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Short review

Post-spaceflight orthostatic intolerance: possible relationship to microgravity-induced plasticity in the vestibular system

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Abstract

Even after short spaceflights, most astronauts experience at least some postflight reduction of orthostatic tolerance; this problem is severe in some subjects. The mechanisms leading to postflight orthostatic intolerance are not well-established, but have traditionally been thought to include the following: changes in leg hemodynamics, alterations in baroreceptor reflex gain, decreases in exercise tolerance and aerobic fitness, hypovolemia, and altered sensitivity of β-adrenergic receptors in the periphery. Recent studies have demonstrated that signals from vestibular otolith organs play an important role in regulating blood pressure during changes in posture in a 1-g environment. Because spaceflight results in plastic changes in the vestibular otolith organs and in the processing of inputs from otolith receptors, it is possible that another contributing factor to postflight orthostatic hypotension is alterations in the gain of vestibular influences on cardiovascular control. Preliminary data support this hypothesis, although controlled studies will be required to determine the relationship between changes in the vestibular system and orthostatic hypotension following exposure to microgravity.

Keywords: Microgravity; Spaceflight; Otolith organ; Sympathetic nervous system

Contents

Abbreviations: B.P., blood pressure; b.p.m., beats per minute; H.R., heart rate

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1. Post-spaceflight orthostatic intolerance: incidence and relevance for space exploration by man

Spaceflight is associated with a number of physiological alterations. One consequence upon return to Earth is orthostatic intolerance, or an inability to remain in an upright posture while maintaining adequate perfusion of the brain. Orthostatic hypotension is a related condition in which blood pressure decreases, typically accompanied by tachycardia, during assuming an upright posture; this problem occurs clinically as part of a number of diseases that are characterized by abnormal regulation and/or inadequate level of activity of the sympathetic nervous system [29,36,37]. For example, orthostatic hypotension is typically associated with pure autonomic failure, Shy–Drager syndrome, failure in the baroreceptor reflex, diabetes, and Parkinson's disease. Thus, orthostatic intolerance should be regarded as a condition with a number of potential etiologies, and not a single disease state with one specific cause.

The first fully-documented case of post-spaceflight orthostatic intolerance was reported following the 34-h Mercury flight in 1963 [49]. Since this time, numerous clinical investigations have established that post-spaceflight orthostatic intolerance occurs in astronauts; the incidence has been reported to range from 15–20% [33] to 64% [6]. It is difficult to accurately access the frequency of occurrence of post-spaceflight orthostatic intolerance because of several factors, including methodological differences between studies, use of variable countermeasures (e.g., volume loading, exercise, or g-suits) by astronauts prior to landing, and the fact that spaceflights have a wide range of durations. Nevertheless, postflight orthostatic intolerance is recognized as a serious health problem that can severely impair the performance of crew members during re-entry into the Earth's atmosphere and immediately after landing. These portions of the flight are among the most demanding, and thus, postflight orthostatic intolerance is regarded as an impediment to manned spaceflight. For example, some astronauts are so severely affected by this condition that they would be unable to rapidly egress from the spacecraft in an emergency during landing. Furthermore, postflight orthostatic intolerance can persist for several days after return to Earth. The recovery time to normal orthostatic function is roughly proportional to flight duration [49], and requires a period of days to weeks [7,48]. Although syncopal incidents are rare after 1 to 2 days postflight, because of this problem, cosmonauts are not allowed to walk unaided for at least 2 days following long-duration flights [49].

2. Factors that produce post-spaceflight orthostatic intolerance: traditional views

Since the recognition of orthostatic intolerance as a major problem in manned spaceflight, a number of possible factors and mechanisms that may contribute to this condition have been evaluated. Although many physiological changes occur during spaceflight, only a small number of these effects have been proposed as potentially contributing to postflight orthostatic intolerance. Furthermore, the possibility that the interaction of a number of physiological changes may be required to produce the condition has not been adequately explored. The mechanisms that have been commonly discussed as generating postflight orthostatic intolerance include: (1) fluid loss and contraction of blood volume [27], (2) attenuation of the gain of the baroreceptor reflex [15], (3) muscle wasting and reduced aerobic fitness [1], (4) an increase in venous compliance [46], and (5) a change in the circulating levels of catecholamines that leads to a down-regulation of β-adrenoreceptors [9].

In microgravity, the hydrostatic pressure gradient is lost, which results in a cephalad fluid shift that is manifested by facial puffiness and jugular venous distention [49]. This fluid shift can elicit a variety of hormonal responses that lead to increased diuresis and fluid loss, including elevated secretion of atrial natriuretic peptide, decreased secretion of vasopressin, and decreased activation of the renin–angiotensin system [49]. In addition, many astronauts experience space motion sickness and emesis, which can also contribute to hypovolemia and a contraction of the blood volume [12]. Thus, it is possible that postflight orthostatic hypotension may result from microgravity-related loss of fluid. This hypothesis is supported by the finding that volume loading with saline prior to landing is an effective countermeasure for postflight orthostatic intolerance in some astronauts [7]. However, many subjects that have been volume loaded still report symptoms of postflight orthostatic intolerance, indicating that additional factors besides hypovolemia must contribute to the development of the condition [6,33].

Changes in the gain of the baroreceptor reflex during spaceflight have also been hypothesized to contribute to the development of postflight orthostatic hypotension. Although several studies involving measurement of heart rate have suggested that the baroreceptor reflex is affected by spaceflight (e.g., Ref. [15]), these experiments are not definitive. Hypovolemia and other factors resulting from spaceflight may produce alterations in cardiac output that, in turn, could lead to changes in heart rate responses during tests of the baroreceptor reflex [28]. Thus, differences in heart rate responses during baroreceptor reflex tests before and after spaceflight may be an epiphenomenon. Furthermore, even if previous studies have accurately predicted the magnitude of changes in baroreflex gain in space, these effects do not appear to be large enough to account for the severity of postflight orthostatic intolerance [3,22].

An increase in venous capacitance in the legs during spaceflight has also been proposed as contributing to postflight orthostatic intolerance, although evidence that sup-

ports this hypothesis is controversial. Data collected following Gemini flights suggested that calf volume increased 12–82% after a brief exposure to microgravity [2]. However, more recent studies on astronauts following the SLS-1 shuttle flight found that postflight leg volume during standing was not significantly different from preflight values [49]. Further studies will be required to determine if leg hemodynamics are altered during spaceflight, and whether these changes may lead to postflight orthostatic intolerance.

Exposure to microgravity also produces changes in the musculoskeletal system that could have secondary effects on cardiovascular function. Spaceflight results in bone demineralization and muscle atrophy [16,20], which can cause a decrease in the level of aerobic fitness and thus, a reduction in blood volume and central venous pressure [8]. Loss of limb muscle mass can also affect leg hemodynamics, resulting in further peripheral blood pooling. However, extensive in-flight exercise acts as an effective countermeasure for the microgravity-related changes in aerobic fitness [8], and astronauts who have exercised vigorously in space still experience postflight orthostatic intolerance [8]. Thus, muscle atrophy during spaceflight cannot exclusively account for this condition.

Spaceflight has also been shown to produce alterations in the concentration of norepinephrine and epinephrine in the blood, which can result in alterations in the sensitivity of β-adrenergic receptors in the smooth muscle of arterioles [8,49]. In contrast, the sensitivity of α-adrenergic receptors in the heart appears to be unaffected by simulated microgravity [9]. Increased sensitivity of β-adrenergic receptors following spaceflight could contribute to orthostatic intolerance, although it seems unlikely that this mechanism can solely account for the severity and time course of postflight orthostatic hypotension. Furthermore, the changes in circulating catecholamine levels during spaceflight and the subsequent effects on peripheral adrenergic receptors are presumably the reflection of other microgravity-related physiological changes, and are not the fundamental cause of postflight orthostatic intolerance. The physiological disturbances during spaceflight that trigger an increased peripheral secretion of catecholamines are yet to be elucidated.

Overall, the hypotheses that were previously proposed to account for the development of postflight orthostatic hypotension have not fully explained the severity of the condition. One possibility is that several of these mechanisms are activated simultaneously, and together lead to orthostatic hypotension after exposure to microgravity. Another possibility is that additional physiological disturbances also contribute to the development of the problem. Recent evidence suggests that morphological changes in the vestibular otolith organs and in the processing of signals from otolith receptors during spaceflight may be linked to postflight orthostatic intolerance. This possibility is considered below.

3. Microgravity-related changes in the vestibular system as a potential contributing factor to post-spaceflight orthostatic intolerance

3.1. Effects of microgravity on the vestibular system

Experiments involving unilateral labyrinthectomies have long provided evidence that the vestibular system is capable of rapid and dramatic plastic changes (e.g., Ref. [19]). Alterations in the pattern of otolith inputs to the central nervous system occur during spaceflight because the otolith organs are no longer exposed to constant gravitational forces. Thus, the otolith organs are no longer affected by tilting the head, but are only stimulated by linear acceleration of the head. A number of lines of evidence suggest that exposure to an altered gravitational environment produces significant adaptation in the vestibular system (e.g., Ref. [38]). Morphological changes have been reported in the otolith organs following 1–2 weeks of exposure to microgravity or 2-g hypergravity, including the number of synapses on hair cells [13,38]. Both vestibulo-spinal and vestibulo-ocular reflexes are also altered following exposure to microgravity or hypergravity; these physiological changes are likely to be the result of both peripheral and central adaptation in the central nervous system. For example, there is considerable evidence that ocular counter-rolling and other components of vestibulo-ocular reflexes are affected by spaceflight [11,44,45,47]. In addition, postural stability with the eyes closed [21,32,61] and the late component of the postural response to perturbation [25] are altered by exposure to microgravity. It is clear that at least part of these adaptive physiological changes are due to plasticity within the central nervous system, because functional changes in vestibulo-ocular reflexes persist for over 11 days postflight, whereas observable morphological alterations in the vestibular periphery recover within 9 days after return to Earth [39]. It is likely that plastic changes in the vestibular system during spaceflight affect all central nervous system functions dependent on signals from the otolith organs.

3.2. Evidence that the vestibular system participates in cardiovascular control in animal models

In a 1-g environment, changes in posture can provide profound challenges to the maintenance of stable blood pressure. For example, standing from a supine position in man results in over a six-fold increase in the length of the orthostatic (hydrostatic) column that must be overcome to allow blood to flow from the distal extremities to the heart [52,53]. Considerable evidence collected over the past few years suggests that the vestibular system participates in making necessary changes in blood pressure during movement and changes in posture. The vestibular system appears to elicit changes in blood pressure mainly through influences on the sympathetic subdivision of the auto-

nomic nervous system, with minimal effects on parasympathetic outflow to the heart [51–53]. The existence of vestibulo-sympathetic reflexes that adjust blood pressure is not surprising, as vestibular afferents provide information to the central nervous system indicating when a change in body position that can affect circulation is occurring. In fact, it is practical for the vestibular system to participate in adjustments for orthostatic hypotension, because it can act to stabilize the circulation during movement even before blood pressure has changed.

Many studies conducted in animals (primarily cats) have demonstrated the presence of vestibulo-sympathetic reflexes. In general, these studies have used one of two strategies:

1. Recording of blood pressure, sympathetic nerve activity, or activity of brainstem cardiovascular-regulatory neurons during selective stimulation of vestibular afferents;
2. Demonstrating that the maintenance of stable blood pressure is compromised by lesions of the vestibular system.

The first of these strategies has been used most often. A number of studies have demonstrated that activity in sympathetic nerves containing fibers that produce vasoconstriction, including the splanchnic nerve, renal nerve, cervical sympathetic nerve, inferior cardiac nerve, and abdominal sympathetic chain, is affected by low-threshold stimulation of branches of the vestibular nerve (see Refs. [51–53] for reviews). Changes in sympathetic nerve activity produced by vestibular nerve stimulation are abolished following lesions of the medial and inferior vestibular nuclei, proving that these responses are due to stimulation of vestibular afferents [57], and not to stimulus spread to other afferents.

A preparation has also been developed that allows for testing the effects of selective natural stimulation of vestibular receptors on sympathetic nerve activity and blood pressure. Vestibular stimulation is produced by rotation of *only* the head (on a stationary body) in animals whose upper cervical dorsal roots are transected to remove neck afferent input, and whose vagus and glossopharyngeal nerves and nerve branches to the upper airway are cut to remove pulmonary, airway, and cardiovascular signals that could potentially be elicited by changes in head position. In some animals, the trigeminal nerves are also transected intracranially to guarantee that cutaneous and proprioceptive inputs from the head do not influence the sympathetic nervous system during head movement. Use of this preparation has shown that natural stimulation of vestibular receptors can have profound effects on outflow of the sympathetic nervous system and blood pressure. For example, head rotations that are 15°–20° in amplitude produce a large change in sympathetic nerve activity. Nose-up pitch of the head of a cat results in an increase in sympathetic nerve activity, whereas nose-down pitch results in a decrease in activity in sympathetic nerves; roll or yaw rotations of the head result in little change in sympathetic outflow [58]. This response pattern would serve to stabilize blood pressure in a quadruped, which has a long longitudinal axis and requires an increase in sympathetic nerve activity to maintain constant blood pressure during nose-up body rotations (as during vertical climbing). The gain of sympathetic nerve responses to sinusoidal pitch rotations of the head is flat across the frequency range of 0.05–1 Hz, and the response phase is near stimulus position at all frequencies [58]. These response dynamics are similar to those of vestibular otolith afferents [18], and suggest that the otolith organs are primarily responsible for producing vestibulo-sympathetic responses.

Nose-up trapezoidal (ramp and hold) head tilts in animals with extensive denervations to eliminate nonlabyrinthine inputs that could be produced by this movement also resulted in pressor responses. On average, a 50° nose-up tilt produced a 20 mmHg increase in blood pressure (illustrated in Fig. 1); these responses were abolished by transection of the VIIIth cranial nerves, demonstrating that they were the result of activation of the vestibular system [50]. The vestibular-elicited changes in blood pressure occurred without a change in heart rate, suggesting that alterations in peripheral vasoconstriction alone can produce these responses [50]. Roll tilt of the head produced no change in blood pressure. Thus, vestibular inputs elicited by nose-up rotations in quadrupeds can generate changes in blood pressure that are appropriate to offset orthostatic hypotension.

Preliminary studies in the cat also showed that head rotations can produce alterations in plasma levels of cate-

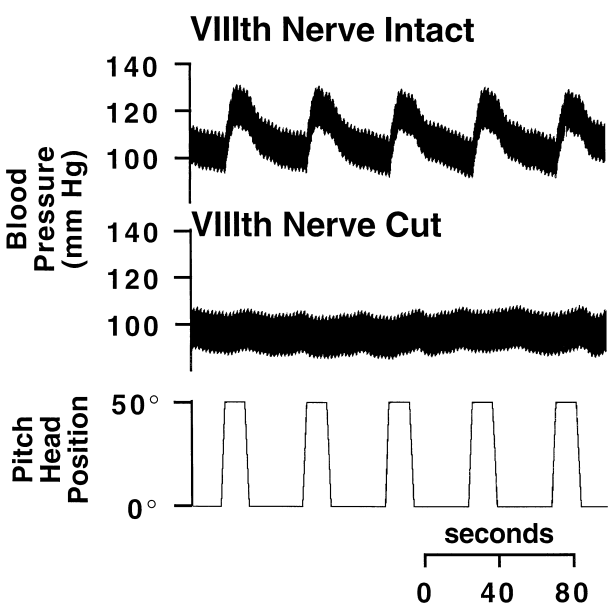

Fig. 1. Experimental evidence demonstrating that vestibular signals elicited by changes in posture produce changes in blood pressure. Increases in blood pressure were elicited during trapezoidal nose-up head rotations in cats with extensive denervations to remove nonlabyrinthine inputs that could be produced by the movements. Transection of the vestibular nerves eliminated these responses. From Ref. [50], used with permission.

cholamines. As shown in Fig. 2, 30 min of head-up tilt of 50° amplitude resulted in a doubling of both norepinephrine and epinephrine levels in the blood [26]. This finding suggests that the vestibular system affects blood pressure via both neural and hormonal mechanisms. It is, thus, possible that some of the observed changes in blood catecholamine levels during spaceflight [9] are the result of alterations in vestibulo-sympathetic reflexes acting on the adrenal gland. This prospect awaits to be explored.

Further evidence that the vestibular system participates in cardiovascular control comes from recordings of activity of brainstem neurons that regulate the sympathetic nervous system, during electrical stimulation of the vestibular nerve or natural stimulation of vestibular receptors in preparations with denervations to remove non-labyrinthine inputs that could be produced by body movement. These studies revealed that $>70\%$ of neurons located in the main pressor area of the brainstem (a portion of the reticular formation of the rostral ventrolateral medulla) receive labyrinthine signals [55,60]. The majority of neurons in the medullary pressor region have responses to vestibular stimulation like the vestibulo-sympathetic reflex: their activity is best modulated by pitch rotations, and their response dynamics are like otolith afferents [55]. However, not all brainstem cardiovascular-regulatory neurons receive vestibular signals. For example, there is little vestibular input to neurons in the nucleus tractus solitarius that receive baroreceptor signals, and presumably participate in the control of blood pressure [56], or to inhibitory interneurons in the baroreceptor reflex pathway located in the caudal ventrolateral medulla [43] (see Fig. 3). Thus, specific neural pathways appear to be responsible for mediating vestibulo-sympathetic responses. It is interesting that baroreceptor and vestibular signals remain segregated in neural circuits until they converge on pre-sympathetic neurons in the rostral ventrolateral medulla. The functional significance of the segregated processing of vestibular and baroreceptor signals remains to be determined.

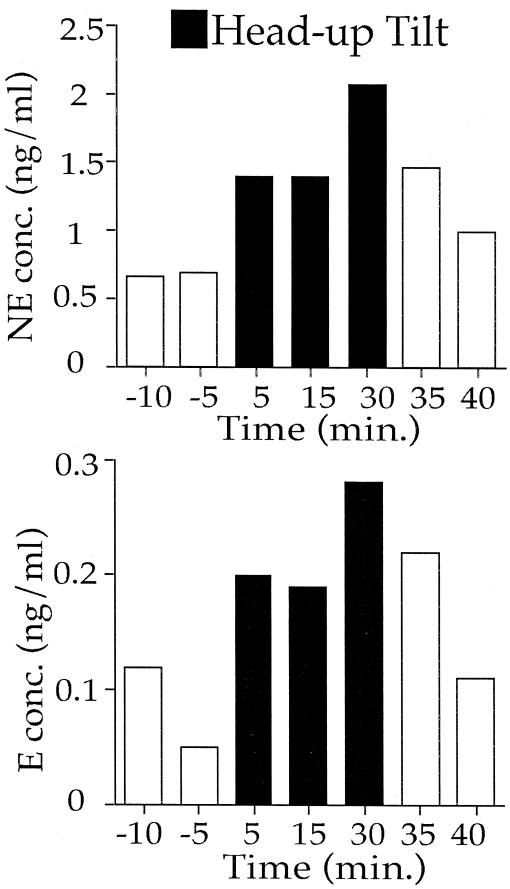

Fig. 2. Blood norepinephrine (NE, top panel) and epinephrine (E, bottom panel) concentrations before, during, and after 50° nose-up tilt of only the head (on a stationary body) in an α-chloralose-anesthetized cat. From 0 to 30 min the head was tilted nose-up by 50° and blood was sampled at indicated times. Nose-up head tilt produced over a two-fold increase in blood catecholamine levels.

The minimal neural circuitry responsible for producing vestibulo-sympathetic responses has been determined using electrophysiological and lesion studies in the cat [42,43,52–54,59]. The vestibulo-sympathetic reflex pathway involves neurons in the medial and inferior vestibular nuclei, the lateral medullary reticular formation, and projections from the pressor area of the rostral ventrolateral medulla to sympathetic preganglionic neurons in the spinal cord. This pathway is illustrated in Fig. 3.

The second strategy used to demonstrate that the vestibular system participates in altering blood pressure during movement and changes in posture has been to show that orthostatic hypotension is more likely following vestibular lesions. Doba and Reis [14] determined that bilateral transection of the vestibular nerves in chloralose-anesthetized, paralyzed cats resulted in large drops in blood pressure during nose-up tilts. We have followed-up these experiments by showing that orthostatic hypotension is also more prevalent during unexpected nose-up tilts in at least some *awake* cats with peripheral vestibular lesions than in vestibular-intact animals [24]. Awake cats were trained to remain sedentary, with limbs extended, on a platform during whole-body nose-up tilt. The tilts were performed under two conditions: (1) the animals could use visual cues to determine body position in space, or (2) the visual field rotated with the animal, so that *no* visual cues indicating position is space were provided. As illustrated in Fig. 4A, blood pressure typically remained stable during 60° nose-up tilt in animals with intact vestibular nerves. Because reflexes produced by baroreceptors and other cardiovascular receptors are feedback-regulated, they are not elicited until a change in blood pressure occurs. Since blood pressure does not change during large nose-up tilts in quadrupeds, other mechanisms that detect the onset of movements that may lead to orthostasis (and which are *not* dependent on a change in blood pressure) also apparently participate in cardiovascular control, and provide for more stable blood pressure than could be produced by feedback regulation alone.

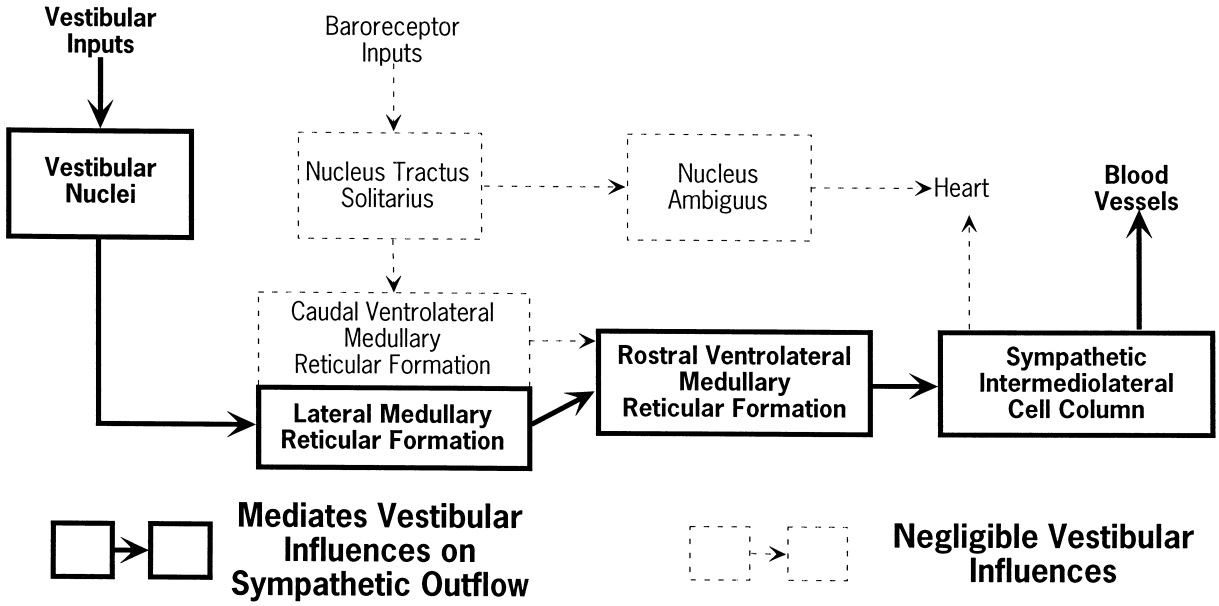

Fig. 3. Schematic illustration of the brainstem and spinal cord pathways that mediate vestibulo-sympathetic and baroreceptor reflexes in the cat. Solid boxes and arrows indicate pathways that convey vestibular signals, whereas dashed boxes and arrows mark the pathways that mediate baroreceptor (but not vestibular) influences on cardiovascular control. Baroreceptor afferents terminate in nucleus tractus solitarius. Baroreceptor effects on the sympathetic nervous system are mediated by inhibitory interneurons in the caudal ventrolateral medulla and pre-sympathetic neurons in the rostral ventrolateral medulla that directly innervate sympathetic preganglionic neurons in the spinal cord. In addition, baroreceptor-sensitive neurons in nucleus tractus solitarius make direct connections with cardiac parasympathetic preganglionic neurons located near nucleus ambiguus. Vestibular signals affect sympathetic outflow through a neural circuit including the vestibular nuclei, neurons in the lateral medullary reticular formation (but excluding cells with powerful baroreceptor inputs), and pre-sympathetic neurons in the rostral ventrolateral medulla. Thus, neurons in the rostral ventrolateral medulla represent the first site of convergence between baroreceptor and vestibular signals in pathways that control sympathetic outflow. The vestibular system appears to have negligible effects on the parasympathetic nervous system and on the control of heart rate. See text for further explanation.

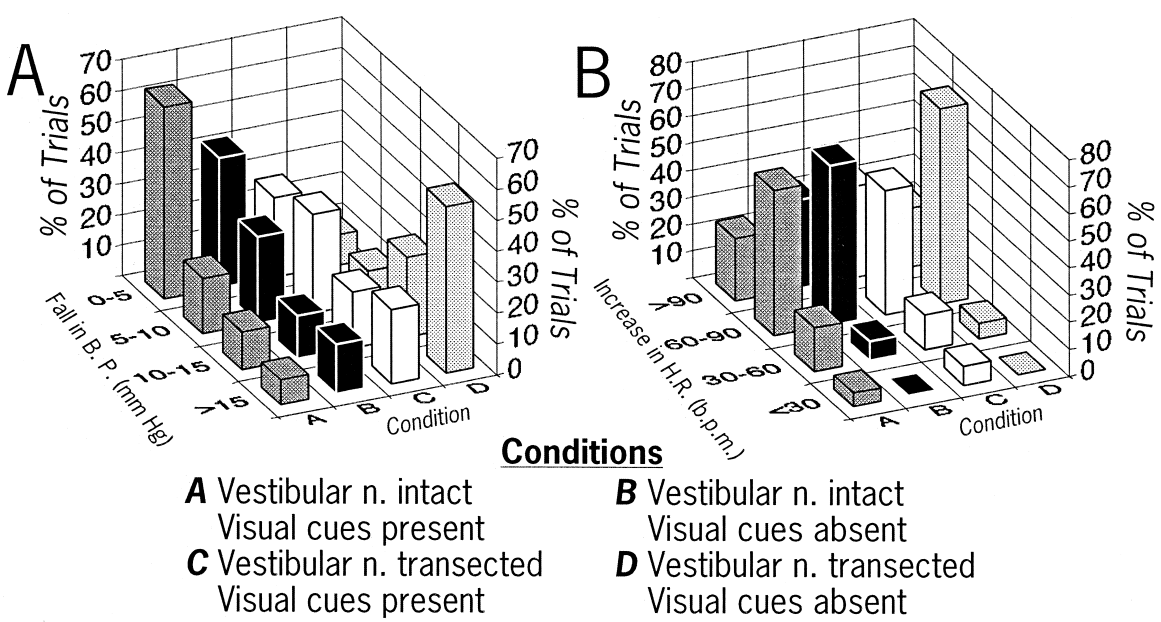

Fig. 4. Effects of 60° nose-up whole-body tilts on mean blood pressure and heart rate in awake cats. Cardiovascular responses were recorded under four conditions, as summarized in the inset of the figure. Data from two animals are pooled in these graphs. (A) Change in mean blood pressure during unexpected nose-up tilts. When the vestibular nerves were intact (Conditions A and B), in most trials blood pressure remained stable during body rotations, particularly when the animals were provided with visual cues indicating body position in space (Condition A). Following vestibular nerve transection (Conditions C and D), a decrease in blood pressure was more common during whole-body tilt. Orthostatic intolerance was particularly frequent when the visual field rotated with the animal (Condition D), and thus, neither visual nor vestibular cues indicating body position in space were provided. (B) Change in heart rate during 60° nose-up tilt. Heart rate increased by a similar amount under all four test conditions, suggesting that orthostatic intolerance resulting from vestibular nerve lesions is *not* the result of a diminished capacity to alter this variable.

Following vestibular nerve transection, orthostatic tolerance was reduced significantly in awake animals. As shown in Fig. 4A, 60° nose-up tilt produced large (> 10 mmHg) drops in mean blood pressure in many more trials after bilateral VIIIth nerve transection than before vestibular inputs were removed. However, large movement-related decreases in blood pressure following VIIIth nerve transections were most often observed during conditions in which the animal could not determine body position in space using visual cues. These findings suggest that vestibular inputs are integrated with other signals, including those from the visual system, in regulating blood pressure during movement and changes in posture.

Fig. 4B illustrates the changes in heart rate that occurred during nose-up tilt in cats, before and after transection of the vestibular nerves and both in the presence and absence of visual cues indicating body position in space. Under all conditions, heart rate increased by a similar amount during nose-up tilt. Thus, the orthostatic intolerance that occurs following vestibular nerve transection does not appear to be the result of a decreased ability to produce compensatory heart rate responses.

Vestibular and visual inputs are two examples of somatic signals that may be involved in triggering compensatory changes in cardiovascular regulation during changes in posture. In addition, recent studies also suggest that proprioceptive inputs from the neck modulate vestibulo-sympathetic responses during head movements. Responses were recorded from the splanchnic nerve during stimulation of C_2 or C_3 nerve branches innervating dorsal neck muscles. In many cases, the threshold for producing the cervico-sympathetic responses was less than twice the threshold for eliciting an afferent volley recordable from the cord dorsum, suggesting that these effects are due to activation of afferents from muscle spindles or Golgi tendon organs [4]. As a result, head rotation on a stable body would be expected to elicit both cervical and vestibular inputs to sympathetic preganglionic neurons. Transection of the C_1–C_3 dorsal roots enhanced responses of the splanchnic nerves to pitch head rotations on a fixed body. Thus, neck and vestibular afferent influences on sympathetic outflow appear to be antagonistic, so that responses will occur during whole body movements, but not head movements on a stationary trunk [5]. The integration of vestibular signals with other sensory inputs indicating body position in the environment must be considered in order to fully appreciate the role of the vestibular system in the regulation of circulation.

3.3. Evidence that the vestibular system participates in cardiovascular control in humans

Although most data indicating that the vestibular system influences the control of blood pressure come from studies in animals, there is also evidence to suggest that vestibulo-cardiovascular influences exist in man. Hemmingway [23] showed that 150° swinging of human subjects who reported no signs of motion sickness resulted in a drop in arterial blood pressure of a few mmHg; the subjects also experienced an average decrease in heart rate of 5 b.p.m. However, no controls were done to demonstrate that the effects were due to activation of labyrinthine receptors. A better-controlled experiment was performed by Essandoh et al. [17], who reported that head-down neck flexion in prone male subjects produces a rapid (latency of < 30 s, when the first measurements were taken) decrease in blood flow in the forearm and calf. These changes in blood flow would serve to maintain blood volume in the systemic circulation, and thus, bolster blood pressure. Recently, Ray et al. [34,35,41] and Normand et al. [31] confirmed these findings, and in addition showed that muscle sympathetic nerve activity and calf vascular resistance is affected by head-down neck flexion in prone subjects. However, head flexion had no effect on activity of skin sympathetic nerves [35]. The mechanisms responsible for the changes in circulation during head flexion were not identified; however, the authors ruled out a number of non-labyrinthine mechanisms that could have produced the responses, including baroreceptors and neck receptors. Thus, it seems probable that the vestibular apparatus was involved in producing the changes in sympathetic nerve activity and cardiovascular function during head flexion.

Although vestibulo-cardiovascular reflexes occur in both man and quadrupeds, some aspects of these responses in humans appear to differ from those in animals. Ray et al. [34] showed that inputs from neck receptors elicited by head down flexion in human subjects do not appear to influence the sympathetic nervous system; in contrast, neck and vestibular inputs elicited by pitch head movements in cats are integrated in an antagonistic manner, and cancel each other [5]. Furthermore, Convertino et al. [10] demonstrated that yaw rotations of subjects resulted in a decreased sensitivity of the carotid–cardiac baroreflex response; in cats, there is no evidence to suggest that yaw stimulation influences the sympathetic nervous system [51–53,58]. Although the physiological significance of the cardiovascular response to yaw stimulation in humans is unclear, as horizontal rotations have no adverse effect on circulation, this is further evidence to suggest that vestibulo-sympathetic responses in humans have properties that are somewhat distinct from those in quadrupeds. These differences are presumably related to the fact that the demands placed on the cardiovascular system are not completely analogous in bipeds and quadrupeds, and vestibular inputs that signal challenges to the maintenance of stable blood pressure may vary between the two groups.

3.4. Possible links between spaceflight-related plasticity in the vestibular system and post-spaceflight orthostatic intolerance

Because the vestibular otolith organs participate in regulating blood pressure, it is reasonable to hypothesize that

adaptive plasticity in the otolith organs and/or the central processing of otolith signals resulting from exposure to microgravity can increase susceptibility for post-spaceflight orthostatic intolerance. Rudimentary evidence that postflight orthostatic intolerance may be the partial result of plastic changes in the vestibular system comes from the work of Mikhaylov et al. [30], as well as from studies by other researchers [49], who reported a significant association between vestibular and cardiovascular dysfunction in subjects after spaceflights of 74–184 days. Furthermore, preliminary studies by Schlegel et al. [40] have indicated that parabolic flight maneuvers that result in multiple exposures to microgravity can induce increased orthostatic intolerance in subjects, including those with little or no fluid loss due to emesis. Because parabolic flight has effects on the vestibular system, but produces few of the other physiological changes (such as muscle wasting) that occur during spaceflight, this may be a good model for determining some of the selective influences of *short-term* adaptive changes in the vestibular system on the cardiovascular system in man. However, other approaches will be required to assess the effects of plasticity in the vestibular system produced by long-term exposure to an altered gravitational environment on regulation of circulation.

4. Methods to test the hypothesis that plastic changes in the vestibular system produced by exposure to altered gravitational environments are linked to alterations in orthostatic tolerance

Clinical studies that correlate severity of orthostatic hypotension with vestibular dysfunction following spaceflight or parabolic flight provide one means to test the hypothesis that postflight orthostatic intolerance is linked to microgravity-related adaptation in the vestibular system. However, this approach is limited for two reasons. First, it is logistically difficult to conduct studies on astronauts in the first few hours immediately following landing, in which plastic changes produced by spaceflight are most prominent. Second, the necessary control experiment, demonstrating that the decrease in orthostatic tolerance following spaceflight is less severe in vestibular-deficient than in vestibular-intact subjects, is impossible to systematically perform in humans. Thus, the use of animals will be crucial to test our hypothesis. Because of the limited ability to conduct experiments in space, early studies could be done using centrifugation (hypergravity) to produce plastic changes in the vestibular system. If our hypothesis is correct, then changes in orthostatic tolerance following long-term centrifugation should be greater in vestibular-intact than in vestibular-deficient animals. It should be possible to perform centrifugation on the same animals before and after performing a peripheral vestibular lesion, so that the link between plastic changes in the vestibular system and alterations in orthostatic tolerance can be made in individual cases. Of course, the physiological adaptations to hypergravity do not completely mirror those to microgravity. Thus, if these preliminary experiments confirm our hypothesis, then similar studies should be considered that involve placing animals in microgravity.

5. Potential countermeasures for vestibular-related orthostatic hypotension

Any countermeasures that reduce plastic changes in the vestibular system during exposure to microgravity would presumably diminish the effects of spaceflight on vestibular–cardiovascular interactions. For example, periods of centrifugation in space may reduce adaptation in the vestibular system, and act as an effective countermeasure for vestibular-related postflight orthostatic hypotension. The finding that multiple sensory cues may be involved in triggering compensatory changes in blood pressure during movement and changes in posture [24] could also potentially be exploited as an effective countermeasure. It is feasible that preflight training could be used to increase the reliance on visual, somatosensory, and other inputs in triggering compensatory changes in blood pressure during movement. If training could accomplish this goal, then alterations in the gain of vestibular–cardiovascular reflexes during spaceflight would result in less marked reductions in postflight orthostatic tolerance. These potential countermeasures should be tested for efficacy.

6. Summary

Considerable evidence suggests that inputs from vestibular otolith organs participate in eliciting changes in sympathetic nervous system activity during movement and changes in posture that are important for the maintenance of stable blood pressure in a 1-g environment. Removal of vestibular inputs compromises the ability to correct blood pressure during movement, and thus, increases susceptibility for orthostatic hypotension. It is also well-established that exposure to unusual gravitational environments results in morphological changes in vestibular otolith organs and adaptation in the processing of signals from these end-organs. Thus, post-spaceflight orthostatic intolerance may stem in part from plastic changes that occur in the vestibular system during exposure to microgravity. Preliminary studies have supported this hypothesis, which now requires more thorough testing to be validated.

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