PHYSIOLOGICAL EVIDENCE THAT THE VESTIBULAR SYSTEM PARTICIPATES IN AUTONOMIC AND RESPIRATORY CONTROL

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Abstract — Electrical or natural stimulation of the vestibular system results in changes in blood pressure and respiratory motor output. An increase in excitatory drive on the sympathetic nervous system occurs during nose-up vestibular stimulation in cats; this response is appropriate to offset orthostatic hypotension that could result from nose-up body rotations during movements such as vertical climbing. In addition, transection of the vestibular nerves in anesthetized or awake cats compromises the ability to correct decreases in blood pressure that result from nose-up body tilt. The vestibular system also has influences on respiratory muscles; these effects are appropriate to participate in making adjustments in the activity of respiratory muscles that are necessary to offset mechanical constraints on these muscles that occur during changes in body position. These data thus suggest that the influences of the vestibular system on the autonomic and respiratory systems serve to maintain homeostasis during movement. © 1998 Elsevier Science Inc.

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Introduction

Physiological evidence has existed for decades to show that vestibular stimulation can result in motion sickness (21,22). However, data also suggest that vestibular stimulation can elicit changes in circulation and respiration that provide for stable blood pressure and blood oxygenation during movement and changes in posture. The importance of vestibular signals in the maintenance of homeostasis is summarized in this review.

Evidence That the Vestibular System Participates in the Regulation of Blood Pressure

The earliest studies that demonstrated a connection between the vestibular system and brainstem systems that regulate circulation employed electrical stimulation of the vestibular nerve and recordings of blood pressure or activity of sympathetic nerves. It was shown that short trains of stimuli delivered to the vestibular nerve produce alterations in blood pressure that are mainly due to changes in activity of sympathetic nerves that regulate peripheral vascular resistance (11,12,17,35,34,41). An example of a response recorded from the splanchnic nerve (a large sympathetic nerve that innervates blood vessels in the abdominal viscera as well as gastrointestinal smooth muscle) following electrical stimulation of the vestibular nerve is illustrated in Figure 1, panel C. Natural vestibular stimulation in cats with denervations to remove nonlabyrinthine inputs that could be elicited by this stimulus was also demonstrated to produce changes in sympathetic nerve activity and blood pressure...
elicited by pitch (nose-up and nose-down rotations), but not by roll (ear down tilt) or yaw (horizontal rotation) (42). Nose-up tilt produces an increase in sympathetic nerve activity, whereas nose-down tilt elicits a decrease in nerve activity, as illustrated in Figure 2, panel A. The gain (relative to stimulus position) of the vestibulo-sympathetic response to sinusoidal pitch rotations is relatively constant across stimulus frequencies, and the response occurs in phase with the stimulus position, as indicated in Figure 2, panel B. These response characteristics are similar to those of otolith afferents (9) and suggest that the otolith organs are predominantly responsible for producing the vestibulosympathetic response. In addition, static nose-up vestibular stimulation, but not ear-down stimulation, produces large (∼20 mmHg) increases in blood pressure (36). Since cats have a long longitudinal axis, the return of blood to the heart is diminished during nose-up pitch of the body unless increases in sympathetic nerve activity occur to redistribute the blood volume and bolster blood pressure. Thus, the effects of the vestibular system on sympathetic outflow and blood pressure are appropriate to partly offset movement-related challenges to the circulatory system.

Other studies have indicated that removal of vestibular inputs compromises the ability of a cat to adjust blood pressure during nose-up rotation of the body. Doba and Reis (8) showed that bilateral transection of the VIIIth cranial nerves in anesthetized and paralyzed cats resulted in a greater drop in blood pressure during 60° or 90° nose-up pitch than in vestibular-intact animals. Our preliminary studies have demonstrated that a similar deficit can be observed during chronic recordings in anesthetized cats following VIIIth nerve transection (13). As shown in Figure 3, rapid and unexpected 60° nose-up tilt can produce a much larger (∼12 mmHg) decrease in blood pressure following vestibular nerve transection than before the transection. However, large movement-related decreases in blood pressure following VIIIth nerve transection were observed only during conditions in which the animal could not determine body position in space using visual inputs; when visual cues were provided, the drop in blood pressure during nose-up tilt was not significantly different than before the VIIIth nerve transection. Furthermore, the impairment in correcting blood pressure following transection of the vestibular nerve persisted for only one week, after which time 60° nose-up tilt produced only a slight decrease in blood pressure, even when the animal was deprived of visual feedback concerning body position in space. Presumably, the animal learned to use somatosensory cues to trigger cardiovascular changes dur-

![Figure 1. Responses recorded from (A) the abdominal nerve, which innervates expiratory muscles, (B) the hypoglossal nerve, which innervates tongue musculature and is active during inspiration, and (C) the splanchnic nerve, which is a sympathetic nerve, following electrical stimulation of the vestibular nerve. Each trace is the average of approximately 250 sweeps. A train of 5 shocks at 500 μA intensity was delivered to the vestibular nerve in the inner ear; this intensity was shown to not produce stimulus spread to the closest nontarget nerve, the facial nerve. Arrows indicate the time at which each shock of the stimulus train was presented. In these examples, vestibular nerve stimulation produced short-latency excitation in the abdominal and hypoglossal nerves and long-latency excitation in the splanchnic nerve; the responses are indicated by an open arrow.](image-url)
Vestibular Function and Homeostasis

It is likely that vestibular signals are integrated with other inputs, including those from the visual and somatosensory systems, in regulating blood pressure during movement and changes in posture.

Neural Pathways That Mediate Vestibular Influences on the Regulation of Blood Pressure

Neuroanatomical, neurophysiological, and lesion studies have elucidated a number of pathways through which vestibular signals can influence the regulation of circulation; these pathways are illustrated in Figure 4. The first connection linking the vestibular apparatus with the sympathetic nervous system occurs in portions of the medial and inferior vestibular nuclei located immediately caudal to the lateral vestibular nucleus; lesions of this area abolish changes in sympathetic nerve activity elicited by either natural or electrical stimulation of the vestibular system (34,41). The major outflow of vestibular signals from the brainstem to sympathetic preganglionic “output” neurons, which are located in the thoracic spinal cord, is mediated by reticulospinal neurons in the rostral ventrolateral medulla. This region is considered to be a major source of excitatory inputs to the sympathetic nervous system (5). More than two-thirds of the neurons in the rostral ventrolateral medulla that project to the vicinity of sympathetic preganglionic neurons respond to vestibular nerve stimulation (45), and lesions of this area abolish the effects of vestibular stimulation on sympathetic outflow (44). A number of regions that may relay vestibular signals to the

Figure 2. Responses of sympathetic and respiratory nerves to natural vestibular stimulation. (A) Averaged splanchnic (sympathetic) and abdominal (expiratory) nerve responses to 15 sinusoidal “wobble” head rotations on a stationary body. Wobble head rotations are a constant-amplitude tilt whose direction moves around the head at constant velocity; in these examples, the rotations were performed at 0.2 Hz. Sympathetic and respiratory nerve activity was recorded from cats in which the upper cervical dorsal roots were transected to remove afferents from the neck, so that the head rotations selectively activated vestibular afferents. Activity in the nerves was dependent on head position, and was maximal when the nose was up and minimal when the nose was down. (B) Gain and phase (relative to stimulus position) of responses to sinusoidal rotations in a plane at or near pitch. Data points are the average of standardized gains and phases from 8 animals in the case of the splanchnic nerve and from 14 animals in the case of the abdominal nerve. Error bars indicate SEM, although for most data points the error bars were too small to be plotted. The response gain was flat across stimulus frequency, and the phase was near stimulus position. Based on data from references 24 and 42.
rostral ventrolateral medulla have been identified, including the lateral reticular formation in the caudal medulla (30,31,37) and the nucleus tractus solitarius (40). Direct projections from the vestibular nuclei to the rostral ventrolateral medulla could also participate in vestibulosympathetic reflexes, as anatomical studies have identified a sparse projection from the medial and inferior vestibular nuclei to the rostral ventrolateral medulla (6). Locus coeruleus could also mediate vestibular-elicited sympathetic responses, because this region both receives vestibular signals (15,16) and has connections with the rostral ventrolateral medulla (7). However, only one brainstem region that contains cardiovascular- regulatory interneurons, the reticular formation of the caudal ventrolateral medulla, appears to be essential in generating vestibulosympathetic responses. Lesions of the caudal medullary reticular formation, but not of the nucleus solitarius or locus coeruleus, abolish vestibulosympathetic responses (30).

Evidence That the Vestibular System Participates in the Regulation of Respiration

The respiratory muscles can be divided into "pump" muscles and "valve" muscles, as reviewed in a recent book (18). The pump muscles consist of the diaphragm, which is the major muscle of inspiration; the abdominal muscles, which are expiratory; and the intercostal muscles, which are both inspiratory and expiratory. These muscles generate the changes in intrathoracic pressure that move air in and out of the lungs. The muscles of the upper airway both

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**Figure 3.** Effects of bilateral vestibular nerve transection on the ability to correct blood pressure during unexpected body tilts. (A) Blood pressure response in an awake cat with vestibular nerves transected to unexpected and rapid whole-body nose-up tilt of 60° amplitude. A drop in blood pressure of about 12 mmHg occurred within a few seconds after the tilt, but subsequently recovered. (B) Change in blood pressure following a 60° nose-up tilt in a single animal before and after transection of the vestibular nerves. Blood pressure was recorded in two testing patterns: 1) a paradigm in which visual surround rotated with the animal, so that no visual cues indicating body position in space were provided, and 2) a paradigm in which the visual surround remained stationary during tilt, so that visual cues indicating body position in space were present. Filled symbols indicate the average of responses recorded for one month before the lesion, and open symbols indicate the average of responses recorded during the one-week period immediately following the lesion. Error bars indicate SEM. Transection of the vestibular nerves compromised the ability of the animal to adjust blood pressure during nose-up tilt when there were no visual cues indicating body position in space.
function as valves that regulate the airflow generated by the actions of the pump muscles and serve to maintain airway patency. In addition, other muscles, whose main function is not respiratory, can if necessary be recruited to aid breathing movements.

Numerous studies have shown that respiratory muscle activity is affected by movement or changes in posture (reviewed in 20,43). However, movement results in the activation of many different receptors that can affect respiration, including pulmonary receptors and stretch receptors in the respiratory muscles. Only recently has the selective role of the vestibular system in adjusting respiratory muscle activity been considered.

Electrical stimulation of the vestibular nerve in decerebrate, paralyzed cats produces a widespread distribution of reflex responses recorded from respiratory muscle nerves (29,41). These nerves include the phrenic nerve (which supplies the diaphragm), intercostal muscle nerves, abdominal muscle nerves, the recurrent and superior laryngeal nerves, pharyngeal branches of the vagus nerve, the glossopharyngeal nerve, and the hypoglossal nerve. Examples of responses recorded from abdominal and hypoglossal nerves during electrical stimulation of the vestibular nerve are illustrated in Figure 1A and B.

Responses to natural vestibular stimulation have been recorded during rotations of the head on a stationary body using a decerebrate, paralyzed preparation in which the upper cervical dorsal roots were cut to remove neck afferent input (24,25). In addition, other nonvestibular inputs that might contribute to the response were

![Figure 4. Model of neural pathways that mediate vestibulosympathetic reflexes. These pathways are plotted on a sagittal section of the cat brainstem approximately 3 mm lateral to the midline. Vestibulosympathetic responses are produced by activation of pitch-sensitive otolith afferents, and involve neuronal connections in the medial and inferior vestibular nuclei, lateral reticular formation of the caudal medulla, and rostral ventrolateral medulla. Vestibulosympathetic responses may also involve processing of signals in nucleus solitarius and locus coeruleus. Abbreviations: AMB, nucleus ambiguus; CN, cuneate nucleus; IVN, inferior vestibular nucleus; LC, locus coeruleus; LR, lateral reticular nucleus; LVN, lateral vestibular nucleus; MVN, medial vestibular nucleus; NTS, nucleus tractus solitarius; RVLM, rostral ventrolateral medulla; SOM, medial nucleus of the superior olive; STN, spinal trigeminal nucleus; SVN, superior vestibular nucleus; T, nucleus of the trapezoid body; VII, facial motor nucleus.](image-url)
eliminated by denervating the upper airway, and cutting the vagus and carotid sinus nerves. Responses have been studied for the phrenic, abdominal, and hypoglossal nerves. Maximum activation in all three nerves occurs during movements that typically are near nose-up pitch, as illustrated in Figure 2A, for the abdominal nerve. The dynamics of the response are consistent with input from the otolith end-organs, as shown in Figure 2B. These reflex responses were abolished by kainic acid injections into the medial and inferior vestibular nuclei or by transection of the VIIIth nerve, proving that they were the result of activation of the vestibular system.

**Functional Significance of Vestibular Influences on Respiration**

The respiratory muscles are multifunctional muscles in the sense that they are involved in a number of behaviors in addition to breathing. These behaviors include coughing, sneezing, vomiting, speech, trunk movements, and aiding venous return to the heart (18). Furthermore, respiratory muscle activity is altered during exercise and locomotion. Because the respiratory muscles are multifunctional, the significance of vestibular influences on these muscles is likely to be multifaceted. One purpose of these influences is presumably to compensate for mechanical constraints on respiration during movement and changes in posture. During the transition to an upright stance in man or whole-body nose-up pitch in quadrupeds, the diaphragm shortens due to the effects of gravity and because it is no longer as well supported and stretched by the contents of the abdominal cavity. Since the efficiency of the diaphragm’s length–tension relationship is thus reduced, increased neural drive is required to maintain the same force of contraction. Increased abdominal muscle activation would serve to increase intra-abdominal pressure and lengthen the diaphragm (by raising it farther into the thorax), thus moving more air out of the lungs during expiration. Therefore, increased respiratory muscle activity during standing in bipeds or nose-up pitch in quadrupeds is essential for maintaining tidal volume (7,32). Tonic influences of the vestibular system on the respiratory muscles under these conditions would seem a practical mechanism to provide the required additional activity in the respiratory muscles.

Changes in posture can also affect the patency of the upper airway, requiring a tonic increase in the activity of upper airway muscles to allow unobstructed air flow. In particular, nose-up tilt of the head in either bipeds or quadrupeds can result in the tongue falling to the back of the throat and blocking the airway: an increase in activity in the tongue protruder muscles is required during nose-up tilt of the head to prevent obstructive apnea (26,27). Tonic influences of the vestibular system on tongue musculature during pitch of the head could thus play an important role in maintaining stable ventilation.

In addition to providing for air flow into and out of the lungs, respiratory muscles have other functions. Most of the respiratory pump muscles play a role in the maintenance of posture. The abdominal and intercostal muscles participate in supporting the trunk, particularly during standing in man and when the long axis is vertical in quadrupeds (for example, during vertical climbing). Even the diaphragm has been attributed a postural role, as this is the only muscle that spans the body cavity and thus can assist in supporting the upper portion of the body (10). Because the vestibular system plays an important role in maintaining posture through its actions on limb muscles (35), it would seem logical for these influences to extend to the respiratory “postural” muscles as well.

Vestibulorespiratory reflexes may also act in concert with vestibulosympathetic reflexes in providing for stable venous return to the heart during movement and changes in posture. An increase in negative intrathoracic pressure resulting from augmented contractions of the diaphragm would result in more blood being “pulled” into the heart; venous return would also be enhanced by increased activity of the abdominal muscles to force blood from the abdomen into the thorax (14,23,46). Thus, an increase in respiratory muscle activity during standing in man or nose-up body pitch in quadrupeds would act synergistically with increases in sympathetic nerve activity to aid in venous return to the heart.
Neural Pathways Mediating Vestibular Influences on Respiration

Vestibular influences on respiration appear to be mediated by the same regions of the vestibular nuclei that participate in vestibulosympathetic reflexes: portions of the medial and inferior vestibular nuclei just caudal to the lateral vestibular nucleus. Lesions of these areas abolish respiratory responses elicited by electrical (41) or natural (24) vestibular stimulation. Most of the axons of the lateral vestibulospinal tract (LVST) must be involved in relaying vestibular signals to respiratory motoneurons in the spinal cord. It is conceivable that these pathways include vestibulospinal and medial reticulospinal neurons that are also responsible for relaying vestibular signals to limb and neck motoneurons, although this possibility is yet to be tested.

Other vestibular connections may also be responsible for "shaping" the properties of respiratory activity. Recent neuroanatomical studies have demonstrated a projection from the superior vestibular nucleus to the vicinity of the pontine respiratory group (2); however, vestibular inputs to pontine respiratory neurons are yet to be evidenced neurophysiologically. Neurons in the raphe nuclei also receive vestibular inputs (38,39); these nuclei have been demonstrated to provide serotonergic inputs to respiratory neurons (3). The role of these connections in generating vestibulorespiratory responses is yet to be tested.

Future Considerations

Studies of vestibulosympathetic and vestibulorespiratory reflexes are still at an early stage in comparison to studies of vestibular-ocular reflexes and vestibulospinal reflexes acting on the limbs and neck. Additional studies are required to elucidate the functional significance of vestibular influences on respiration and circulation. To determine the neuronal circuitry that underlies these responses, and to begin to establish how vestibular inputs interact with other inputs that are important for the maintenance of homeostasis (for example, inputs from baroreceptors, pulmonary receptors, lung receptors, and so on). The clinical implications of disturbances in vestibular-autonomic and vestibular-respiratory responses that occur on earth and during exposure to microgravity also await elucidation.

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