Responses of sympathetic outflow to skin during caloric stimulation in humans

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Cui, Jian, Satoshi Iwase, Tadaaki Mano, and Hiroki Kitazawa. Responses of sympathetic outflow to skin during caloric stimulation in humans. Am. J. Physiol. 276 (Regulatory Integrative Comp. Physiol. 45): R738–R744, 1999.—We previously showed that caloric vestibular stimulation elicits increases in sympathetic outflow to muscle (MSNA) in humans. The present study was conducted to determine the effect of this stimulation on sympathetic outflow to skin (SSNA). The SSNA in the tibial and peroneal nerves and nystagmus was recorded in nine subjects when the external meatus was irrigated with 50 ml of cold (10°C) or warm (44°C) water. After nystagmus, the SSNA in tibial and peroneal nerves decreased to 50 ± 4% (with baseline value set as 100%) and 61 ± 4%, respectively. The degree of SSNA suppression in both nerves was proportional to the maximum slow-phase velocity of nystagmus. After nystagmus, the SSNA increased to 166 ± 7 and 168 ± 6%, respectively, and the degree of motion sickness symptoms was correlated with this SSNA increase. These results suggest that the SSNA response differs from the MSNA response during caloric vestibular stimulation and that the SSNA response elicited in the initial period of caloric vestibular stimulation is different from that observed during the period of motion sickness symptoms.

The sympathetic nervous system; skin sympathetic nerve activity; vestibulovestibular reflex; caloric test; microneurography

The vestibular system is known to influence the sympathetic nervous system and circulatory functions (24, 27). Studies of this influence have focused on the vestibulovestibular reflex and its role in correcting disturbances in homeostasis that occur after postural changes (6, 27, 30). In animal experiments, the neurons in the nucleus of the solitary tract (NTS) and rostral ventrolateral medulla (RVLM) (28–31) and the neurons in the parabrachial nucleus (1) have been demonstrated to be involved in the vestibulautonomic reflex. Although animal studies have also demonstrated increases or decreases in sympathetic outflow to renal, splanchnic, and cardiac vessels during stimulation of the vestibular system (15, 27), only a few studies have examined the sympathetic response to vestibular stimulation in humans (4, 19–21, 23). The skin sympathetic nerve activity (SSNA), which mediates cutaneous circulation and sweating (2, 3, 9), was recently reported to show no significant change during natural stimulations of either otoliths with head-down neck flexion or horizontal semicircular canals with yaw head rotation in humans (20, 21). In previous studies (5, 13), we observed that the sympathetic outflow to muscle (MSNA) from the tibial nerve in humans was enhanced after caloric vestibular stimulation; the effect of such stimulation on the sympathetic outflow to the skin has not yet been clarified.

It is well established that vestibular inputs are involved in producing motion sickness symptoms (27). Facial pallor and cold sweating are characteristic symptoms of motion sickness (7, 12, 14, 16). The patterns of skin blood flow responses in the forehead and in the finger during vestibular irritation were reported to be different before and after observab.

Methods

Subjects. Four male and five female healthy volunteers (age 29 ± 2 yr, height 163 ± 2 cm, weight 58 ± 4 kg) participated in the present study. Written informed consent was obtained from each subject. The study was approved by the Human Research Committee, Research Institute of Environmental Medicine, Nagoya University.

Experimental design. All experiments were performed with the subjects in the supine position in a sound- and light-proof room. The ambient temperature was set at 25°C. After a 10-min rest, two stimulations were administered: 1) vestibular stimulation produced by exposing the tympanic membrane to cold (50 ml, 10°C) (5, 13) or warm (50 ml, 44°C) (18) water for 1 min through an injection syringe, and 2) control stimulation produced by irrigating cold (50 ml, 10°C) or warm (50 ml, 44°C) water only on the auricle via an injection syringe for 1 min, with the inner part of the external meatus plugged with cotton. Because the SSNA is very sensitive to...

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R738 0363-6119/99 $5.00 Copyright © 1999 the American Physiological Society
mental or somatosensory (sound, touch, light, or electrical) stimulation (2, 3, 9–11, 17), these stimulations would cause nonspecific responses of SSNA in the present study. To differentiate these nonspecific responses, we chose auricular irrigation as a control stimulation. Other than the vestibular stimulation, the auricular irrigation could be expected to cause the local thermal, touch, mental stress, and other stimuli as those in the external meatus irrigation. We also suspected that cold and warm water irrigations might be helpful to differentiate the influence of local thermal stimulation if the results would differ between the two conditions as in our previous study (5).

The operator entered the sound- and light-proof room for preparation just 30 s before the irrigation. After the irrigation, the operator left the room immediately and the variables were recorded for 4 min. In the next 30-s period, the operator asked the subject about subjective symptoms such as rotation sensation and nausea, and the objective symptoms (e.g., sweating and facial pallor) were observed. The subject was then allowed to rest for 2 min 30 s before the next irrigation. The irrigation side was alternated, and the external meatus and auricular irrigations were conducted in a random order. The number of irrigations depended on the subjective complaints and was limited to a maximum of eight times for external meatus irrigation and four times for auricular irrigation.

Measurements. Multiunit recordings of postganglionic sympathetic nerve activity were obtained with two tungsten microelectrodes inserted selectively in skin fascicles of the tibial and peroneal nerves simultaneously using a microneurographic double-recording technique. The SSNA was identified using the criteria of previous studies (2, 10, 11). The main criteria for the identification of SSNA were 1) activity nonsynchronous with the heart beat and irregular burst activity with a duration of 300–500 ms, 2) the generation of reflex bursts, during mental or somatosensory (sound, pain, light, or electrical) stimuli, 3) elicited by a deep breath, and 4) followed by sweating or a reduction in skin blood flow. The neural signals were amplified (DAM-6A, World Precision Instruments, New Haven, CT), filtered (bandwidth of 500–5,000 Hz), rectified, and integrated in a resistance-capacitance network with a time constant of 0.1 s to obtain a mean voltage display of SSNA.

The region of skin innervated by the impaled nerve fascicle was determined by lightly stroking the skin to obtain a cutaneous mechanoreceptor discharge. The skin blood flow was measured with laser Doppler flowmeters (ALF21, Advance, Tokyo, J apan), with two probes attached to the skin of the sole and the dorsum pedis ipsilateral to the microneurographic recording (17). The ventilated capsule method (Kenz-Persprio, Suzuken, Nagoya, J apan) was used for the determination of the sweat expulsion. Two plastic capsules were fixed on the sole and the dorsum pedis ipsilateral to the microneurographic recording (17). Another capsule was fixed on the forehead to measure the facial sweating (7). The skin electrodermal activity was also used to detect the sweat formation in the sweat gland (11), which was recorded by a bioelectric amplifier (AB-621G, Nihon Kohden, Tokyo, J apan) with Ag-AgCl electrodes applied within the receptive skin area of the fascicle impaled by the microelectrode. The instantaneous heart rate was monitored by electrocardiography using a bioelectric amplifier (AB-621G, Nihon Kohden).

A horizontal electrooculogram was recorded using a direct current amplifier with electrodes placed on bilateral temporal areas and a reference electrode taped to the skin of the glabella (26). The electrooculogram signal was calibrated by asking the subject to look at a target at ±10° horizontally. All signals were recorded in a multichannel FM magnetic data recorder (KS-616U, Sony-Magnescope, Tokyo, J apan).

Data quantification and analysis. All data were digitized by offline processing and analyzed using Lab View software (National Instruments, Austin, TX). The starting point of the irrigation was defined as the 0-s point for each stimulation in all time parameters. The averages of SSNA, skin blood flow, and heart rate for the 1-min period between −100 s and −40 s before irrigation served as baseline values.

The total activity of SSNA was defined as the sum of the “burst area” of the full-wave rectified and integrated neurographic recording (25) over a 10-s period, which was calculated with a computer. The period chosen was based on the following two considerations. 1) The period should be long enough to eliminate the influence of the spontaneous rhythm in SSNA, and 2) the period should be short enough to characterize the dynamic responses of SSNA in the time course of vestibular stimulation. Because the longest rhythm in SSNA that has been reported to date is the respiration rhythm (period ~4 s) (2), the 10-s period was enough to eliminate the influence of the spontaneous rhythms in SSNA and to provide an accurate assessment of SSNA in the present study.

The final data of the total activity of SSNA are expressed in arbitrary units by setting the averaged baseline value as 100%. The latency and duration of SSNA enhancement or suppression were identified after the data of SSNA were interpolated in 1-s intervals by the cubic spline function (25). The latency and the duration of nystagmus were measured from the electrooculogram trace. The slow-phase velocity (SPV) of the nystagmus was calculated from the average slope of the electrooculogram trace in the slow-phase period over a 10-s period (26). The cross-correlation between the SPV of the nystagmus and SSNA was computed to clarify the time relationships among the nystagmus and SSNA responses (5). We chose to measure the average blood flow over a 10-s period as the percentage of the baseline to eliminate the interindividual and interindividual differentiations (12). The skin electrodermal activity was used to identify the burst of SSNA and was not analyzed quantitatively. The Graybiel motion sickness scores (8) were judged from the subjective complaints such as dizziness or nausea and from observed sweating and facial pallor during the study. In the case of modest symptoms, the score was mainly judged from the subjective complaints.

Values are expressed as means ± SE. We applied a one-way ANOVA to assess the changes of the parameters in irrigation, nystagmus, and after nystagmus. Paired Student's t-test was used for the evaluation of differences between the double recordings of the SSNA from tibial and peroneal nerves, and the unpaired t-test was used for the evaluation of differences between the different irrigations. P values <0.05 were regarded as significant.

RESULTS

Original recordings of an electrooculogram, skin electrodermal activity at the foot, sweating rate at the forehead, skin blood flow in the dorsum pedis and sole, and integrated SSNA in the peroneal and tibial nerves induced by the external meatus irrigation in a representative subject are shown in Fig. 1.

Nystagmus and motion sickness symptoms. Nystagmus was evoked after each of the external meatus irrigations with cold water (22 of 22 irrigations) and after most of the external meatus irrigations with warm water (18 of 23 irrigations). The data in the cases in which nystagmus was not evoked after the external
meatus irrigation were excluded from further analyses. The nystagmus began before the end of the irrigation (46 ± 3 s, n = 40) and lasted ~2 min (133 ± 8 s, n = 40).

One subject did not experience any symptom of motion sickness during exposure to seven separate external meatus irrigations (Graybiel score ≤ 1), and the other subjects experienced the symptoms after one or several external meatus irrigations. Once the symptoms occurred, they were evoked again in the next external meatus irrigation. No vomiting occurred during the present study.

No nystagmus and no motion sickness symptoms were evoked after the auricular irrigations with cold water (13 times) or warm water (14 times).

Time course of SSNA responses. The time course of the average responses of the total activity of SSNA is shown in Fig. 2. A triphasic response of SSNA was induced by the external meatus irrigations. There was a strong SSNA enhancement that began before the irrigation and ended during the irrigation (from −20 to +40 s), whereas a suppression of SSNA was observed during the nystagmus; the SSNA was then enhanced again with the weakening SPV of the nystagmus (Fig. 2; P < 0.05 vs. baseline, ANOVA). The time course of SSNA responses was similar in the tibial and peroneal nerves. For the total activity of SSNA in the individual irrigation, the maximum value in the irrigation, the minimum value during the period of nystagmus that was determined in the electrooculogram, and the maximum value of SSNA after nystagmus were searched. The averaged results are shown in Table 1. The results are slightly different from those shown in Fig. 2.
Table 1. Maximum total activity of SSNA around irrigation, minimum total activity of SSNA in suppression period, maximum total activity of SSNA after nystagmus, average SBF, and average instantaneous heart rate in 3 phases of SSNA response

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<td>Tibial SSNA, %</td>
<td>100</td>
<td>100</td>
<td>232 ± 14*</td>
<td>230 ± 14*</td>
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<td>50 ± 4*†‡</td>
<td>86 ± 3</td>
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<td>Peroneal SSNA, %</td>
<td>100</td>
<td>100</td>
<td>209 ± 9*</td>
<td>217 ± 11*</td>
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<td></td>
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<td>61 ± 4*†‡</td>
<td>87 ± 4</td>
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<td>SBF in sole, %</td>
<td>100</td>
<td>100</td>
<td>46.5 ± 2.9*</td>
<td>45.1 ± 4.6*</td>
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<td>210.2 ± 18.0*‡‡</td>
<td>127.6 ± 19.6</td>
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<tr>
<td>SBF in dorsum pedis, %</td>
<td>100</td>
<td>100</td>
<td>46.7 ± 5.6*</td>
<td>49.9 ± 5.6*</td>
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<td>Heart rate, beats/min</td>
<td>71.0 ± 0.8</td>
<td>71.5 ± 1.3</td>
<td>68.4 ± 0.7*</td>
<td>68.7 ± 1.1*</td>
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<td>69.9 ± 0.7</td>
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<td>71.6 ± 0.8</td>
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<td>n</td>
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Values are means ± SE of 9 subjects. Total activity of skin sympathetic nerve activity (SSNA) is shown in arbitrary units; average baseline value was set as 100%. Skin blood flow (SBF) is expressed as percentage of baseline. I, SSNA enhancement period around irrigation; II, SSNA suppression period; III, SSNA enhancement period after nystagmus. *P < 0.05 vs. baseline, †P < 0.05 vs. auricular irrigation, ‡P < 0.05 vs. peroneal SSNA or vs. SBF in dorsum pedis.

because the time courses were not exactly the same in the individual irrigation.

There was also a strong SSNA enhancement in the two nerves that began before the irrigation and ended after the auricular irrigation (from −20 to +80 s; Fig. 2; P < 0.05 vs. baseline, ANOVA). After the enhancement, the SSNA recovered to the baseline value, although a modest SSNA suppression was observed in some cases. Then, there was no obvious SSNA enhancement.

SSNA enhancement during irrigation. Regarding the SSNA enhancement during irrigation, there was no significant difference in the peak value of this enhancement between the external meatus and auricular irrigations (P > 0.74). There was also no clear difference in the latency of the enhancement between the two kinds of irrigation. However, the duration of the SSNA enhancement induced by auricular irrigation was longer than that induced by external meatus irrigation (Fig. 2). The averaged response peak of SSNA in the tibial nerve was significantly higher than that in the peroneal nerve (Table 1, P < 0.05).

SSNA suppression during nystagmus. After external meatus irrigation, a suppression of SSNA was observed during the nystagmus. Although a modest SSNA suppression was also observed after auricular irrigation in some cases, the SSNA suppression during nystagmus induced by external meatus irrigation exhibited a shorter latency and longer duration (Fig. 2). In addition, the minimum values of SSNA in the nystagmus after external meatus irrigation were significantly lower than those after auricular irrigation (Table 1, P < 0.05).

The cross-correlogram revealed that the SSNA response had a negative correlation with the SPV of nystagmus near 0 s (r = −0.71 ± 0.05 for tibial SSNA and r = −0.67 ± 0.05 for peroneal SSNA), which means that the time delay of SSNA suppression to nystagmus was <10 s. There were significant positive correlations between the duration of nystagmus and the duration of the SSNA suppression in the tibial nerve (r = 0.57, P < 0.05) and in the peroneal nerve (r = 0.66, P < 0.05). Significant negative correlations between the maximum SPV of nystagmus and the minimum values of SSNA in the tibial (r = 0.62, P < 0.05) and peroneal nerves (r = 0.64, P < 0.05) were revealed. There was no significant correlation between the Graybiel score and the minimum values of SSNA in the tibial (r = 0.22, P < 0.05) or peroneal nerves (r = 0.11, P < 0.05). The averaged minimum value of SSNA in the tibial nerve was significantly lower than that in the peroneal nerve after external meatus irrigation (Table 1, P < 0.05).

SSNA enhancement after nystagmus. The SSNA was enhanced again after nystagmus in some cases (23 of 40 cases), whereas it only recovered to the baseline in the other cases. In individual subjects, once this SSNA enhancement occurred, it occurred again after the subsequent external meatus irrigations. There were no significant correlations between the maximum SPV of the nystagmus and the maximum values of the SSNA in the tibial nerve (r = 0.01, P < 0.05) and peroneal nerve (r = 0.39, P < 0.05). Significant positive correlations were found between the Graybiel score and the maximum value of the SSNA in both the tibial (r = 0.54, P < 0.01) and peroneal nerves (r = 0.56, P < 0.01). There was no significant difference in the total activity of this SSNA enhancement between the tibial and peroneal nerves (P = 0.16).

Differences between effects of cold and warm irrigation. The maximum SPV of the nystagmus induced by cold irrigation was significantly higher than that induced by warm irrigation (40 ± 4 to 27 ± 3 degrees/s, P < 0.05). Although the SSNA response during nystagmus induced with cold irrigation was lower than that induced with warm irrigation, there was no significant difference in the SSNA responses during the irrigation, during nystagmus, or after the nystagmus between the cold and warm irrigations (P > 0.10).

Skin blood flow. The skin blood flow in the sole and the dorsum pedis showed changes opposite to those of the SSNA responses (Fig. 1). The average values of skin blood flow in the three phases of the SSNA response are shown in Table 1. During irrigation, the skin blood flow decreased significantly (P < 0.005) in the first SSNA enhancement period, and there was no significant difference in the average value of the skin blood flow between the external meatus and auricular irrigations (P > 0.10). During nystagmus, the skin blood flow was significantly increased compared with the baseline (P < 0.01) and the average skin blood flow value in the sole was significantly higher than that in the dorsum pedis. After nystagmus, the skin blood flow in the sole
was significantly decreased compared with the baseline, whereas the skin blood flow in the dorsum pedis only recovered to the baseline.

Sweating and skin electrodermal responses. No obvious sweating in the sole or dorsum pedis was detected by the ventilated capsule method in this experiment. The skin electrodermal activity at the foot showed some activity near the 0-s point in each irrigation. In the cases in which motion sickness symptoms occurred, the skin electrodermal activity showed stronger activity than in the cases with no motion sickness symptoms. Sweating at the forehead was recorded after nine irrigations in four subjects when motion sickness symptoms occurred (Fig. 1). The sweating at the forehead occurred after several stimulations, and, once initiated, it occurred again in the subsequent external meatus irrigations.

Heart rate. In the period of irrigation, the heart rate was decreased in some cases and increased in other cases. The average heart rate during irrigation was significantly decreased compared with the baseline in both the external meatus and auricular irrigations, and there was no significant difference in the average heart rate between the external meatus and auricular irrigations (Table 1, P > 0.10). The heart rate decrease was observed during both cold and warm water irrigations, and began after the start of the irrigation and ended with the end of the irrigation. The heart rate recovered to the baseline after irrigation.

DISCUSSION

We have confirmed that sympathetic outflow to the skin in humans is influenced by caloric vestibular stimulation. The external meatus irrigation induced a triphasic response of SSNA, i.e., enhancement, suppression, and enhancement. The SSNA changes in the tibial and peroneal nerves exhibited similar patterns. The SSNA response was evoked bilaterally, because it was similar regardless of the direction of the nystagmus. The cold and warm irrigations used in the present study caused a difference in stimulation strength; however, the patterns of SSNA response were similar after each type of irrigation, which differed from that of our previous study of MSNA (5).

Vestibular stimulation and nonspecific factors. In the present study, the stimulation of the vestibular system indicated by nystagmus was much later than the beginning of irrigation (averaged 46 s), and the strongest stimulation indicated by the maximum SPV of evoked nystagmus was after the irrigation. The SSNA enhancement around the irrigation should be considered a nonspecific response in the present study, because it occurred before the nystagmus. This was also indicated by the finding that a similar SSNA enhancement was produced by the auricular irrigation. This SSNA enhancement began after the entrance of the operator into the experiment room but before the irrigation. Therefore, the SSNA enhancement before irrigation might be due to mental stress. During the irrigation, mental stress, touch, and local thermal stimulation activated SSNA (2, 3, 9–11, 17). The heart rate decrease during the irrigation could also be considered a nonspecific response, because it occurred before the nystagmus and was also observed in auricular irrigation. The mechanism underlying this heart rate decrease during the water irrigation is still not clear and should be clarified by further studies.

SSNA inhibition by caloric vestibular stimulation. The SSNA suppression after the external meatus irrigation occurred only during the nystagmus. The SSNA suppression during nystagmus was not a simple rebound response of the first enhancement by the irrigation, because the SSNA suppression during nystagmus showed shorter latencies, longer durations, and much lower values than those after auricular irrigation.

Because the SPV of nystagmus indicates the degree of the imbalance of the activities between the two vestibular nuclei produced by caloric vestibular stimulation (18) and because the degree and the duration of the SSNA suppression were correlated with the degree and duration of the vestibular imbalance, respectively, this SSNA suppression during nystagmus can be considered an effect of vestibular stimulation. In addition, the cross-correlogram between the SPV of nystagmus and the SSNA showed that the SSNA had a negative correlation with the SPV of nystagmus near 0 s, which indicates that the vestibular stimulation is one of the determinant factors of the SSNA suppression. These results indicate that SSNA is suppressed during caloric vestibular stimulation, and the degree of the inhibition depends on the stimulation level of the vestibular nuclei. The increase of the skin blood flow also suggests that SSNA is suppressed during nystagmus.

Nonspecific factors such as mental stress can also be expected to be in effect during nystagmus. These factors would tend to increase SSNA simultaneously during caloric vestibular stimulation. The difference of SSNA responses between the auricular and external meatus irrigations indicates that the caloric vestibular stimulation induced quite a large response in SSNA.

Although SSNA was suppressed in both nerves during nystagmus, the tibial SSNA showed lower values than the peroneal SSNA. Previous studies showed that the SSNA in the tibial nerve that innervates the glabrous skin is more sensitive to arousal or mental stimuli and that the SSNA in the peroneal nerve that innervates hairy skin is more sensitive to the thermal environment (10, 11, 17). Thus the present results might hint that the neural pathway that has some influence on SSNA during caloric vestibular stimulation might be related to the pathway used in the response to mental stimuli. However, considering the conditions of the experiment and the nature of the technique, this difference in SSNA during nystagmus should be confirmed by further studies.

SSNA enhancement and motion sickness symptoms. The present results indicate that the SSNA enhancement after nystagmus is related to sympathetic activation due to motion sickness symptoms, because this enhancement was correlated to the Graybiel score of motion sickness symptoms. The sweating at the forehead after nystagmus was consistent with the observa-
tion in motion sickness syndrome (7). The reduction in plantar skin blood flow was also concordant with the observation of skin blood flow reduction in the fingertip during motion sickness symptoms (12). Our results may constitute direct evidence of the sympathetic activation in motion sickness symptoms. Because some subjective complaints were equivocal for the modest symptoms, it was difficult to judge the score of motion sickness symptoms accurately in these cases. The SSNA by microneurography may be useful as an objective parameter in the study of motion sickness.

SSNA in the peroneal nerve in humans has been reported to show no significant change during either head-down neck flexion or yaw head rotation, which would stimulate otoliths or bilateral horizontal semicircular canals, respectively (20, 21). It is possible that the nonphysiological stimulation of a unilateral semicircular canal with a caloric test in the present study produces a response different from those obtained by physiological vestibular stimulations. The caloric test mimics an acute peripheral vestibular imbalance. The unilateral stimulation causes a "sensory mismatch" in vestibular inputs from the two sides. During unilateral stimulation, the canal afferents from the two sides provide a contradictory indication that movement is occurring, while otoliths, vision, and proprioception signal that the head is stationary. Such a sensory conflict is well known as the basic condition for evoking motion sickness (22). The suppression of SSNA might be a response in the initial phases of motion sickness, because it is reported that with motion sickness onset there is a brief flushing of the face before the pallor in some subjects (16). Motion sickness symptoms were reported by most of the subjects (8 of 9) in the present study, whereas no motion sickness symptom was reported during the studies with natural vestibular stimulations (20, 21). This difference in motion sickness symptoms between the reported experiments (20, 21) and ours might indicate that both the suppression and enhancement of SSNA induced by caloric vestibular stimulation are sympathetic responses in motion sickness.

The present results showed that the initial SSNA suppression was followed by an SSNA enhancement. After a constant or repeated stimulation, the sympathetic nervous system was highly activated, and then the obvious symptoms such as cold sweating occurred. The motion sickness symptoms evoked in the present study were not very serious; we observed no vomiting during the experiments. The SSNA enhancement after nystagmus might thus represent only the sympathetic response to stimulation of this intensity. If stronger stimulation had been applied, the enhancement might be followed by a reduction in sympathetic tone or by an ongoing parasympathetic rebound, which is manifested in increased nausea and vomiting, as observed in our previous study (13).

We demonstrated in a previous study that caloric vestibular stimulation can evoke a modest MSNA suppression followed by a strong enhancement during nystagmus (5), whereas in the present study the SSNA was strongly suppressed during nystagmus and enhanced after nystagmus. The different serial responses of SSNA and MSNA suggest that caloric vestibular stimulation can elicit different sympathetic outflows to various vascular beds.

Our previous and present results show that caloric vestibular stimulation induces fluctuations in the sympathetic outflow to muscle and skin. It was reported that MSNA did not change significantly with caloric vestibular stimulation in humans, even when dizziness and nausea were reported by the subjects (4). The discrepancy between this finding and our previous results seems to derive from the analysis methods used. In our previous study, the MSNA in a 10-s period was assessed and was observed for 5 min, whereas in the reported study MSNA was assessed only for four 30-s periods. The fluctuation in the sympathetic response might not be observed due to the mutual counteracting during the 30-s period. Therefore, in the present study we also processed the data in a short period to observe the dynamic character of the SSNA response.

In summary, we found that the SSNA was inhibited during nystagmus evoked by caloric vestibular stimulation, whereas the SSNA was activated during motion sickness symptoms after the nystagmus ceased. The results indicate that the response of sympathetic outflow to the skin fluctuated during the time course of vestibular stimulation.

**Perspectives**

Facial pallor and cold sweating are considered typical sympathetic symptoms in motion sickness syndrome. However, the response of sympathetic outflow to skin seems more complex than a simple activation. Facial pallor is thought to be caused by a reduction in the amount of blood present in the skin rather than a reduction in the blood flow through the skin during motion sickness (12, 16). The present results also showed that the skin blood flow in the dorsum pedis was not significantly decreased during motion sickness, although the total activity of SSNA was significantly increased. These observations might hint that the vasoconstrictor and sudomotor nerve activities in the SSNA are not activated synchronously in motion sickness syndrome. The vasoconstrictor and sudomotor nerves during the time course of vestibular stimulation should be studied further. Such studies could be expected to provide much information regarding the sympathetic outflow during motion sickness in humans.

This study was carried out as part of the Space Utilization Frontier’s Joint Research Project promoted by the National Space Development Agency of Japan.

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Received 21 April 1998; accepted in final form 18 November 1998.

**REFERENCES**

1. Balaban, C. D. Vestibular nucleus projections to the parabra
cchial nucleus in rabbits: implications for vestibular influences on