Research Paper

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Effect of neurovestibular stimulation on autonomic regulation

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Conditions associated with nausea and vomiting, such as motion sickness or side effects of medications, are commonly associated with a clinical picture consistent with parasympathetic activation and sympathetic withdrawal. It can be postulated, therefore, that vestibular stimulation contributes to sympathetic withdrawal. To test this hypothesis five normal volunteers, 24–33 years old, were studied during caloric vestibular stimulation while monitoring muscle sympathetic nerve activity directly through a needle electrode placed in a peroneal nerve. The ear was irrigated with water at a flow rate of 450 ml/min and 37°C. The water temperature was sequentially lowered by 7°C intervals until intolerable side effects developed or a temperature of 16°C was reached. Nystagmus was induced in all subjects, but heart rate, blood pressure, muscle sympathetic nerve activity and plasma norepinephrine levels did not change significantly during or after caloric stimulation, even when the subjects felt dizzy and nauseated. No evidence of sympathetic withdrawal was observed in any subject either by muscle sympathetic nerve activity or plasma norepinephrine measurements. In conclusion, we have found that selective vestibular stimulation is not accompanied by significant changes in the sympathetic nervous system function. In particular, no sympathetic withdrawal was observed. It could be argued that lack of sympathetic stimulation is an inadequate response to the symptoms associated with caloric stimulation.

Keywords: neurovestibular stimulation; caloric tests; muscle sympathetic nerve activity; autonomic nervous system

Introduction

Vestibular stimulation, such as induced by motion sickness or vestibular dysfunction, is accompanied by nausea, sometimes advancing to vomiting. In most species studied, the phenomenon of vomiting depends critically on input to or direct pharmacological stimulation in the vicinity of the nucleus of the solitary tract (NTS).[1] Significantly, the NTS receives third-order afferent inputs from the vestibular system[1] and the fastigial nucleus, and these afferent neurons also impinge on the nucleus ambiguous and the dorsal motor nucleus of the vagus.[2] There is also a close reciprocal axonal connectivity between the NTS and the area postrema, another important chemoreceptor trigger zone for emesis.[3] The NTS is also important in cardiovascular regulation. It is in these nuclei where the first synapse of the carotid sinus baroreflex is located,[4] and the NTS provides an important inhibitory influence on the rostral ventrolateral medulla, such that stimulation of this nucleus results in sympathetic inhibition.[5] The NTS, therefore, may provide a link between neurovestibular input and sympathetic regulation.

There is significant evidence of an interaction between vestibular and sympathetic pathways.[6] The nature of this interaction, however, is not completely defined. Earlier studies showed that caloric stimulation of the labyrinth in rabbits elicited a decrease in blood pressure.[7] However, electrical stimulation of the vestibular nerve induces either an increase in splanchnic sympathetic nerve activity or a decrease in renal sympathetic nerve activity.[6]

There is indirect evidence that such a link may also exist in humans. In a variety of clinical circumstances, for example, nausea and vomiting are closely linked to parasympathetic activation and concomitant sympathetic withdrawal. Furthermore, many drugs that can cause nausea and vomiting (e.g. cryptenamine, digitalis) also elicit this pattern of autonomic disturbance. Finally, the pharmacological management of nausea and vomiting frequently employs agents that attenuate parasympathetic tone (scopolamine, promethazine, prochlorperazine, etc.) or enhance sympathetic activation (ephedrine, methylphenidate, amphetamine).

An interaction between neurovestibular and autonomic pathways may be of importance not only in the clinical situations described above, but may also be of relevance in space flight. The neurovestibular system is especially challenged by the environment of weightlessness.[5] It undergoes a complex adaptive process as astronauts reach microgravity, which is probably pivotal in the development of the space motion sickness syndrome. Space motion sickness occurs in two-thirds of astronauts, reducing their work efficiency, interfering with their nutrition and contributing to their sense of disorientation. Of interest, there is evidence that sympathetic activity is decreased in space. Plasma norepinephrine levels, measured in a limited number of astronauts, are low during the first day of space

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flight, when space motion sickness is most prominent.[8] Taken together, these observations suggest that neurovestibular disturbance and its attendant effects could contribute to the impaired sympathetic activity observed in space.

Even though an association between vestibular stimulation and reduced sympathetic activity seems likely, to our knowledge this hypothesis has not been tested. Therefore, the purpose of the present study was to determine the effect of vestibular stimulation on sympathetic nerve activity. Vestibular stimulation was produced by exposing the tympanic membrane to cold water (caloric stimulation). Sympathetic activity was monitored by direct recording of sympathetic nerve traffic (microneurography) and concomitant measurements of plasma norepinephrine.

Methods

Five healthy volunteers of both genders were studied. They were 24–33 years old (mean 29 ± 2). Subjects were not taking any medications and had no history or evidence of ear disorders or vestibular problems. The protocol was approved by the Vanderbilt University Institutional Review Board. Volunteers were informed of the characteristics of the study and gave written consent.

Instrumentation

Subjects were studied fasted and in the supine position. Heart rate was monitored by surface electrocardiography coupled to a rate computer. Blood pressure was measured continuously with an automated device (Finapres 2300; Ohmeda, Englewood, CO, USA). Signals were displayed on a TA-2000 thermal array recorder (Gould Inc., Cleveland, OH, USA).

Nystagmus was monitored by electro-oculography (electronystagmography) with electrodes placed in both temporal areas and connected through an isolated preamplifier to a universal signal conditioner (Gould Inc.). A reference electrode was taped to the skin of the glabella. Ear irrigation was performed with a Varistaltic peristaltic pump (Manostat, New York, NY, USA) set at 0.4 mA to obtain a 450 ml/min water infusion rate. Water temperature was maintained constant during each irrigation with a Isotemp immersion circulator (model 730; Fisher Scientific, Pittsburgh, PA, USA).

Measurement of muscle sympathetic nerve activity

Sympathetic nerve activity was measured as previously described.[9] The approximate location of the right peroneal nerve at the level of the fibular head was determined by transdermal electrical stimulation (10–60 V, 0.01 ms), which produced painless muscle contraction of the foot. Electrical stimulation was done with a stimulator connected to an isolation unit (S88 and SIUTB; Grass Instruments, Quincy, MA, USA). A tungsten needle electrode, with a shaft diameter of 200 μm and an uninsulated tip diameter of 1–5 μm, was inserted into the nerve. A similar electrode with a larger uninsulated tip was inserted subcutaneously near the recording electrode to serve as a reference electrode. The recording electrode was positioned within the nerve to obtain multiunit recordings of sympathetic efferent activity. Placement of the electrode was guided by electrical stimulation (1–4 V, 0.01 ms), which produced muscle twitches of the foot but not paresthesia. The electrode was then switched to a recording mode and fine adjustments of its position were made to obtain a satisfactory recording site as described below. Recorded signals were fed to a preamplifier (amplification 1000) and were filtered using a band width between 700 and 2000 Hz. The filtered signal was rectified, amplified (amplification 100) and integrated in a resistance-capacitance network using a time constant of 0.1 s (Nerve Traffic Analysis System 662C-3; University of Iowa Bioengineering, Iowa City, IA, USA). The final signal was monitored using a storage oscilloscope (S111A; Tektronics, Beaverton, OR, USA) and recorded after fourfold amplification (TA-2000 recorder; Gould Inc.).

Criteria for an adequate muscle sympathetic nerve activity recording were as follows: (a) electrical stimulation produced muscle twitches but no paresthesia; (b) stretch of the tendons in the foot evoked proprioceptive afferent signals, whereas cutaneous stimulation by slight stroking of the skin did not; (c) held expiration increased neural activity at a site where arousal stimuli did not; and (d) nerve activity increased during hypotensive phase of the Valsalva maneuver and was suppressed after the release of Valsalva during blood pressure overshoot. Muscle sympathetic nerve activity was also monitored throughout the study using a loudspeaker. This helped in the identification of potential artefacts, such as electrostatic discharges, which were also identified in the integrated neurogram by their rapid onset and shorter duration.

Data analysis

Plasma catecholamine levels were measured by high-pressure liquid chromatography and electrochemical detection, as described previously.[10] Measurements of muscle sympathetic nerve activity were made from the original tracings of the integrated voltage neurograms by using a digitizer tablet coupled to Sigma Scan software (Jandel Scientific, Corte Madera, CA, USA) in a microcomputer. The amplitude of each 'burst' was measured in millimeters. Total activity was defined as the sum of 'burst' amplitude over a 30-s period and expressed in arbitrary units. Statistical analysis was done using the Number Cruncher Statistical Software (NCSS, Kaysville, UT, USA). Analysis of variance with repetitive measures was used for multiple comparisons. Criterion of significance was $p < 0.05$. Results are expressed as mean ± SEM.

Results

Subjects were allowed to rest in a quiet room for 30 min after instrumentation so that all cardiovascular and microneurographic parameters had returned to resting values. Baseline measurements were recorded (heart rate, blood pressure and muscle sympathetic nerve activity) and venous blood samples were drawn for plasma catecholamine determinations. Water was then instilled in the left ear at a temperature of 37°C for 5 min. The temperature was sequentially lowered by 7°C each time until intolerable side effects developed as defined by the volunteer or until a temperature of 16°C was reached. We waited 5 min between irrigations or until symptoms ceased. The subjects were informed ahead of time of all procedures that were to be performed, and that they might produce discomfort, in order to avoid anticipatory reactions. Subjects were asked to keep their eyes closed during caloric stimulation to avoid eye fixation. Nystagmus was elicited in all cases. The slow phase movements of the nystagmus were always directed toward the stimulated ear. Subjects were asked to score the discomfort felt during the ear irrigation performed with the coldest water used (during caloric nystagmus) on a scale from 0 (no dizziness or nausea) to 10 (intolerable dizziness or nausea). Volunteers were not asked to discriminate between dizziness and nausea. Baseline heart rate, blood pressure and muscle sympathetic nerve activity did not change significantly during or after caloric stimulation in any subject, even in those who felt dizzy and nauseated. Only one out of five subjects did not develop symptoms (Table 1).

Electronystagmography showed significant activity during caloric stimulation in every subject. On the other hand, neither muscle sympathetic nerve activity nor hemodynamic parameters changed significantly during caloric stimulation compared to baseline or recovery recordings. The average time-course of the sympathetic and hemodynamic parameters recorded during the coldest water irrigation are shown in Figure 1. A representative tracing (subject 5) of these parameters is shown in Figure 2. The temperature at which nystagmus was first elicited was not related to the reported severity of symptoms and is represented in Table 1 for each subject. Likewise, no correlation was observed between the severity of symptoms and the observed changes in heart rate, blood pressure and muscle sympathetic nerve activity. Blood samples were collected 3 min after the end of each caloric stimulation or development of symptoms to measure plasma catecholamine levels. Baseline norepinephrine and epinephrine levels were 203 ± 38 and 15 ±7 pg/ml, respectively. Three minutes after a 5 min instillation of water at 37°C, plasma norepinephrine and epinephrine levels were 195 ± 43 and 26 ± 15 pg/ml, respectively. Three minutes after maximal caloric stimulation plasma norepinephrine and epinephrine levels were 225 ± 64 and 20 ± 10 pg/ml, respectively, and were not significantly different from baseline or after instillation of water at 37°C.

Table 1. Effect of caloric stimulation on vestibular symptoms

Subject	Irrigation temperature (°C)	Caloric nystagmus	Vestibular symptoms* (0–10 scale)
1	30	+	8
2	23	+	3
3	30	+	8
4	16	+	0
5	23	+	7

* Vestibular symptoms include dizziness and nausea.

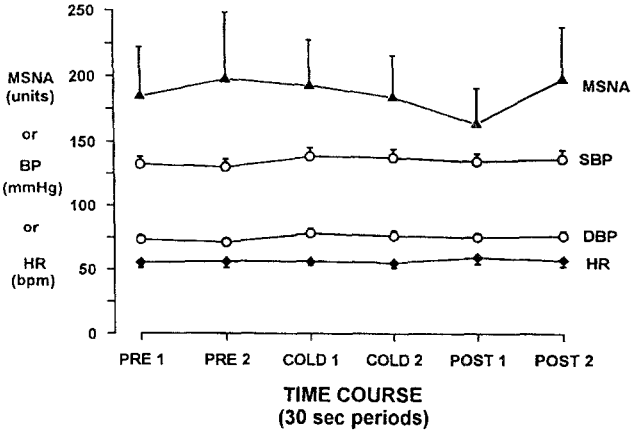

Figure 1. Cardiovascular and sympathetic parameters during maximal caloric stimulation in five normal volunteers. Line graphs show measurements taken during two 30 s periods before stimulation (PRE1 and PRE2), during the last minute of caloric stimulation (COLD1 and COLD2) and the first minute after stimulation was stopped (POST1 and POST2). Nystagmus was evoked in all cases. No significant differences were found in any of these parameters. Results are expressed as mean ± SEM. MSNA, muscle sympathetic nerve activity; BP, blood pressure; HR, heart rate; DBP, diastolic BP; SBP, systolic BP

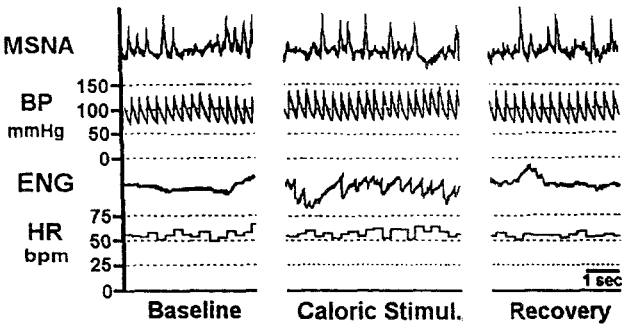

Figure 2. Representative tracing obtained in subject 5 showing measurements of muscle sympathetic nerve activity (MSNA), blood pressure (BP), electronystagmography (ENG) and heart rate (HR) obtained during resting conditions (baseline), caloric stimulation and after recovery

Discussion

Conditions associated with nausea are commonly accompanied by clinical signs suggestive of parasympathetic activation and sympathetic withdrawal, leading in some cases to neurogenic (vasovagal) reactions.

The space motion sickness observed during adaptation to the environment of microgravity is also temporarily associated with a decrease in plasma norepinephrine levels reflecting a decrease in sympathetic activity. This is an unexpected finding inasmuch as it could be predicted that the stress and activities associated with space flight would produce sympathetic activation rather than withdrawal. It could be hypothesized, therefore, that motion sickness can induce or contribute to sympathetic withdrawal.

On the other hand, studies on motion sickness have failed to reveal evidence of significant changes in cardiovascular autonomic function. Motion sickness induced by optokinetic stimulation, for example, produced either no consistent changes in heart rate and blood pressure[11] or small increments in heart rate.[12,13] Furthermore, Hu *et al.* found a decrease in sinus arrhythmia during optokinetic stimulation, suggesting a decrease, rather than the expected increase in parasympathetic activity.[13] Other studies have shown an increase in heart rate and plasma catecholamine levels (epinephrine increasing more than norepinephrine) during motion sickness induced in a rotating chair. Under these conditions, however, it is difficult to dissociate the effects produced by body movement to those produced solely by vestibular stimulation.

The purpose of this study was to determine the effects of selective vestibular stimulation on sympathetic nerve activity. Two features of this study make it particularly different from previous human investigations. First, we focused on the effects of selective vestibular stimulation in the absence of visual inputs or physical rotational movement. To our knowledge, the effect of selective vestibular stimulation on the autonomic nervous system has not been determined previously. Second, we directly monitored muscle sympathetic nerve activity using microneurographic techniques, a methodology not previously used in the study of motion sickness. This method is particularly sensitive when trying to monitor sympathetic withdrawal, which causes an abrupt reduction or even complete disappearance of the integrated sympathetic neurogram.[14] By comparison, plasma norepinephrine levels are not as sensitive an indicator of sympathetic withdrawal.[15] For example, phenylephrine increases blood pressure and induces a compensatory baroreflex-mediated sympathoinhibition. This is associated with a 67% reduction in muscle sympathetic nerve activity but only a 26% reduction in plasma norepinephrine levels.[16] Furthermore, changes in plasma norepinephrine are delayed in relation to changes in sympathetic nerve traffic. Nonetheless, a decrease in plasma norepinephrine can be detected after 3 min of phenylephrine infusion[16] and, therefore, should be evident in our study if sympathoinhibition had occurred.

Our results indicate that vestibular stimulation, severe enough to produce nystagmus, dizziness and nausea, had no effect on heart rate, blood pressure, muscle sympathetic nerve activity or plasma norepinephrine levels. In particular, no evidence of sympathetic withdrawal was evidenced in any subject. These findings argue against our initial hypothesis that an interplay exists between vestibular input and autonomic cardiovascular control. It must be noted that measurements of sympathetic activity are restricted to the peroneal nerve innervating calf muscles. Sympathetic withdrawal may still have occurred in other vascular beds but the lack of changes in heart rate and blood pressure do not fit with a significant alteration in autonomic cardiovascular function. Furthermore, the lack of changes in plasma norepinephrine levels do not fit with a significant decrease in overall sympathetic activity.

It could also be argued that the side effects evoked by caloric stimulation in our volunteers should produce sympathetic stimulation and that our failure to observe an increase in sympathetic activity is an abnormal response. It is possible, therefore, that vestibular stimulation indeed suppressed a compensatory activation of the sympathetic nervous system. Even considering these caveats we can conclude that vestibular stimulation of the semicircular canal afferents does not produce sympathetic withdrawal. Our results agree with previous observations made with optokinetic stimulation, where autonomic cardiovascular regulation is not significantly affected.[11] This conclusion does not necessarily apply to other forms of motion sickness. Because our stimulation was restricted to the vestibular system, it remains possible that other conditions that evoke nausea can be associated with sympathoinhibition.

In conclusion, selective vestibular stimulation, strong enough to produce nystagmus and evoke nausea, is not accompanied by significant changes in autonomic nervous system function, as determined by the lack of changes in heart rate, blood pressure, plasma norepinephrine levels and muscle sympathetic nerve activity.

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References

1. Yates BJ, Grelot L, Kerman IA, Balaban CD, Jakus J, Miller AD. Organization of vestibular inputs to nucleus tractus solitarius and adjacent structures in cat brain stem. *Am J Physiol* 1994; **267:** R974–R983.
2. Balaban CD, Beryozki G. Vestibular nucleus projections to nucleus tractus solitarius and the dorsal motor nucleus of the vagus nerve. *Exp Brain Res* 1994; **98:** 200–212.
3. Miller AD, Leslie RA. The Area Postrema and vomiting. *Frontiers Endocrinol* 1994; **15:** 301–320.

4. Spyer KM. Neural organization and control of the baroreceptor reflex. *Rev Physiol Biochem Pharmacol* 1981; **88:** 24–124.
5. Homick JL, Vanderploeg JM. The neurovestibular system. 1989; 154–166.
6. Yates BJ. Vestibular influences on the sympathetic nervous system. *Brain Res Rev* 1992; **17:** 51–59.
7. Spiegel EA. Effect of labyrinthine reflexes on the vegetative nervous system. *Arch Otolaryngol* 1946; **44:** 31–72.
8. Leach CS, Alfrey C, Suki WN, Leonard JI, Rambaut PC. Fluid-electrolyte regulation during space flight. 1992; 3.3.3-1—3.3.3-16.
9. Costa F, Biaggioni I. Role of adenosine in the sympathetic activation produced by isometric exercise in humans. *J Clin Invest* 1994; **93:** 1654–1660.
10. Goldstein DS, Polinsky RJ, Garty M *et al.* Patterns of plasma levels of catechols in idiopathic orthostatic hypotension. *Ann Neurol* 1989; **26:** 558–563.
11. Johnson WH, Sunahara FA, Landolt JP. Motion sickness, vascular changes accompanying pseudo-Coriolis-induced nausea. *Aviat Space Environ Med* 1993; **64:** 367–370.
12. Uijtdehaage SHJ, Stern RM, Kock KL. Effects of scopolamine on autonomic profiles underlying motion sickness susceptibility. *Aviat Space Environ Med* 1993; **64:** 1–8.
13. Hu S, Grant WF, Stern RF, Koch KL. Motion sickness severity and physiological correlates during repeated exposures to a rotating optokinetic drum. *Aviat Space Environ Med* 1991; **62:** 308–314.
14. Costa F, Biaggioni I. Microneurographic evidence of sudden sympathetic withdrawal in carotid sinus syncope, and treatment with ergotamine. *Chest* 1994;**106:**617–620.
15. Onrot J, Wiley RG, Fogo A, Biaggioni I, Robertson D, Hollister AS: Neck tumor with syncope due to paroxysmal sympathetic withdrawal. *J Neurol Neurosurg Psychiat* 1987; **50:** 1063–1066.
16. Eckberg DL, Rea RF, Andersson OK *et al.* Baroreflex modulation of sympathetic activity and sympathetic neurotransmitters in humans. *Acta Physiol Scand* 1988; **133:** 211–231.