

Patterning of sympathetic nerve activity in response to vestibular stimulation

I. A. Kerman,^{1,2*} R. M. McAllen³ and B. J. Yates^{1,2}

Departments of ¹Neuroscience and ²Otolaryngology, University of Pittsburgh, Pittsburgh, PA, USA; and ³Howard Florey Institute of Experimental Physiology and Medicine, University of Melbourne, Parkville, Victoria, Australia

[Received 7 March 2000; Accepted 23 March 2000]

ABSTRACT: Growing evidence suggests a role for the vestibular system in regulation of autonomic outflow during postural adjustments. In the present paper we review evidence for the patterning of sympathetic nerve activity elicited by vestibular stimulation. In response to electrical activation of vestibular afferents, firing of sympathetic nerves located throughout the body is altered. However, activity of the renal nerve is most sensitive to vestibular inputs. In contrast, high-intensity simultaneous activation of cutaneous and muscle inputs elicits equivalent changes in firing of the renal, superior mesenteric and lumbar colonic nerves. Responses of muscle vasoconstrictor (MVC) efferents to vestibular stimulation are either inhibitory (Type I) or are comprised of a combination of excitation and inhibition (Type II). Interestingly, single MVC units located in the hindlimb exhibited predominantly Type I responses while those located in the forelimb and face exhibited Type II responses. Furthermore, brachial and femoral arterial blood flows were dissociated in response to vestibular stimulation, such that brachial vascular resistance increased while femoral resistance decreased. These studies demonstrate that vestibulosympathetic reflexes are patterned according to both the anatomical location and innervation target of a particular sympathetic nerve, and can lead to distinct changes in local blood flow. © 2000 Elsevier Science Inc.

KEY WORDS: Vestibulosympathetic reflexes, Renal nerve, Muscle vasoconstrictor, Exercise, Blood flow, Cat.

INTRODUCTION

Postural changes require the engagement of various efferent systems, including recruitment of somatic motoneurons that produce muscle contraction, and activation of complementary autonomic outflows to ensure adequate blood supply to contracting muscles while maintaining adequate perfusion of the brain. Classically, two types of inputs have been implicated in this coordination of autonomic and motor responses. One such input, commonly referred to as ‘central command’, is thought to originate from the forebrain and is believed to simultaneously affect autonomic and somatic motor outflows [18]. Sensory inputs from working muscles as well as from the arterial and cardiopulmonary stretch receptors have also been implicated in autonomic regulation during postural ad-

justments and exercise [7]. It is important to note that central command inputs act in a feedforward manner, engaging autonomic outflows simultaneously with those of the somatic motor system. In contrast, inputs from somatic afferents (i.e., working muscle) and visceral afferents (i.e., baroreceptors and atrial stretch receptors) function in a feedback manner, altering sympathetic output in response to muscle contraction and decreases in blood pressure and blood volume.

Previous work has suggested that multiple inputs participate in autonomic regulation during exercise and movement; presumably these inputs are dependent on prevailing physiological conditions [7]. Accordingly, it is likely that afferent inputs from vestibular endorgans participate in regulation of sympathetic nerve activity during movement and postural changes. The vestibular system can quickly and accurately detect the head’s position in space [20], and thus appears to be ideally designed for eliciting autonomic adjustments during postural changes. However, in order to achieve homeostasis, these autonomic adjustments must be precisely patterned across body tissues and body regions. For example, if cardiac output remains constant, then an increase in blood flow to one body region must be offset by a decrease in flow to other regions for blood pressure to remain stable. In the present paper we will review the evidence for the existence of vestibulosympathetic reflexes (VSR), and will then discuss our recent findings in cats regarding the patterning of these responses.

REGIONAL DIFFERENCES IN THE EXPRESSION OF VSR

The existence of VSR was suggested by early studies in which caloric and electrical labyrinthine stimulation were used to produce alterations in cardiovascular function and in sympathetic nerve activity [2,4,12,13,15–17]. Accordingly, Spiegel reported a drop in blood pressure in response to caloric stimulation of the labyrinth in humans [15], pointing to the existence of vestibulo-autonomic interactions. However, caloric stimulation can activate non-vestibular afferents, and may also induce nausea, thus complicating interpretation of these results. Subsequent electrophysiological investigations showed that electrical activation of vestibular afferents can produce both excitation and inhibition of sympathetic nerve discharge [2,4,12,16,

* Address for correspondence: Dr. Ilan A. Kerman, Department of Otolaryngology, University of Pittsburgh, Eye and Ear Institute, Room 113, 203 Lothrop Street, Pittsburgh, PA 15213, USA. Fax: +1-(412)-647-2080; E-mail: Kerman@neurosci.bns.pitt.edu

17]. However, in some of these studies, the VIIIth nerve was stimulated intracranially, possibly resulting in direct current spread to the brainstem or adjacent cranial nerves. Therefore, it is not clear whether vestibular inputs influence a wide variety of sympathetic nerves, or if only a subset of these nerves respond to vestibular activation.

To determine how widespread are the influences of the vestibular system on sympathetic outflow, we simultaneously recorded activity of several sympathetic nerves while unilaterally electrically stimulating vestibular afferents [10]. In these experiments, a pair of ball-shaped electrodes was implanted into the inner ear so that a bipolar electrical stimulus could be delivered to activate vestibular afferents. This method allows for powerful activation of afferents from all vestibular endorgans, albeit a non-physiological stimulus that produces an input that signals simultaneous head movement in multiple directions. However, this is a very selective method for stimulation of vestibular afferents and is well-suited for the investigation of the basic properties of VSR. Furthermore, during these experiments animals were paralyzed to prevent muscle contraction elicited by vestibular stimulation from indirectly resulting in cardiovascular responses.

The sympathetic nerves recorded from in this study included those that innervate the kidney (renal nerve), the adrenal gland (adrenal nerve), the gastrointestinal tract (celiac, superior mesenteric and lumbar colonic nerves), the bladder (hypogastric nerve) and the external carotid artery (external carotid nerve). Figure 1 illustrates examples of responses to vestibular nerve stimulation recorded in these experiments. Interestingly, although the responses consisted of a mixture of excitation and inhibition, the waveforms recorded from multiple nerves in a particular animal were of the same shape. In some animals, these responses were predominantly excitatory (Fig. 1A), whereas in others, they consisted of a combination of excitatory and inhibitory potentials, such that inhibition was followed by excitation (Fig. 1B), or excitation was followed by inhibition (Fig. 1C). The animal-to-animal variability in the shape of sympathetic nerve responses to vestibular stimuli likely reflected differences in the placement of labyrinthine stimulating electrodes.

The finding that vestibular stimulation leads to alterations in the activity of a variety of sympathetic nerves suggests that labyrinthine inputs have potential to produce changes in autonomic function throughout the body. It also raises the question of whether different sympathetic nerves have unequal sensitivities to vestibular inputs. This type of quantitative question is difficult to answer, because a variety of factors (such as differences in the contact between a nerve and the recording electrode) may contribute to variability in the size of whole nerve responses to a particular stimulus. One way to control for this variability is to 'calibrate' responses by comparing them to maximal changes in nerve activity. In these experiments, maximal postganglionic nerve activation was produced by electrically stimulating all preganglionic inputs to the ganglion that the postganglionic nerve arose from. Figure 2 illustrates responses simultaneously obtained from the renal and external carotid nerves to preganglionic stimulation. Note the similarity in the magnitude of discharges in response to preganglionic stimulation in both cases. In contrast, the magnitudes of renal and external carotid nerve responses to vestibular activation were very different, with the latter being considerably smaller (Figs. 2A2, B2).

Postganglionic nerve responses to vestibular stimulation were quantified by measuring the area under the curve and expressing this value as a fraction of maximal nerve activation produced by preganglionic stimulation [10]. Pooled data illustrated in Fig. 3 demonstrate that the renal nerve is especially sensitive to vestibular stimulation because the size of responses

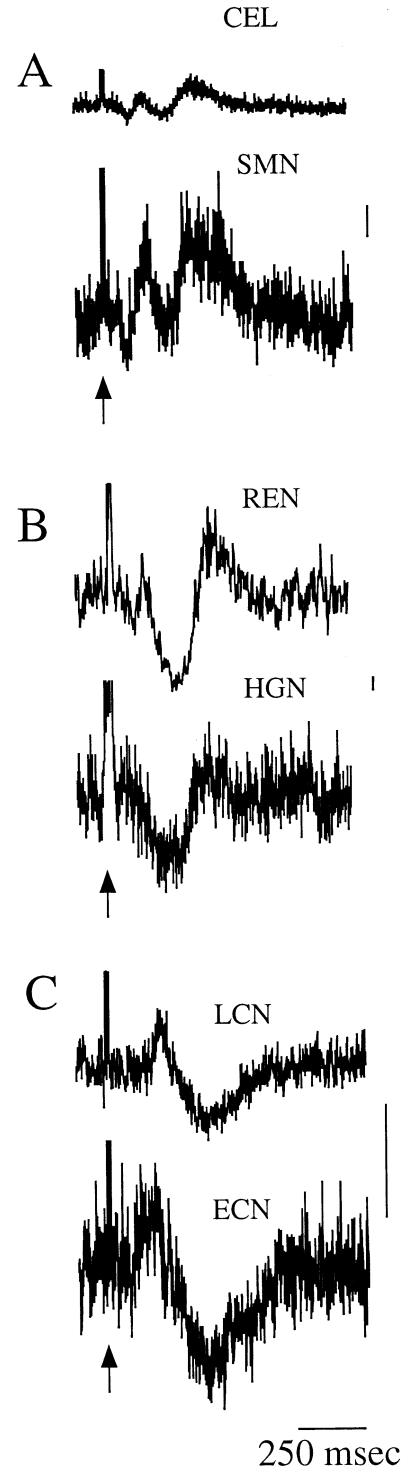


FIG. 1. Averaged sympathetic nerve responses to electrical stimulation of vestibular afferents. Results from three different experiments are illustrated. In the first animal (A) activities of the celiac (CEL) and superior mesenteric (SMN) nerves were recorded. In the other two cats activities of renal (REN) and hypogastric (HGN) nerves (B) as well as lumbar colonic (LCN) and external carotid (ECN) (C) nerves were sampled. Arrows at the bottom of the panel indicate the time of the electrical stimulus; stimulus intensities were $500 \mu\text{A}$ (A, C) and $350 \mu\text{A}$ (B). Within each trace upward deflections from baseline represent excitation, while downward deflections represent inhibition. Scale bars: $1 \mu\text{V}$. Data from [10].

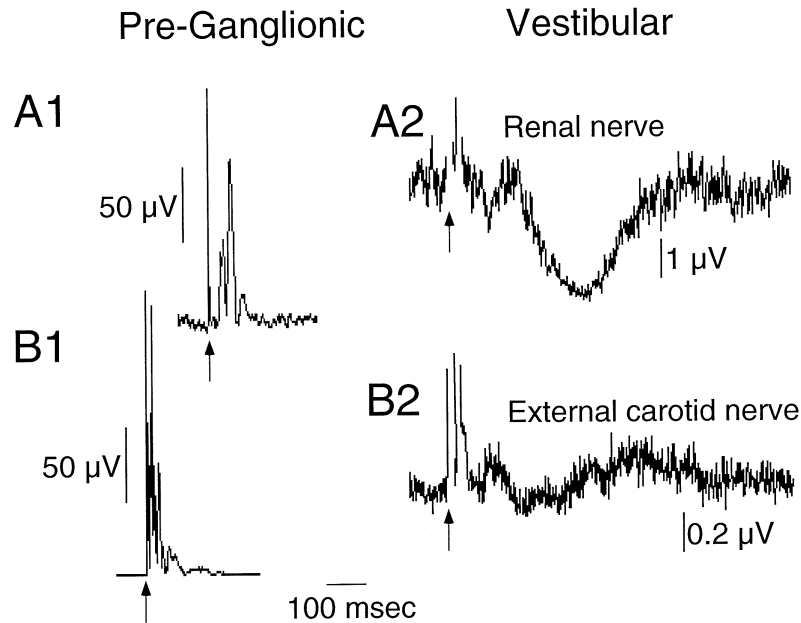


FIG. 2. Comparison of the magnitude of vestibulosympathetic reflexes (A2, B2) to maximal nerve activation produced by preganglionic stimulation (A1, B1). Responses illustrated for the renal nerve (A1, A2) and the external carotid nerve (B1, B2) were recorded from the same animal. Preganglionic inputs to the renal nerve were activated by stimulation of the thoracic splanchnic nerves (A1), while the cervical sympathetic chain was stimulated to produce maximal activation of the external carotid nerve (B1). Responses to preganglionic stimulation are shown at a much lower gain than those to vestibular stimulation. Data from [10].

of that nerve were significantly ($p < 0.05$, analysis of covariance, followed by *post-hoc* analysis using Student's *t*-test) greater than in any of the other nerves sampled. In contrast, responses of the external carotid nerve were significantly ($p <$

0.05) smaller than those in the other nerves, except for the hypogastric nerve.

To determine whether this pattern of responses was unique to VSR, or was elicited by other somatic inputs, we compared responses of the same nerves to activation of inputs from skin and muscle [9]. In these experiments, muscle and cutaneous inputs were activated by electrical stimulation of nerves from the hind-limb or forelimb containing both muscle and cutaneous afferents. The stimulus was delivered at high enough intensity to activate group III or IV afferents, thus producing the classical somatosympathetic reflex [14]. The magnitude of the somatosympathetic reflexes was quantified in the same fashion as for VSR; namely, the magnitude of the response was standardized to maximal nerve activation produced by preganglionic stimulation. Figure 3 compares the patterning of somatosympathetic reflexes and VSR recorded from the same group of animals. Overall, cutaneous and muscle inputs had a much more powerful influence on sympathetic nerve activity than did vestibular inputs, since every nerve had a much larger response to stimulation of limb afferents than inputs from the vestibular labyrinth. However, it appears that vestibular inputs elicit more specific patterning of sympathetic nerve responses than do inputs from muscle and skin, since labyrinthine inputs preferentially influence renal nerve activity whereas stimulation of skin and muscle afferents leads to equivalently large responses in the renal, mesenteric and lumbar colonic nerves [9,10]. Therefore, it seems that different types of somatic inputs elicit different patterns of sympathetic outflow.

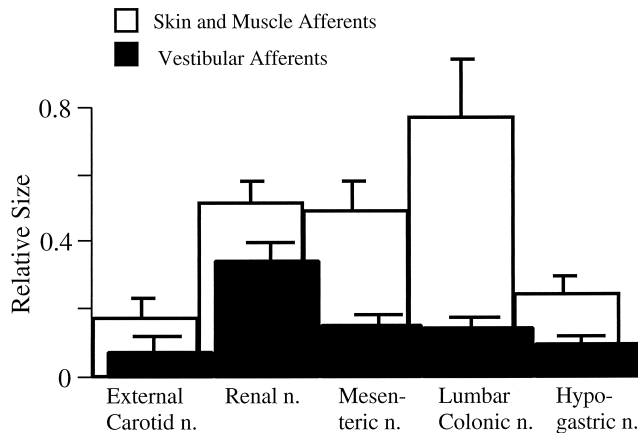


FIG. 3. Comparison of the size of somatosympathetic and vestibulosympathetic reflexes in different sympathetic nerves. The magnitudes of responses to activation of muscle and skin afferents were quantified and compared to those elicited by stimulation of vestibular afferents in anesthetized animals. The two types of inputs led to distinct patterning of sympathetic outflow. Activities of lumbar colonic, superior mesenteric and renal nerves were most powerfully, but approximately equally, affected by skin plus muscle afferent activation (analysis of covariance, $p < 0.05$). In response to vestibular stimulation, renal nerve responses were larger than those of the other nerves ($p < 0.05$). Data from [9,10].

ANATOMICAL PATTERNING IN THE EXPRESSION OF VSR

As discussed above and illustrated in Fig. 3, there are clear regional differences in the expression of VSR. It has been

suggested that these reflexes contribute to regulating cardiovascular functions during postural adjustments and movement [22, 23]. Therefore, it is possible that differences in the magnitude of VSR recorded from different sympathetic nerves reflect the relative proportion of fibers in each nerve that innervate vascular smooth muscle. Single-fiber recording experiments have shown that sympathetic nerves differ in their relative content of vasoconstrictor fibers [1,5]; these fibers are identified by having activity that is synchronized with the cardiac cycle and which is selectively inhibited by blood pressure increases [1]. Since the efferent fibers in the renal nerve consist almost entirely of this type, it seems likely that vestibularly-elicited responses recorded from this nerve are mainly due to activation of fibers innervating vascular smooth muscle. This notion that VSR are mediated selectively by vasoconstrictor efferents is supported by comparison of the large size of renal responses to the small magnitude of responses in the hypogastric nerve, which is made up largely of non-vasoconstrictor efferents [6]. However, VSR recorded from the external carotid nerve, which like the renal nerve is believed to be comprised mainly of vasoconstrictor fibers because its activity is completely silenced by blood pressure increases [3,19], are small in magnitude. The finding that the size of responses is much smaller in the external carotid nerve than the renal nerve may either be due to the fact that these nerves innervate organs with different functions, or may reflect intrinsic rostro-caudal differences in the expression of VSR.

To determine whether there are rostro-caudal differences in the expression of VSR, we recorded from single fibers of the same functional type, muscle vasoconstrictor (MVC), at rostral and caudal levels along the body axis [11]. These recordings were performed simultaneously from either the hindlimb (fascicles split from the peroneal nerve) and the forelimb (radial nerve), or the hindlimb and face (facial nerve). Single MVC unit responses to unilateral electrical vestibular stimulation fell into two categories: those that responded predominantly with inhibition (Type 1; Fig. 4A) and those that contained an excitatory peak that preceded the inhibition (Type 2; Fig. 4A). Fibers of both types were always recorded in every animal, and were frequently present side-by-side at the same time in the same nerve fascicle. It was clear, therefore, that their divergent responses to vestibular stimulation could not be attributed to different positioning of the stimulating electrodes. The distribution of these two types of responses varied with respect to the rostro-caudal location of the efferent fiber. Accordingly, MVC efferents located in the hindlimb exhibited predominantly Type 1 (inhibitory) responses, while 60% of forelimb units and over 80% of units in the face exhibited Type 2 responses. These findings suggest that the vestibular system has the potential to differentially influence the excitability of vasoconstrictor efferents located at different rostro-caudal levels.

However, although these findings predict that vestibular stimulation would elicit regionally specific alterations in local blood flow and vascular resistance, experimental verification is required to prove this assumption. For this purpose, we simultaneously recorded mean blood pressure and blood flow to the forelimb and hindlimb in a group of paralyzed animals [8]. Results from one of these animals are illustrated in Fig. 5. This figure shows that 30 s of electrical stimulation of vestibular afferents leads to relatively small (<10 mmHg) decreases in blood pressure, which are accompanied by increases in femoral (hindlimb) arterial blood flow and decreases in brachial (forelimb) arterial flow. Presumably, blood pressure changes during vestibular stimulation were small in magnitude because of these

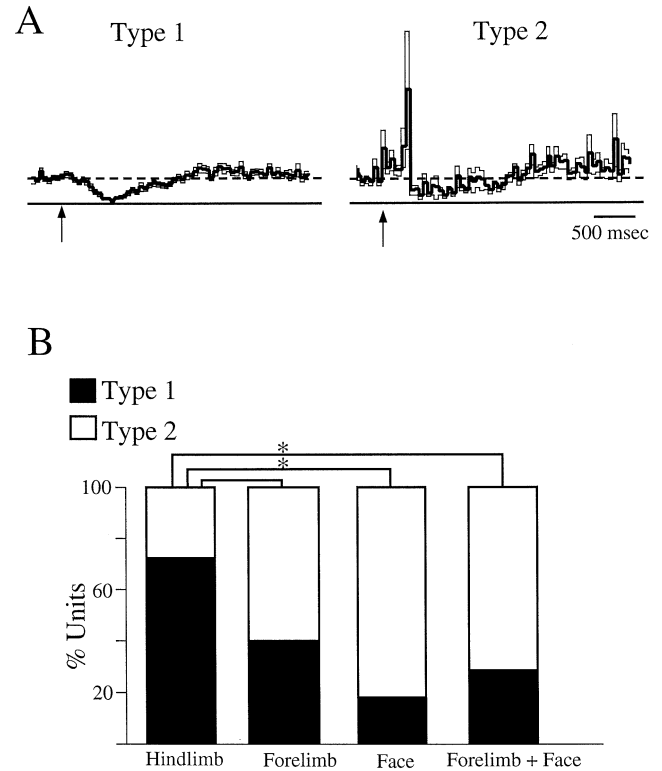


FIG. 4. Single vasoconstrictor efferent responses to vestibular stimulation were classified as Type 1 (inhibitory) or Type 2 (early excitation followed by inhibition) based on their shape. Responses were pooled by averaging individual post-stimulus time histograms (50 ms bin width) (panel A); prior to averaging, counts within each bin were normalized with respect to the mean activity level of the unit during the pre-stimulus period (stimulus onset is shown by arrows at the bottom of each graph). The mean response is indicated by thick lines, and thinner lines indicate SEM. Horizontal dashed lines indicate baseline activity levels, while solid horizontal lines correspond to zero activity levels. Distribution of neurons exhibiting Type 1 and Type 2 responses differed depending on their rostro-caudal location. Accordingly, neurons with Type 1 responses made up over 70% of units in the hindlimb population, while their proportion was 40% in the forelimb and less than 20% in the face. When neurons located at rostral levels (in the face and the forelimb) were pooled together, the prevalence of those with Type 1 responses was less than 30%. Differences between the hindlimb and the face, as well as between the caudal (hindlimb) and the rostral (forelimb and face) locations reached statistical significance (chi-square, $p < 0.05$) and are indicated with asterisks. Data from [11].

reciprocal alterations in blood flow to different body regions. No change in heart rate accompanied these cardiovascular responses. To determine whether the vestibularly elicited changes in blood flow were passively mediated or were due to active vasoconstriction or vasodilation, vascular resistance was calculated from changes in blood pressure and flow [8]. As illustrated in Fig. 5, femoral vascular resistance decreased and brachial resistance increased during vestibular stimulation. It is noteworthy that these vascular resistance changes elicited by vestibular stimulation parallel the shortest-latency vestibularly evoked responses of muscle vasoconstrictor fibers supplying each limb [11].

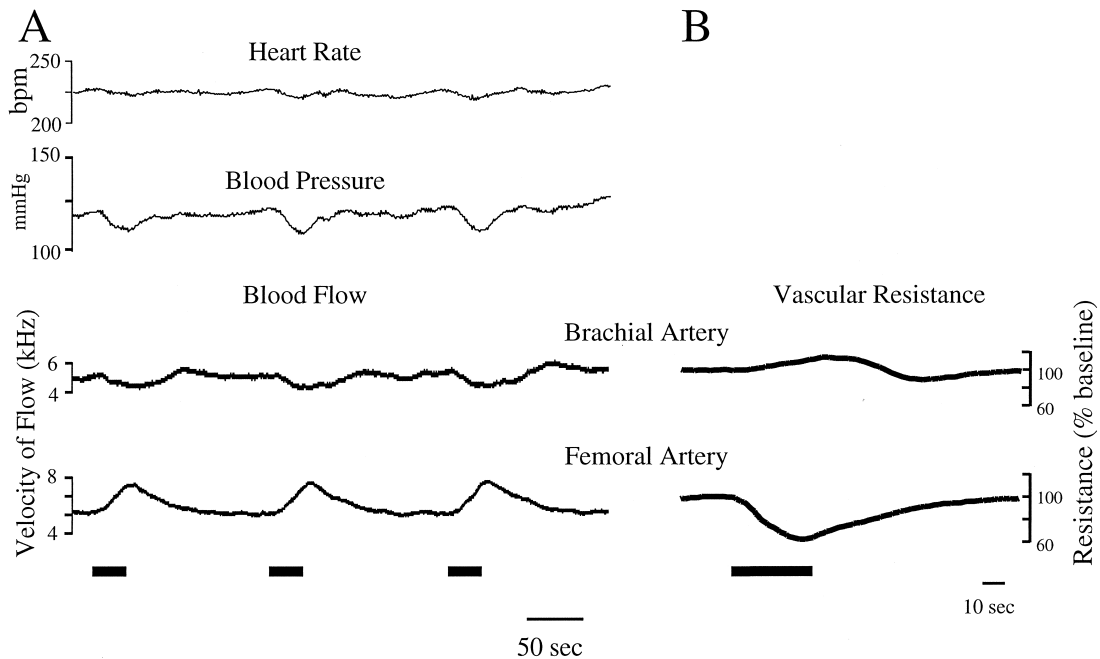


FIG. 5. Regional blood flow alterations in response to electrical vestibular stimulation. Ipsilateral vestibular stimulation (30-s continuous train, 0.2-ms pulse width, 333 Hz, 1.7 times vestibulo-ocular reflex threshold) was delivered during times indicated by thick bars at the bottom (A). This stimulus produced depressor responses that were accompanied by small heart rate changes, increases in blood flow to the hindlimb and decreases in flow to the forelimb. In (B), resistance was calculated as blood pressure divided by the blood flow signal, and was averaged over 10 stimulus trials. Vestibular stimulation produced a decrease in femoral artery vascular resistance and an increase in brachial resistance. Data from [8].

CONCLUSIONS

The work reviewed in this paper has demonstrated that activation of vestibular afferents results in very precise influences on sympathetic function. Results of experiments utilizing recordings from whole nerves and single sympathetic efferents have suggested that VSR are patterned according to a nerve's target organ, as well as its rostro-caudal location. These differences in vestibularly elicited nerve activity have a functional role since vestibular stimulation also produces regional hemodynamic changes, which parallel the changes in vasoconstrictor efferent activity. Electrical activation of vestibular afferents leads to withdrawal of sympathetic vasoconstrictor tone in the hindlimb and subsequent increase in femoral blood flow, while the opposite changes take place in the forelimb.

However, because of use of electrical vestibular stimuli in these experiments, particularly since these stimuli were unilateral, it is difficult to determine the functional implication of our findings. For example, nose-up natural vestibular stimulation has been reported to elicit pressor responses [21], as opposed to depressor responses evoked by electrical stimulation. Therefore, future studies should employ natural vestibular stimuli to determine whether a reciprocal activation of forelimb and hindlimb vasoconstrictor efferents is produced during movement, and to establish the patterns of changes in regional vascular resistance evoked by postural alterations in different directions. Nonetheless, it seems likely that VSR serve a preparatory role to ensure adequate blood supply to muscles involved in righting reflexes, while also maintaining adequate perfusion of the brain.

ACKNOWLEDGEMENTS

The authors' research is supported by the National Institutes of Health of the United States (grants R01 DC00693, R01 DC03732, and P01 DC03417 to B.J. Yates) and by the National Health and Medical Research Council of Australia (block grant 983001 to the Howard Florey Institute). During the course of this research, I.A. Kerman was supported by NASA's Graduate Student Researcher Program, fellowship GSRP 97-125.

REFERENCES

1. Bahr, R.; Bartel, B.; Blumberg, H.; Janig, W. Functional characterization of preganglionic neurons projecting in the lumbar splanchnic nerves: Vasoconstrictor neurons. *J. Auton. Nerv. Syst.* 15:131-140; 1986.
2. Cobbold, A. F.; Megirian, D.; Sherrey, J. H. Vestibular evoked activity in autonomic motor outflows. *Arch. Ital. Biol.* 106:113-123; 1968.
3. Dorward, P. K.; Burke, S. L.; Janig, W.; Cassell, J. Reflex responses to baroreceptor, chemoreceptor and nociceptor inputs in single renal sympathetic neurones in the rabbit and the effects of anaesthesia on them. *J. Auton. Nerv. Syst.* 18:39-54; 1987.
4. Ishikawa, T.; Miyazawa, T. Sympathetic responses evoked by vestibular stimulation and their interactions with somato-sympathetic reflexes. *J. Auton. Nerv. Syst.* 1:243-254; 1980.
5. Janig, W. Pre- and postganglionic vasoconstrictor neurons: Differentiation, types, and discharge properties. *Annu. Rev. Physiol.* 50:525-539; 1988.
6. Janig, W.; Schmidt, M.; Schnitzler, A.; Wesselmann, U. Differentiation of sympathetic neurones projecting in the hypogastric nerves in terms of their discharge patterns in cats. *J. Physiol.* 437:157-179; 1991.
7. Kaufman, M. P.; Forster, H. V. Reflexes controlling circulatory, ventilatory, and airway responses to exercise. In: Rowell, L. B.; Shepherd, J. T., eds. *Handbook of physiology. Section 12: Exercise: Regulation and integration of multiple systems.* New York: Oxford University Press; 1996:381-447.

8. Kerman, I. A.; Emanuel, B. A.; Yates, B. J. Vestibular stimulation leads to distinct hemodynamic patterning. *Am. J. Physiol.* 279:R118–R125; 2000.
9. Kerman, I. A.; Yates, B. J. Patterning of somatosympathetic reflexes. *Am. J. Physiol.* 277:R716–R724; 1999.
10. Kerman, I. A.; Yates, B. J. Regional and functional differences in the distribution of vestibulosympathetic reflexes. *Am. J. Physiol.* 265:R824–R835; 1998.
11. Kerman, I. A.; Yates, B. J.; McAllen, R. M. Anatomical patterning in the expression of vestibulosympathetic reflexes. *Am. J. Physiol.* 279:R109–R117; 2000.
12. Megirian, D.; Manning, J. W. Input-output relations in the vestibular system. *Arch. Ital. Biol.* 105:15–30; 1967.
13. Miyazawa, T.; Ishikawa, T. Separation of the medullo-spinal descending pathway for somatic and autonomic outflow in the cat. *Brain Res.* 334:297–302; 1985.
14. Sato, A.; Schmidt, R. F. Somatosympathetic reflexes: Afferent fibers, central pathways, discharge characteristics. *Physiol. Rev.* 53:916–947; 1973.
15. Spiegel, E. A. Effect of labyrinthine reflexes on the vegetative nervous system. *Arch. Otolaryngol.* 44:61–72; 1946.
16. Tang, P. C.; Gernandt, B. E. Autonomic responses to vestibular stimulation. *Exp. Neurol.* 24:558–578; 1969.
17. Uchino, Y.; Kudo, N.; Tsuda, K.; Iwamura, Y. Vestibular inhibition of sympathetic nerve activities. *Brain Res.* 22:195–206; 1970.
18. Waldrop, T. G.; Eldridge, F. L.; Iwamoto, G. A.; Mitchell, J. H. Central neural control of respiration and circulation during exercise. In: Rowell, L. B.; Shepherd, J. T., eds. *Handbook of physiology. Section 12: Exercise: Regulation and integration of multiple systems.* New York: Oxford University Press; 1996:333–380.
19. Weaver, L. C. Organization of sympathetic responses to distension of urinary bladder. *Am. J. Physiol.* 248:R236–240; 1985.
20. Wilson, V. J.; Melvill Jones, G. *Mammalian vestibular physiology.* New York: Plenum Press; 1979.
21. Woodring, S. F.; Rossiter, C. D.; Yates, B. J. Pressor response elicited by nose-up vestibular stimulation in cats. *Exp. Brain Res.* 113:165–168; 1997.
22. Yates, B. Vestibular influences on the autonomic nervous system. *Ann. N.Y. Acad. Sci.* 781:458–473; 1996.
23. Yates, B. J.; Kerman, I. A. Post-spaceflight orthostatic intolerance, possible relationship to microgravity-induced plasticity in the vestibular system. *Brain Res. Rev.* 28:73–82; 1998.