated in part from this level while the other major respiratory muscles are supplied from more rostral segments. For this reason, respiratory neurons in the medulla and upper cervical cord were tested for antidromic activation from the upper lumbar cord. Possible synaptic connections between descending respiratory neurons and abdominal motoneurons were then tested by taking cross-correlations between the firing of these neurons and abdominal nerve activity. There is a large projection to the lumbar cord from expiratory neurons in the ventral respiratory group caudal to the obex; however, cross-correlation analysis indicated that there are few strong monosynaptic connections between these neurons and abdominal motoneurons. This study provided important information for use in the project described below.

(7) A. The development of a "fictive vomiting" preparation, and
B. Role of ventral respiratory group expiratory neurons in abdominal muscle control during vomiting (publications 6, 9, 11-13).

The fictive locomotion preparation has been a productive paradigm for studying central pattern generation without the problems of movement and peripheral feedback. No comparable model was available for vomiting. Therefore, we developed a "fictive vomiting" preparation in decerebrate, paralyzed cats to enable us to identify brain stem neurons that have the appropriate firing pattern to drive the diaphragm and abdominal muscles during vomiting. Fictive vomiting was defined by a characteristic pattern of co-activation of abdominal and phrenic nerves, elicited by emetic agents, that would be expected to produce vomiting in unparalyzed animals.

A central question regarding respiratory muscle control during vomiting is whether these muscles are activated via the same brain stem pre-motor neurons that provide descending respiratory drive and/or by other descending input(s). This question was addressed in regard to expiratory neurons in the caudal ventral respiratory group (VRG). Some of these neurons have the appropriate firing pattern during fictive vomiting to contribute to abdominal muscle control; however, other as yet unidentified inputs can also produce abdominal muscle activation during vomiting as was shown by severing the axons of VRG expiratory neurons.