Altered response in cutaneous sympathetic outflow to mental and thermal stimuli in primary palmoplantar hyperhidrosis

Satoshi Iwase [a,*], Takehiko Ikeda [a,b], Hiroki Kitazawa [a], Shigetaka Hakusui [c], Junichi Sugenoya [d], Tadaaki Mano [a]

[a] *Department of Autonomic and Behavioral Neurosciences, Division of Higher Nervous Control, Research Institute of Environmental Medicine, Nagoya University, Nagoya 464-01, Japan*
[b] *Department of Anesthesiology and Intensive Care, Hamamatsu University School of Medicine, Hamamatsu 431-31, Japan*
[c] *Department of Neurology, Nagoya Daini Red-Cross Hospital, Nagoya 466, Japan*
[d] *Department of Physiology, Aichi Medical University, Aichi 480-11, Japan*

Abstract

Skin sympathetic nerve activities (SSNAs) were recorded simultaneously from the tibial and peroneal nerves by microneurography at an ambient temperature of 25°C in five subjects with primary palmoplantar hyperhidrosis. The resting activity of the tibial SSNA innervating the sole (glabrous skin) increased moderately (36.5 ± 1.5 bursts/min), while mental arithmetic provoked marked responses ($\underline{}3.3 \pm 457.4\%$ compared with the resting level) in the hyperhidrosis group compared with the control normohidrosis group ($n = 5$, $\underline{} \pm 4.2$ bursts/min and $142.2 \pm 58.4\%$, respectively). Differentiation of the tibial SSNA into sudomotor (innervating sweat glands) and vasoconstrictor (innervating presphincter of skin vessels) revealed that this SSNA enhancement was attributable to not only sudomotor but also vasoconstrictor components during mental arithmetic. In contrast, the responses in the peroneal SSNA (innervating the dorsum pedis, hairy skin) of the hyperhidrosis group were only slightly changed, exhibiting no significant difference from those in the normohidrosis group. Reflex bursts elicited by sound and electric stimulation were normal in amplitude and latency. When the ambient temperature was elevated to 30°C, the tibial SSNAs became more enhanced than did the peroneal SSNAs. The tibial SSNA was markedly enhanced in the hyperhidrosis group ($290.0 \pm 78.5\%$) compared with the normohidrosis group ($78.3 \pm 25.4\%$). We conclude that the excessive responses in SSNA to the palmar and plantar glabrous skin to both mental and thermal stimuli may be responsible for the profuse sweating in subjects with primary palmoplantar hyperhidrosis.

Keywords: Hyperhidrosis; Skin sympathetic nerve activity; Sudomotor; Vasoconstrictor; Microneurography

1. Introduction

Hyperhidrosis is a pathological condition in which sweating exceeds that required for thermoregulation [4], and can be very distressing and a source of intense embarrassment, interfering with social and work commitments. Hyperhidrosis that is secondary to endocrinological abnormalities, inflammatory conditions, or cerebrovascular diseases must be distinguished from primary hyperhidrosis, which usually occurs early in adolescence and is characterized by excessive sweating in the palms, axillae, or soles

[7]. Epidemiological studies suggest that 0.6–1.0% of the population suffers from this condition [1].

Most patients with primary hyperhidrosis are young women, some of whom suffer from excessive and obvious sweat dripping from the hands [20]. Since the most effective treatment for primary hyperhidrosis of the palms and soles (palmoplantar hyperhidrosis) is sympathectomy of the thoracic or lumbar region [5,20], it is suspected that these patients may also suffer from hyperactivity in sympathetic outflow to the skin (skin sympathetic nerve activity, SSNA), which contains sudomotor (SM) as well as vasoconstrictor (VC) nerve activities [10]. The SM nerve activities accelerate sweating by stimulating the sweat glands, and VC activities constrict the presphincter of the skin vessels.

Corresponding author. Tel.: +81 52 7893883; fax: +81 52 7895047; e-mail: iwase@riem.nagoya-u.ac.jp

Since the hyperhidrotic area is limited to the glabrous skin, and it has been clarified that skin sympathetic nerve activity to the glabrous skin behaves differently from that to the hairy skin [12,19], it is beneficial to measure the resting activities and the responses to the various arousal stimuli in the sympathetic outflow to the glabrous skin and to the hairy skin simultaneously.

To clarify the changes which occur in the discharge patterns elicited from the tibial and peroneal SSNAs in patients with primary palmoplantar hyperhidrosis, we monitored the alterations in their SSNAs from the tibial nerve to the sole (glabrous skin) and peroneal nerve to the dorsum pedis (hairy skin) following arousal stimuli including mental, thermal, electrical, and sound ones.

2. Methods

The subjects were five palmoplantar hyperhidrotic patients, two men and three women described in Table 1. All of the five subjects complained of excessive sweating in the palms and soles, which was further exaggerated during mental tension. Physical examination confirmed that all of the subjects suffered from profuse palmoplantar sweating but no other abnormality. No definite causes for secondary hyperhidrosis, e.g., thyroid disease, malignant tumor, pheochromocytoma, menopausal disorder, or carcinoid syndromes were found in any subjects.

The aim and benefits of this study were fully explained to the subjects, and their prior consent was obtained for participation. As a control, we used the mean values of the resting activity and the responsiveness to mental and physical stimuli of five healthy and normohidrotic men (age: 25.3 ± 4.2, mean $\pm$ SD).

The subjects lay on a bed in the supine position in a sound-proof room maintained at an ambient temperature of

Table 1
List of the subjects

Case	Age	Gender	Height (cm)	Weight (kg)
1	18	M	160	55
2	37	M	167	57
3	21	F	152	47
4	23	F	164	52
5	24	F	155	48
Mean	24.6		159.6	51.8
SD	7.3		6.2	4.3

25°C. SSNAs were recorded from the tibial and peroneal nerves simultaneously using a double recording technique of microneurography, and were identified as a SSNA burst based on these criteria: the activity (1) consisted of spontaneous, irregular, pulse-asynchronous efferent burst discharges, recorded from the skin nerve fascicles; (2) was followed by peripheral vasoconstriction or perspiration; (3) was elicited following an almost constant latency by mental stress and sensory stimuli (sound, pain, electrical stimulation of the peripheral nerve trunk, etc.); and (4) was elicited by a deep breath [8,9]. Two tungsten microelectrodes with a tip diameter of 1 μm and an impedance of 3–5 MΩ were inserted into the skin fascicle of the tibial and peroneal nerves, respectively (Fig. 1).

The nerve action potentials obtained were fed into a preamplifier (with a gain of 1,000 ×, DAM-6A, World Precision Instruments, Hamden, CT), passed through band-pass filters (500–5,000 Hz, E-3201A, NF Circuit Design, Yokohama), and displayed on a cathode ray oscilloscope (Tektronix 5113, Tektronix, Beaverton, OR). The SSNAs were simultaneously monitored by loud speakers. Nerve signals were discriminated to gain the signal to noise ratio, fully rectified, integrated with a time constant of 0.1 s, and displayed on a thermal pen recorder (Recti-
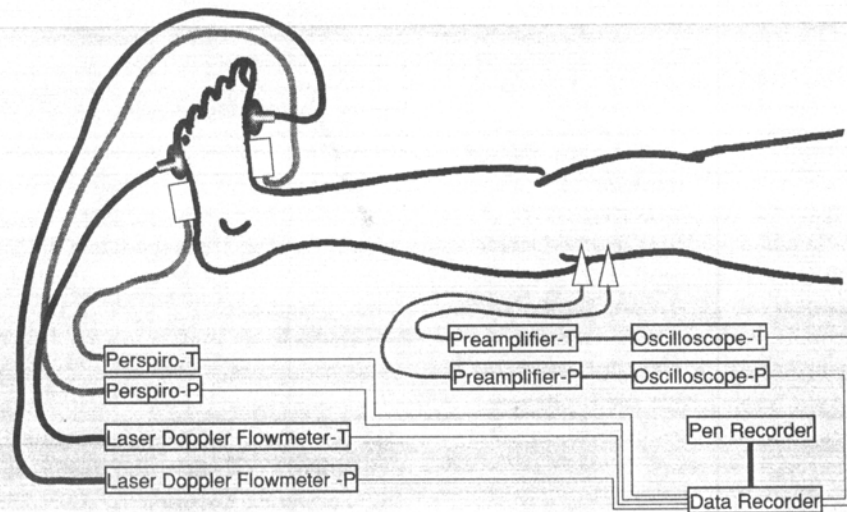

Fig. 1. Diagram of the experimental set-up. Two sets of microneurography, sweat measurement devices, and laser Doppler flowmeters were fixed to the foot and leg. Suffix T denotes the tibial route, and P means the peroneal route.
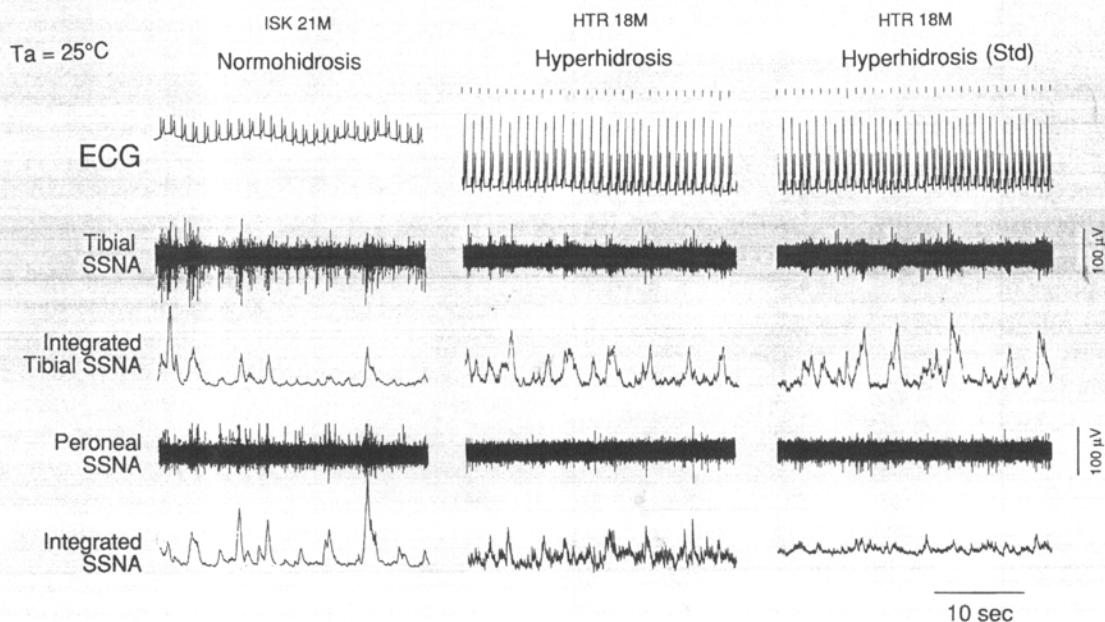
Fig. 2. Resting activity of skin sympathetic nerve in a control normohidrosis group subject (left), and in a hyperhidrosis group subject (middle and right). The gain of the integrated peroneal SSNA in the middle panel was adjusted to show the synchronous discharges as shown in the tibial SSNA. In the right panel, the integrated peroneal SSNA was adjusted to set the integrated reflex bursts in both nerves at the same amplitude. Analogous tibial and peroneal discharges are seen in the middle panel, and enhanced tibial SSNA discharges are exhibited in the right panel.

Horiz, NEC-San-ei, Tokyo) or a thermal array recorder (WS-682G, Nihon Kohden, Tokyo).

The ventilated capsule method (Kenz-Perspiro, Suzuken, Nagoya) was employed for quantification of sweating, and blood flow was measured with a laser Doppler flowmeter (ALF 21, Advance, Tokyo), with two probes attached to the skin of the sole and the dorsum pedis ipsilateral to the microneurographic recording. According to the effector responses, SSNAs were differentiated as SM when sweat expulsion or a skin potential change occurred, as VC when a reduction in skin blood flow occurred, as mixed when both were observed, and as unidentified when neither were observed. All data were stored in an FM magnetic data recorder (KS-616U, Sony Magnescale, Tokyo) and analyzed by off-line processing.

After the subjects rested in a relaxed state for more than 30 min, resting activity was recorded for 15 min as a control reading. The tasks used to activate SSNA were presented in the following order in all of the subjects: (1) mental arithmetic, (2) sound stimulation from a starting pistol, (3) electric stimulation, (4) deep breathing. Mental arithmetic was requested of the subjects as subtraction of 7 from 100 for seven times, two-digit addition and subtraction for seven times, and multiplication of two-digit numbers and one-digit numbers for seven times. The mental arithmetic was such a level as the 6th grade students could solve. Sound stimulation was rendered by a starting pistol with an interval of more than 30 s. Electric stimulation of pulse duration of 1 ms was administered by an electric stimulator at the wrist joint using a supramaximal strength

to elicit the contraction of the thenar muscles with enough length of intervals (more than 30 s). Deep breathing was done voluntarily by the subject at an arbitrary timing ("as rapid as possible"). The reason for using voluntary deep and rapid breathing as a stimulus was that an order to breathe might not have elicited the reflex SSNA to the arousal stimuli. The ambient temperature was then elevated to 30°C, and the response to thermal stimuli was
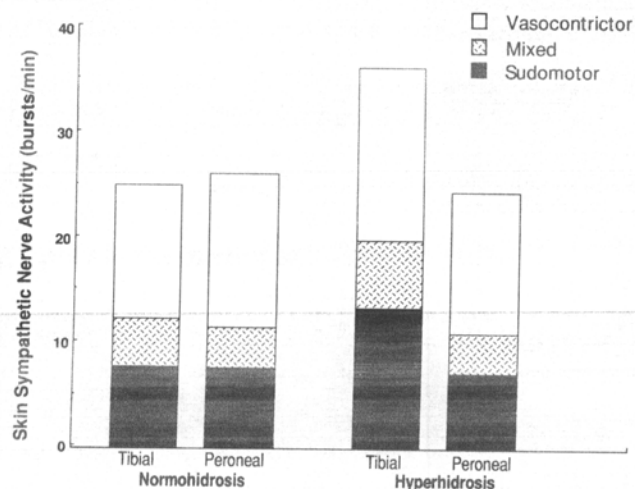

Fig. 3. Comparison of the skin sympathetic nerve activity in the control normohidrosis ($n = 5$) and primary palmoplantar hyperhidrosis subjects ($n = 5$). The burst rate of the vasoconstrictor (VC) component is not significantly different between the hyperhidrosis and the normohidrosis groups. An increase in sudomotor activity contributed to the SSNA enhancement in the hyperhidrosis group. Unidentified bursts were deleted.

observed for 10 min after the ambient temperature had reached 30°C. The observation was continued for 10 min after the ambient temperature reached at 30°C, and the recording for this 10 min period was compared with that of the last 15 min period of the control reading.

SSNA was quantified as the number of bursts per min (burst rate) for resting activity. The resting activity for individuals was calculated from the mean burst rate of the last 15 min period of the control reading. The total activity of the SSNA was quantified as the sum of the amplitudes from full-wave rectified and integrated neurograms at a time constant of 0.1 s. The responsiveness of SSNA was standardized as a percentage change from the total activity at the resting state per min (control reading) as 100%.

For the evaluation of inter-individual differences among the nerves, the amplitudes of the integrated SSNA were standardized using the maximum reflex burst observed after the electric or sound stimulation set as the same amplitude, using an amplifier and a discriminator to set the noise levels as the same. For the inter-individual comparison among subjects, the resting activity was compared by 'burst rate', and the responsiveness of SSNA to various stimuli was compared by 'percentage change from the resting total activity' for standardization. Values are expressed as mean ± SD, and the Student's t-test was employed for comparison. P values less than 0.05 were considered significant.

3. Results

All five subjects showed hyperhidrosis in both their palms and soles. At the resting state, the sweat rate at the sole of all hyperhidrosis subjects exceeded 20 μg cm^{-2} min^{-1}. Sweating from the dorsum pedis at rest was subthreshold level, and was sometimes not detected by the ventilated capsule method. Unidentified bursts were deleted from the data.

3.1. Resting skin sympathetic nerve activity in hyperhidrosis

The tibial and peroneal SSNAs exhibited nearly synchronous discharges at an ambient temperature of 25°C. In the control normohidrosis group, burst discharges from the tibial and peroneal nerves had relatively equal amplitudes. The discharge patterns of the tibial and peroneal SSNAs in the normohidrosis were almost the same when the gain of the peroneal SSNA was adjusted. In contrast, the discharges from the tibial nerve in the hyperhidrosis group were high in burst amplitude compared with those from the peroneal nerve, suggesting that the difference between tibial and peroneal SSNAs is the number of spikes participating in bursts (Fig. 2).

The resting tibial SSNA burst rate in the palmoplantar hyperhidrosis group was 36.5 ± 1.5 bursts/min, and was significantly higher than in the control group (25.3 ± 4.2, $p < 0.05$, Fig. 3). In the normohidrosis group, the VC component was comparatively higher than the SM component, whereas the SM component in the hyperhidrosis group was significantly higher compared with the normohidrosis group (13.5 ± 2.2 vs 7.8 ± 2.7 bursts/min, $p < 0.05$, Fig. 3). The VC component exhibited no significant difference between the hyperhidrosis and normohidrosis groups.

The resting peroneal SSNA burst rate in the hyperhidrosis group exhibited no significant difference from that in the normohidrosis group. Therefore, the resting peroneal SSNA burst rate was significantly lower than that in the tibial SSNA in the hyperhidrosis subjects due to the higher percentage of unidentified bursts in the peroneal SSNA than in the tibial SSNA. The percentage of mixed bursts
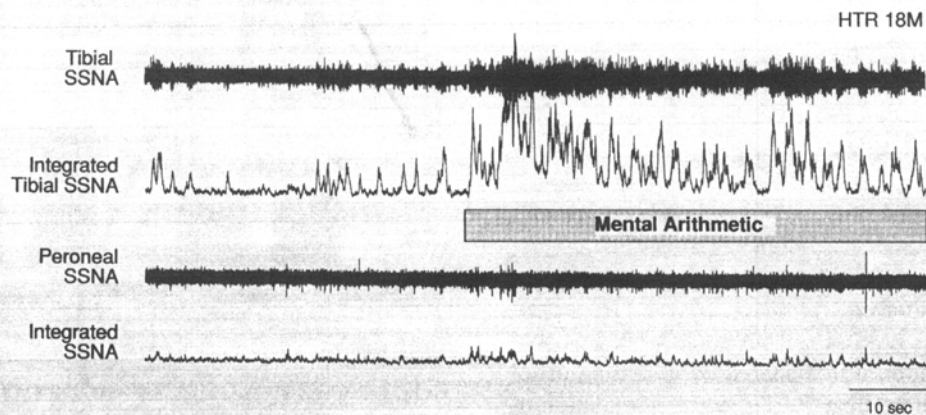

Fig. 4. Changes in the tibial and peroneal SSNAs in response to mental arithmetic in hyperhidrosis subjects. Mental arithmetic caused a marked enhancement in the tibial SSNA but only slight increases in the peroneal SSNA.
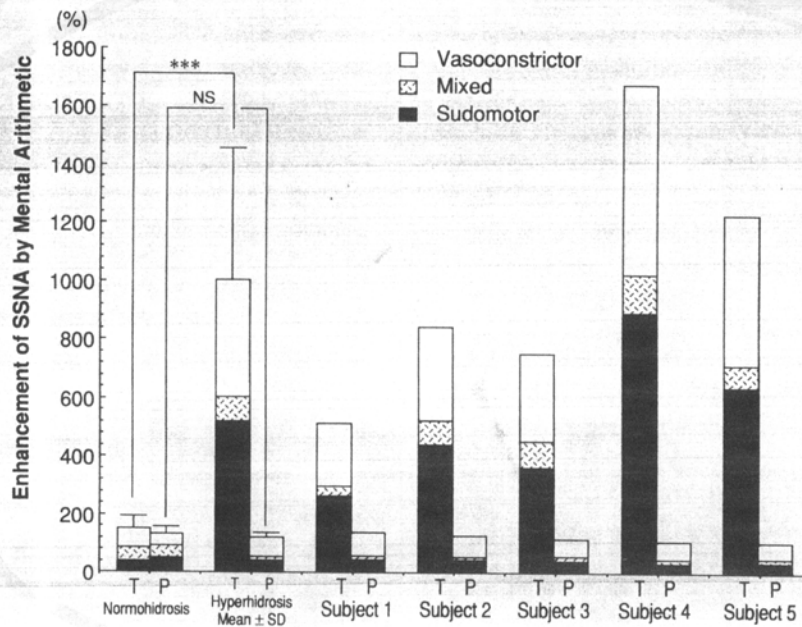
Fig. 5. Changes in the tibial (T) and peroneal (P) skin sympathetic nerve activity and sudomotor and vasoconstrictor components by mental arithmetic. Marked enhancements in the hyperhidrosis compared with normohidrosis are observed from resting activities in the control and hyperhidrosis subjects. The resting level was set at 100%. The increase in total SSNA from the resting level in the hyperhidrosis group is three to eight times as much as those observed in the normohidrosis group. The individual data for hyperhidrosis subjects (subject 1–5) are also shown. ***: $p < 0.001$. N.S., not significant.

showed no significant difference between the normohidrosis and hyperhidrosis groups ($18.2 \pm 2.8\%$ vs $17.5 \pm 3.6\%$).

3.2. Responses of skin sympathetic nerve activity to mental arithmetic

Mental arithmetic markedly enhanced the tibial SSNA, although the peroneal SSNA exhibited only a slight change in the hyperhidrosis group (Fig. 4). The tibial SSNA was enhanced to $1,003 \pm 457.4\%$ by mental arithmetic, which

was significantly greater than the change in the normohidrosis group ($p < 0.001$). In contrast, the peroneal SSNA was only slightly enhanced, to $117.2 \pm 12.6\%$, and there was no significant difference compared to the normohidrosis values ($123.8 \pm 25.3\%$, Fig. 5).

The differentiation of SSNA into SM, VC, or mixed revealed that not only the SM bursts but also the VC bursts were enhanced by mental load in the tibial SSNA ($51.2 \pm 1.9\%$ in SM, and $40.2 \pm 1.8\%$ in VC when all SSNA bursts were regarded as 100%), whereas the VC component dominated in the peroneal SSNA by mental arithmetic
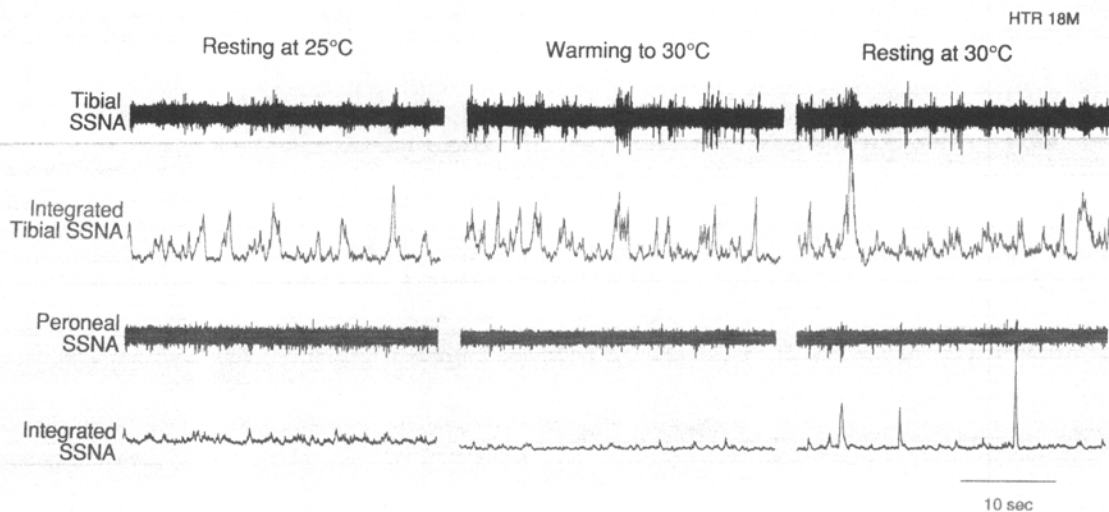

Fig. 6. Changes in tibial and peroneal SSNAs after raising the room temperature to 30°C in a hyperhidrosis subject. The warmer room temperature caused tibial SSNA three to four times greater than those seen in the normohidrosis group, while slight changes from the thermoneutral temperature values were observed in the peroneal SSNA.
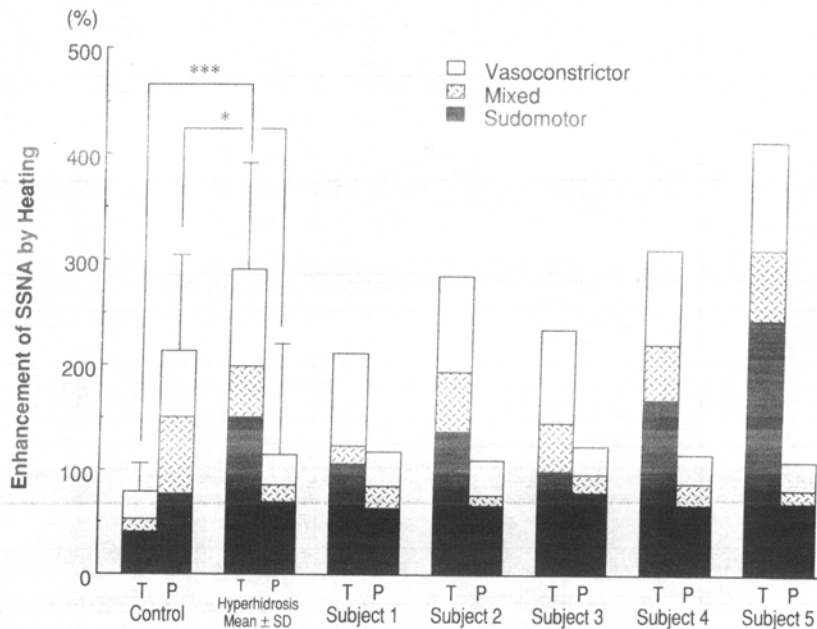
Fig. 7. Changes in the tibial (T) and peroneal (P) skin sympathetic nerve activity and sudomotor and vasoconstrictor components. Enhancements from resting activities in the control and five primary palmoplantar hyperhidrosis subjects were compared after raising the room temperature from 25 to 30℃. The increases from the resting level in total SSNA taking tSSNA at 25℃ as 100% was enhanced by approximately three-fold in the hyperhidrosis group. The enhancement in the peroneal nerve was very slight compared with the enhancement in the peroneal nerve in the control group. The individual data for hyperhidrosis subjects (subject 1–5) are also shown. *: $p < 0.05$; ***: $P < 0.0001$.

$(32.0 \pm 2.6\%$ in SM, and $55.6 \pm 3.4\%$ in VC when all SSNA bursts were regarded as 100%, Figs. 5 and 8).

3.3. Responses of skin sympathetic nerve activity to sound and electric stimulation

Sound and electric stimulation also induced reflex SSNA bursts with certain latencies [14]. The reflex bursts elicited

by sound and electric stimulation in the hyperhidrosis subjects were normal in their amplitudes and latencies; however, the spontaneous discharges, which were SSNA discharges not elicited by sound or electric stimuli, in the tibial nerve between each sound and electric stimulation were enhanced in their frequencies and burst amplitudes. Since we set the maximum response to sound or electric stimulation at the same level to standardize both the
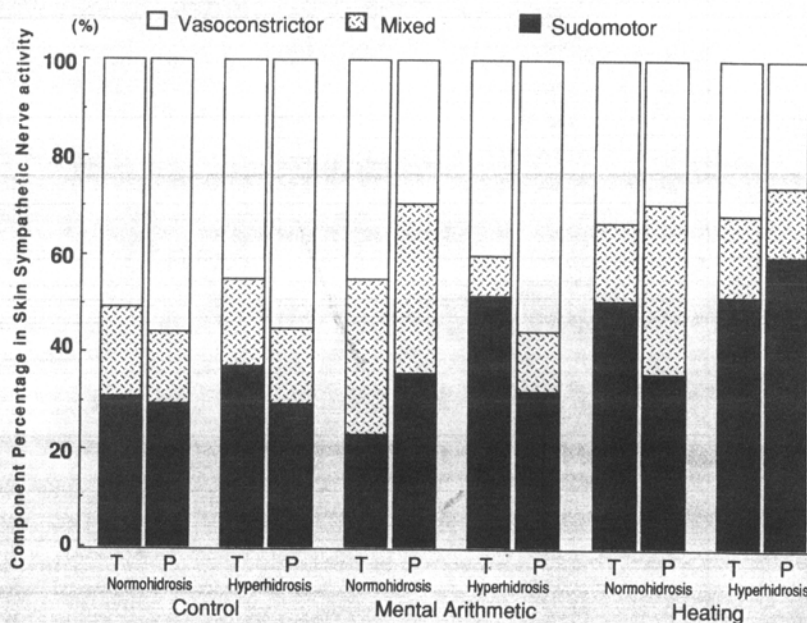

Fig. 8. Percentage changes in SSNA bursts into SM, mixed, and VC components. Changes in components were expressed as a percentage when mental arithmetic tasks and heating were administered to normohidrosis and hyperhidrosis subjects. T: tibial SSNA, P: peroneal SSNA. Percentages of SM in the hyperhidrosis group were increased by the mental arithmetic and heating.

inter-individual differences and the differences between the tibial and peroneal nerves, there was no significant difference in amplitudes and latencies of the hyperhidrosis subjects compared with those of the normohidrosis group.

3.4. Responses of skin sympathetic nerve activity to thermal stress

Elevating the ambient temperature to 30°C also enhanced both the tibial and peroneal SSNAs in the hyperhidrosis group, but the magnitude of the enhancement was more prominent in the tibial SSNA (Fig. 6). The tibial SSNA was significantly enhanced to $290.0 \pm 78.5\%$ of the resting level as compared with the enhancement in the control group (to $78.3 \pm 25.4\%$ of the resting level, $p < 0.001$). The peroneal SSNA of the hyperhidrosis subjects was significantly less enhanced, to $114.4 \pm 6.1\%$, from the resting SSNA compared with the control group (to $213.2 \pm 62.6\%$ of the resting level, $p < 0.05$, Fig. 7).

The enhancement by the thermal environment was SM-dominant in the hyperhidrosis subjects in both the tibial ($50.6 \pm 6.4\%$ in SM, and $33.2 \pm 6.8\%$ in VC when all SSNA bursts were regarded as 100%) and peroneal ($59.8 \pm 4.0\%$ in SM, and $26.0 \pm 3.5\%$ in VC when all SSNA bursts were regarded as 100%) SSNA, whereas those in the control group were slightly VC-dominant in both the tibial ($23.3 \pm 4.5\%$ in SM, and $45.1 \pm 8.3\%$ in VC when SSNA bursts were regarded as 100%) and the peroneal SSNA ($35.8 \pm 7.2\%$ in SM, and $29.6 \pm 6.7\%$ in VC when all SSNA bursts were regarded as 100%, Fig. 8).

4. Discussion

Hyperhidrosis often seems a 'minor' and non-life-threatening problem to observers, but it can be devastating for the patients themselves. It usually appears in childhood, worsens during adolescence, and subsides with advancing age in some patients. The patients often visit an outpatient clinic on the occasion of an entrance examination, employment, or marriage [9]. The differentiation of normal sweating from hyperhidrosis is subjective, and the condition thus lacks a precise definition, although attempts to measure the normal rates of insensible loss from the skin have reported 8–15 μg cm^{-2} min^{-1} as a norm [15]. Using this value, it is reasonable to categorize all of the five present subjects as having palmoplantar hyperhidrosis. Almost all of the studies referring to hyperhidrosis to date have simply documented the treatment of the condition; there have been few reports on the mechanism of the development of hyperhidrosis. The present study sought to elucidate the neural mechanisms of hyperhidrosis by measuring the sympathetic outflow to the skin directly in the peroneal nerve, utilizing a double-recording microneurographic technique.

SSNA was first recorded by Hagbarth et al. [8] in 1972.

The SSNA contains SM and VC components. Mixed bursts is considered to contain both SM and VC components. The SM activity correlates well to the slope of sweat expulsions in a linear manner [12,19,21], and exhibits regional differentiation [19] in glabrous and hairy skin. The VC activity also shows a linear correlation to the magnitude of skin blood flow reduction [12] and regional differentiation [19].

In the present study, the resting tibial SSNA became moderately or markedly enhanced while the resting peroneal SSNA was slightly suppressed in the palmoplantar hyperhidrosis subjects. The analogous discharge patterns of tibial and peroneal SSNAs suggested the synchronous supraspinal origin of the mental and thermal SM and VC outflows, with much interaction between mental and thermal SM and VC activities. This synchronicity theory is supported by a study of sweat expulsions [16]. Suppression of the peroneal SSNA may be due to the compensatory suppression of sweating in the hairy skin for the glabrous skin.

In the present study, it was found that the SSNA responsiveness to mental stimuli was markedly enhanced, three to eight times as much enhanced in the tibial nerve as compared with the normohidrosis group, although the reflex bursts to sound or electric stimulation seem to remain nearly unchanged. In contrast, the enhancement in the peroneal nerve of the hyperhidrosis subjects exhibited no significant difference from that of the control normohidrosis subjects. These results are well explained by the sweating model proposed by Ogawa and Sugenoya (Fig. 9) [17]. Based on the distribution of sweat glands, they estimated two sweating centers, mental and thermal. The mental sweating center is thought to control palmoplantar sweating, and the thermal center controls sweating in the hairy skin. The thermoregulatory center in the hypothalamus accelerates the thermal sweating center, whereas the mental sweating centers in the neocortex (higher mental activities) and limbic system (emotional) accelerates the palmoplantar sweating. Suppressive effects may take place from the thermoregulatory center to the mental sweating center, and from the neocortex to the thermal sweating center.

A similar model could be also hypothesized in vasoconstriction (Fig. 9). The mental SM and VC center in the cerebral subcortex [13] may thus play a role of gain controller, and supersensitivity of these mental SM and VC centers is estimated to evoke the palmoplantar hyperhidrosis. This hypothesis is supported by the finding that the symptoms of hyperhidrosis usually subside during sleep, like sleep-related decrease in sympathetic outflow [18,22].

Elevating the ambient temperature enhanced the tibial SSNA in the present hyperhidrosis subjects. However, our previous study [19] showed that heat exposure usually enhances the peroneal SSNA in normohidrotic subjects. In the control normohidrosis subjects, the SSNA to the hairy skin responds to thermal stress more than does the SSNA to glabrous skin [2,3,19]. This contradictory SSNA en-
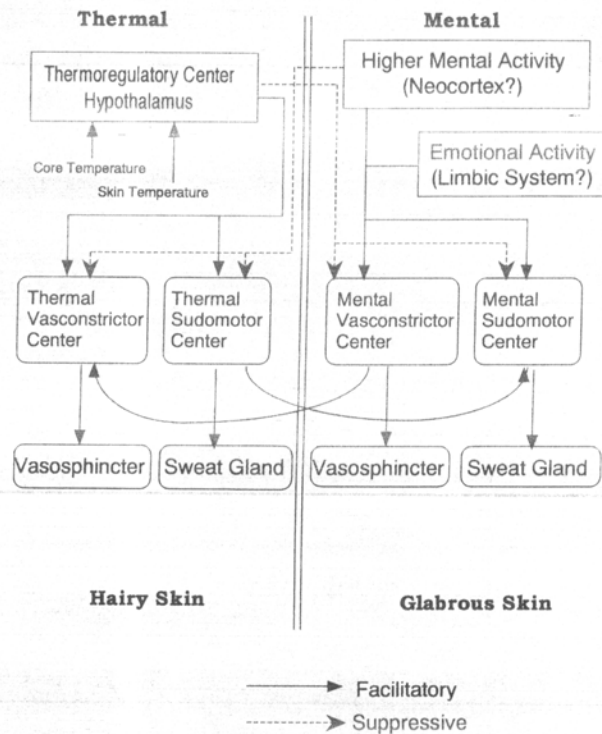
Fig. 9. Schematic model for central mechanism of thermal and mental sweating and vasoconstriction. (Modified from Ogawa and Sugenoya [17].)

hancement might be provoked by an easy excitation of the mental sweating center, probably because the ambient temperature elevation is perceived as thermal stress. Furthermore, the differentiation of SSNA to SM and VC components in the tibial and peroneal nerves observed in the present hyperhidrosis subjects also revealed contrasting results in comparison with those in the control normohidrosis group. The percentage of SM and VC in the tibial nerve did not change, i.e., both components were enhanced by thermal stress proportionally. However, the peroneal SM component in the hyperhidrosis subjects exhibited no marked change by the elevation of the ambient temperature to 30°C, suggesting that the less-enhanced peroneal SSNA was due to a less-enhanced peroneal SM component. This unchanged SM activity after heating might contribute to the thermoregulatory control of the hyperhidrosis.

Cloward postulated that hyperhidrosis may be secondary to the hyperresponse to the mental or emotional stimulation of the sympathetic nervous system, and may originate in the cerebral cortex [6]. Our results support his postulation and also suggest that the altered input gains to the sweating and vasomotor center in the hypothalamus from the subcortical emotional center and the thermoreceptive center might be responsible for the condition of primary palmoplantar hyperhidrosis.

The changes in SM and VC activities in SSNA of aged hyperhidrosis subjects could be examined in a future study, since age-related changes in sympathetic outflow [11] might

be responsible for the subsidence of the palmoplantar hyperhidrotic symptoms with advancing age.

In conclusion, the responses of sympathetic outflow to the glabrous skin to mental or thermal stimuli were exaggerated in the palmoplantar hyperhidrosis subjects. Altered input gains to the sweating and vasoconstrictive centers, probably in the hypothalamus from the subcortical emotional center, and the thermoreceptive center might be responsible for the profuse sweating in the glabrous skin, i.e., palms and soles in primary palmoplantar hyperhidrosis subjects.

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