

Interrelations of vasoconstrictor sympathetic outflow to skin and core temperature during unilateral sole heating in humans

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Abstract

The purpose of the present study was to clarify how skin sympathetic nerve activity (SSNA) influences the core temperature during local heating of the unilateral sole of the foot for 60 min. We recorded SSNA microneurographically from the tibial or peroneal nerve simultaneously with skin blood flow, sweat rate at heated and non-heated sites, with tympanic temperature (T_{ty}) as the core temperature. Sole heating began to suppress vasoconstrictive SSNA (vasoconstrictor) after 3.4 ± 1.1 min, decrease T_{ty} after 7.4 ± 2.0 min, activate vasoconstrictor after 33.4 ± 2.2 min, and increase T_{ty} after 45.5 ± 2.7 min. Regarding the interaction between vasoconstrictor and T_{ty} during sole heating, we found the following: (1) the capability to suppress vasoconstrictors (decrease rate) showed positive correlations with the time delay from vasoconstrictor suppression to the T_{ty} decrease ($r = 0.752$, $p < 0.05$), and with the T_{ty} decrease rate ($r = 0.795$, $p < 0.05$), (2) the T_{ty} decrease rate was inversely related to the capability to activate vasoconstrictors (increase rate) ($r = -0.836$, $p < 0.05$), and (3) the capability to activate vasoconstrictors was inversely related to the time delay from vasoconstrictor activation to the T_{ty} increase ($r = -0.856$, $p < 0.05$) and showed a positive correlation with the T_{ty} increase rate ($r = 0.819$, $p < 0.05$). These significant correlations indicate that the capability to control vasoconstrictors to the skin is one of the determinant factors maintaining core temperature in human thermoregulatory function. In conclusion, human thermoregulatory function is largely dependent on the suppression and activation capability of vasoconstrictors. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

The sympathetic nerve activity leading to human skin includes vasoconstrictor nerve activity to control skin blood flow, and sudomotor nerve activity to regulate sweating (Bini et al., 1980). In addition, vasodilator nerve activity may play a role in controlling human thermoregulation. Skin sympathetic nerve activity (SSNA) can be recorded by microneurography (Hagbarth et al., 1972; Bini et al., 1980; Iwase et al., 1988; Mano, 1998) and we demonstrated that components of vasoconstrictor and sudomotor nerve activities are different between the tibial and the peroneal nerves, and that the thermal environment alters the ratio of sudomotor and vasoconstrictor components in our previous study (Okamoto et al., 1994). However, the temporal relationship between SSNA and core temperature has not been clarified by time series analysis. Based on these findings, we analyzed the relationship between vaso-

constrictors and the tympanic temperature and demonstrated a correlation between vasoconstrictor activation and core temperature rise during local cooling (Sawasaki et al., 2001). Therefore, core temperature and vasoconstrictors may interact with each other in the human thermoregulatory system in the cooling condition, whereas little is known about the relationship between them under the heating condition.

The effect of local heating has not been studied in relation to SSNA. There are several ways to warm the human body by heating the sole, e.g. kotatsu (foot warmer with blanket), hot water bottle (yutampo), floor heating, and electric carpet, most of which heat the sole because these parts contain arteriovenous anastomoses (AVA) with rich blood flow, but few studies have never been made at thermoregulatory responses to local heating of the sole of the foot from the viewpoint of the interrelationship between vasoconstrictors and core temperature. The present study was designed to clarify how the suppressed or activated SSNA influences the core temperature in humans during unilateral sole heating to 40°C. We microneurographically recorded SSNA from the tibial or peroneal

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nerves, and observed how these activities changed due to local heating to 40°C simultaneously with skin blood flow and sweat rate at heated and non-heated sites. We also analyzed the correlations between vasoconstrictors and tympanic temperature measured as the core temperature to examine how capabilities to suppress and to activate SSNA influence thermoregulatory functions in humans, as briefly reported previously (Michikami et al., 2000).

2. Methods

2.1. Subjects

The subjects were 14 medical students aged 21.6 ± 0.6 year; height, 171.2 ± 1.6 cm; weight, 63.7 ± 1.4 kg (mean \pm SE). Before the experiment, a thorough explanation was given to the subjects, and their informed consent was obtained in written form. The protocol was approved by the Committee on Human Research, Research Institute of Environmental Medicine, Nagoya University.

2.2. Skin sympathetic nerve activity

SSNA was recorded from the left tibial or the peroneal nerve at the popliteal fossa using a tungsten microelectrode with a tip diameter of 1 μ m, and an impedance of 3–5 M Ω (26-05-1, Frederik Haer, Bowdoinham, ME) percutaneously without anesthesia. The criteria for identification of nerve activity were as reported previously (Bini et al., 1980; Iwase et al., 1988; Mano, 1998; Wallin, 1992). The nerve action potentials were fed into a preamplifier ($\times 20,000$, Kohno Instruments, Kohno II, Nagoya), passed through band-pass filters (500–5000 Hz, E-3201A, NF Circuit Design, Yokohama), and displayed on a cathode ray oscilloscope (Tektronix 5113, Tektronix, Beaverton, OR). The SSNA was simultaneously monitored on a loud speaker. Nerve signals were discriminated to determine sufficient signal to noise ratio, fully rectified, integrated with a time constant of 0.1 s, and displayed on a thermal pen recorder (Recti-Horiz, NEC-San-ei, Tokyo). All data were stored on a multichannel digital data recorder (Sony Precision Technology, PC216AX, Tokyo).

2.3. Skin blood flow, sweat rate, skin and core temperatures

Skin blood flow, sweat rate, and skin temperature were measured at the bilateral soles and the left lateral calf (hairy skin). Skin blood flow was measured by laser Doppler flowmetry (ALF 21, Advance, Tokyo) with a time constant of 0.1 s using a probe with a subcutaneous measurement span of 0.7 mm. The sweat rate was determined by the ventilated capsule method (Kenz-Perspiro OSS-100, Suzuken, Nagoya). Skin temperature was measured using a thermistor (Sensor Technica, Seto, Aichi)

with a precision of 0.05°C, and the core temperature was represented by the tympanic temperature (T_{ty}) (Sato et al., 1996; Walpoth et al., 1994; Brinell and Cabanac, 1989) using a thermistor with a precision of 0.01°C. These temperatures were linearized (Takara THR-C, Techno Seven, Yokohama), and displayed on a digital thermometer. These data were also stored in the digital data recorder.

2.4. Heating pad

The heating pad was made from a specially prepared composite of tetra-fluoro-ethylene resin (Polyflun) and conductive carbon (Fluotron, Daikin Industries, Tokyo), which measured $300 \times 150 \times 1.1$ mm. It was heated according to the voltage between the two terminals, and the voltage required to produce 40°C was confirmed prior to the experiments.

2.5. Protocol

Subjects wore T-shirts and short pants. They rested in the supine position in a dark and quiet room with a room temperature of 27°C, and relative humidity of 40%. The heating pad was fixed to the left sole, and heating was initiated when the core temperature became constant for > 10 min. The temperature of the heating pad was raised to 40°C to allow perception of an adequate warm sensation in the first 10 min, and was maintained at the same voltage for the remaining 50 min.

2.6. Identification of vasoconstrictor and sudomotor nerve activities

SSNA burst followed by a transient reduction in laser Doppler blood flow was identified as a vasoconstrictor, and SSNA burst followed by sweat expulsion characterized by a transient, pulsatile increase in sweat rate was identified as a sudomotor (Sugenoya et al., 1990). SSNA burst followed by both skin blood flow reduction and sweat expulsion was identified as a mixed burst, and counted as both a vasoconstrictor and sudomotor.

2.7. Statistical analysis

The averaged data before heating for 10 min were recorded as the baseline reading. During 60 min of heating, the value for a 1-min period was averaged as a 3-min running average. The results are expressed as means \pm SE. Statistical analysis was done using repeated measures analysis of variance (repeated measures ANOVA), then Fisher's PLSD was performed. The capability to suppress vasoconstrictors during local heating was measured as the vasoconstrictor reduction rate, i.e. the slope of the regression line between time in minutes and vasoconstrictor burst rate for 15 min before the trough. The capability to activate vasoconstrictors was measured as the increase rate of vasocon-

strictor, i.e. the slope of the regression line between time in minutes and vasoconstrictor burst rate for 15 min after the beginning of the increase in the vasoconstrictor. The T_{ty} decrease rate was defined as the slope of the regression line between time in minutes and T_{ty} change for 15 min before the trough. The T_{ty} increase rate was defined as the slope of the regression line between time in minutes and the change in T_{ty} for 15 min after the trough. Regression

analysis was employed to analyze the relationship between SSNA and T_{ty} . Significance was accepted at $p < 0.05$.

3. Results

Of the total 14 subjects, SSNA was recorded in eight subjects, including the tibial and peroneal nerve recording in four subjects respectively. The core temperature mea-

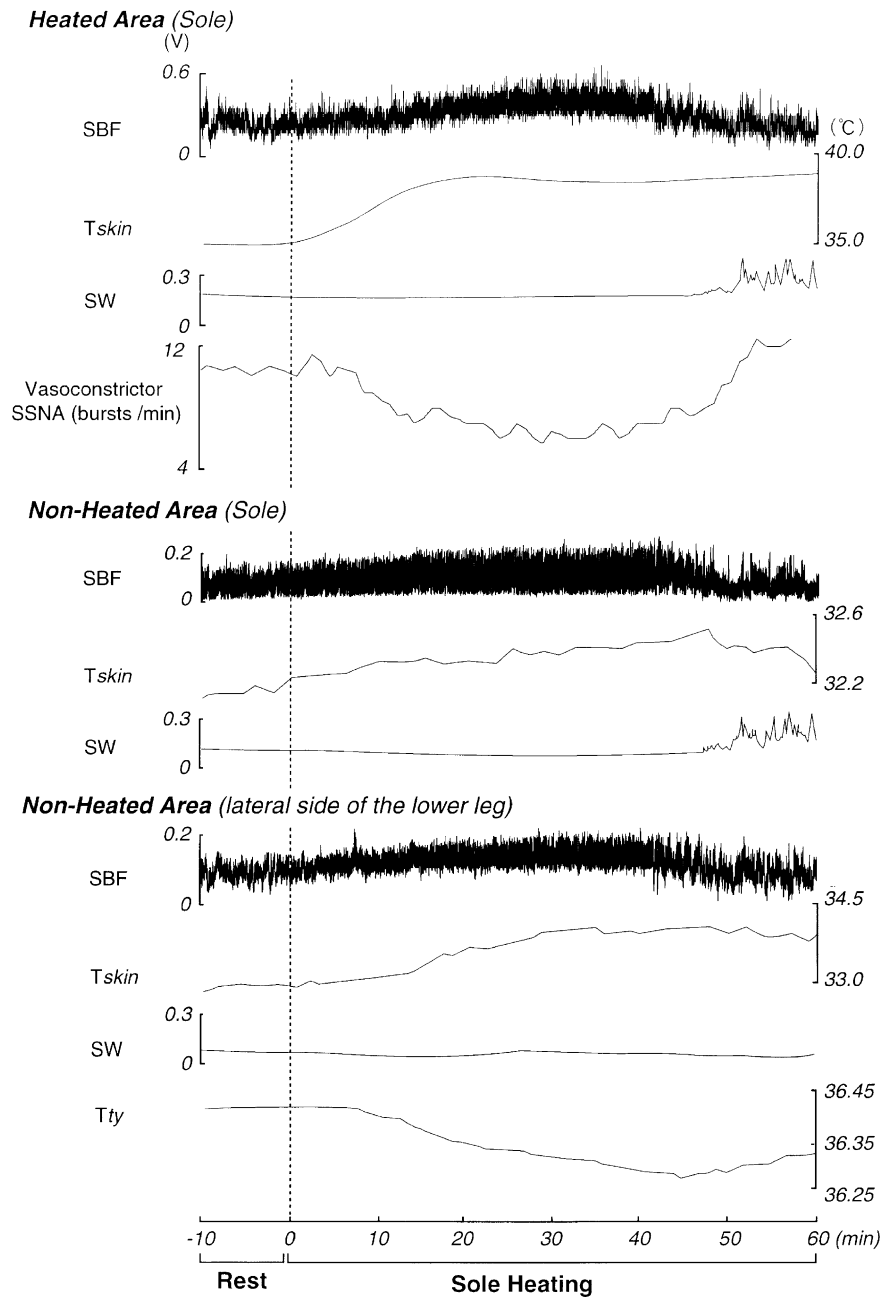


Fig. 1. Changes in skin blood flow, skin temperature, tympanic temperature and sweating during sole heating. Traces show skin blood flow (SBF), skin temperature (T_{skin}), and sweat rate (SW) at the heated area (sole), non-heated area (contralateral sole), and non-heated area of the lateral side of the lower leg and the vasoconstrictor recorded from the tibial nerve. The lowest trace shows the tympanic temperature (T_{ty}) as the core temperature. Sole heating of the sole of the foot increased the skin blood flow with a reduction in vasoconstrictors and skin temperature at heated and non-heated areas, and subsequently T_{ty} decreased. In the late stage, there was a reduction in skin blood flow with a rise in vasoconstrictors, and then tympanic temperature increased. Sweating was observed at bilateral soles.

sured as the tympanic temperature (T_{ty}) was reduced in all subjects during the course of sole heating for 60 min.

3.1. Skin blood flow, vasoconstrictor, and core temperature during sole heating

After local heating of the sole of the foot at 40°C, skin blood flow increased in both heated and non-heated soles and in the non-heated lateral calf. The skin temperatures of these areas also increased, while the T_{ty} measured as the core temperature decreased (Fig. 1). Skin blood flow reduced concomitantly with both the tibial and peroneal vasoconstrictor suppressions after heating. Midway during sole heating, vasoconstrictors were enhanced, and skin blood flow was reduced. Then, T_{ty} increased with a certain latency, followed by sweating and a decrease in skin temperature.

The time delay from sole heating to vasoconstrictor suppression was 3.4 ± 1.1 min, and the time for the decrease in core temperature was 7.5 ± 0.6 min after sole heating ($n = 8$). The latency of vasoconstrictor activation was 33.4 ± 2.2 min, and the latency for the increase in (T_{ty}) was 45.5 ± 2.7 min after sole heating ($n = 8$). After sole heating, the vasoconstrictor activity was significantly reduced from the pre-heated value of 10.7 ± 0.4 to 7.8 ± 0.5 bursts/min ($p < 0.005$, $n = 4$) in the tibial nerve, and 13.7 ± 0.6 to 8.6 ± 0.9 bursts/min in the peroneal nerve ($p < 0.001$, $n = 4$) at 33.4 ± 2.2 min. The skin blood flow in the heated sole was significantly increased to 4.5 ± 1.1 times that before the pre-heated value, 1.8 ± 0.2 times in the non-heated sole, and 1.9 ± 0.2 times in the non-heated lateral calf ($p < 0.005$, $n = 8$) at 33.4 ± 2.2 min. The skin blood flow in the heated area was significantly larger than that in the non-heated area ($p < 0.005$). The T_{ty} measured

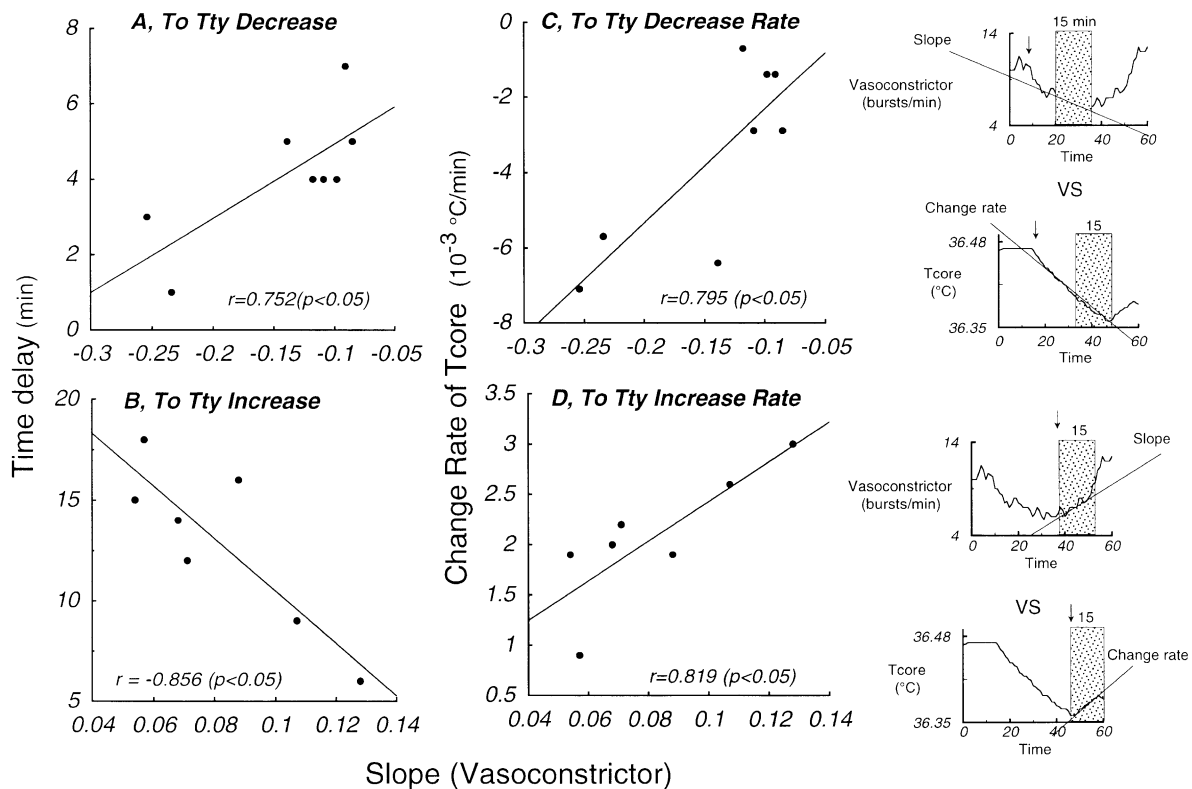


Fig. 2. Correlation between capability to suppress vasoconstrictors and time delay from vasoconstrictor suppression to the T_{ty} decrease (A), the capability to activate vasoconstrictors and time delay from vasoconstrictor activation to the T_{ty} increase (B), the capability to suppress vasoconstrictors and the T_{ty} decrease rate (C), and the capability to activate vasoconstrictors and the T_{ty} increase rate (D). (A) The capability to suppress vasoconstrictors was defined as the slope of the regression line between time in minutes and the vasoconstrictor burst rate for 15 min before the trough. There was a significant positive correlation between the capability to suppress vasoconstrictors and the time delay from vasoconstrictor suppression to the T_{ty} decrease ($r = 0.752$, $n = 8$, $p < 0.05$). (B) The capability to activate vasoconstrictors was defined as the slope of the regression line between time in minutes and the vasoconstrictor burst rate for 15 min after the start of the vasoconstrictor increase. The capability to activate vasoconstrictors was inversely related to the time delay from vasoconstrictor activation to the T_{ty} increase ($r = -0.856$, $n = 7$, $p < 0.05$). (C) The T_{ty} decrease rate was defined as the slope of the regression line between time in minutes and the T_{ty} change before the trough. In eight subjects, there was a significant positive correlation between the capability to suppress vasoconstrictors and the T_{ty} decrease rate ($r = 0.795$, $n = 8$, $p < 0.05$). (D) The T_{ty} increase rate was defined as the slope of the regression line between time in minutes and the change in T_{ty} for 15 min after the trough. One subject was excluded because sole heating was terminated before the T_{ty} rise reached 15 min. In seven subjects, there was a significant positive correlation between the capability to activate vasoconstrictors and the T_{ty} increase rate ($r = 0.819$, $n = 7$, $p < 0.005$).

was significantly reduced by $0.11 \pm 0.02^\circ\text{C}$ at the T_{ty} trough (at 45.5 ± 2.7 min) ($p < 0.001$, $n = 8$).

3.2. Sudomotor and sweat rate

The sweat rate at the hairy skin (non-heated lateral calf) was lowered below the threshold level (Fig. 1), while sweating in the sole exhibited various patterns. There was an increase in accordance with T_{ty} increase in some subjects, while increases were associated with a decrease in T_{ty} in other subjects, or no sweating was observed until the end of sole heating in others. The sudomotor SSNA showed no significant changes during sole heating, despite significantly higher sudomotor SSNA in the tibial than in the peroneal nerve ($p < 0.0001$).

3.3. Relationship between vasoconstrictors and tympanic temperature (T_{ty})

In eight subjects in whom SSNA recordings were successful, the time delay from vasoconstrictor suppression to T_{ty} decrease (4.1 ± 0.6 min, $n = 8$), and from vasoconstrictor activation to T_{ty} increase (11.3 ± 1.3 min, $n = 8$) during the sole heating exhibited interindividual differences. A significant positive correlation was observed between the vasoconstrictor reduction rate and the time delay from vasoconstrictor suppression to the T_{ty} decrease (Fig. 2A, $r = 0.752$, $n = 8$, $p < 0.05$).

Although one of the subjects was excluded as sole heating was terminated before the T_{ty} rise, the capability to activate vasoconstrictors was inversely related to the time delay from vasoconstrictor activation to the T_{ty} increase (Fig. 2B, $r = -0.856$, $n = 7$, $p < 0.05$).

A significant positive correlation was observed between the capability to suppress vasoconstrictors and the T_{ty} decrease rate (Fig. 2C, $r = 0.795$, $n = 8$, $p < 0.05$).

There was a significant positive correlation between the capability to activate vasoconstrictors and the T_{ty} increase rate after T_{ty} began to increase during sole heating (Fig. 2D, $r = 0.819$, $n = 7$, $p < 0.005$).

3.4. Relationship between T_{ty} and vasoconstrictors

We analyzed the effects of T_{ty} on the capability to activate SSNA as defined above. The T_{ty} decrease rate was inversely related to the capability to activate vasoconstrictors ($r = -0.839$, $p < 0.05$). However, there was no significant correlation between the magnitude of difference between the peak and trough in T_{ty} and the capability to activate vasoconstrictors ($r = 0.737$, $p = 0.06$).

4. Discussion

The present study demonstrated that localized heating of the sole of the foot to 40°C induced (1) vasoconstrictor

suppression at 3.4 ± 1.1 min, (2) a decrease in tympanic temperature (T_{ty}) as core temperature at 7.5 ± 0.6 min, (3) vasoconstrictor activation at 33.4 ± 2.2 min, (4) an increase in T_{ty} at 45.5 ± 2.7 min, after sole heating. Moreover, we found that (1) the capability to suppress vasoconstrictors showed positive correlations with time delay from vasoconstrictor suppression to the T_{ty} decrease (as shown in Fig. 2A) and T_{ty} decrease rate (Fig. 2B), (2) the T_{ty} decrease rate was inversely related to the capability to activate vasoconstrictors, and (3) the capability to activate vasoconstrictors was inversely related to the time delay from vasoconstrictor activation to the T_{ty} increase (Fig. 2C) and a positive correlation with the T_{ty} increase rate (Fig. 2D). This is the first study examining that T_{ty} and neural control of skin circulation interact with each other during sole heating and showing that the T_{ty} initial drop is closely related to vasoconstrictor suppression.

The responses to sole heating could be divided into two phases: a primary response involved vasoconstrictor suppression and an initial T_{ty} drop induced by sole heating (disturbance), and a secondary response (> 45 min) involved a protective response of human thermoregulatory function against the drop in T_{ty} .

4.1. Primary response

The T_{ty} initial drop continued for 45 min on average after sole heating. Although this initial drop was consistent with previous studies showing progressive increases in forearm blood flow after the initiation of heating (Wyss et al., 1974, 1975; Johnson et al., 1976), no study has focused on the T_{ty} initial drop in relation with the capability to suppress vasoconstrictors in humans. Local heating is known to induce vasodilatation in the lower limbs due to suppressed vasoconstrictor tone (Lewis and Pickering, 1931; Gibbon and Landis, 1932; Roddie and Shepherd, 1955) and hypothermia has been attributable to peripheral vasodilatation which increases heat loss (Sessler et al., 1991), but the relationship between sympathetic nerve activity controlling thermoregulatory effector response and core temperature during local heating has never been examined. In the present study, there was a significant correlation between the capability to suppress vasoconstrictors and the T_{ty} decrease rate (Fig. 2C). This study confirmed that the drop in core temperature is closely related to suppression of neural sympathetic outflow to the skin. Thus, T_{ty} initial drop was probably due to sympatho-suppression-induced vasodilatation which increases the heat loss to the environment. Moreover, although there were marked interindividual differences in the time delay from vasoconstrictor suppression to the T_{ty} decrease, a significant correlation between the capability to suppress vasoconstrictors and the delay in the T_{ty} decrease (Fig. 2A) indicates that greater vasoconstrictor suppression is associated with a shorter onset of the drop in T_{ty} . These results suggest that this capability is a determinant factor in thermoregulatory function in humans.

Vasoconstrictor activation (33 min) and a subsequent T_{ty} rise (45 min) were observed with a time delay (11 min in average). The T_{ty} decrease rate before the trough was inversely related to the capability to activate vasoconstrictors, indicating that a greater drop in core temperature is associated with greater activation of vasoconstrictors. This T_{ty} decrease stimulates the cold neurons in the hypothalamus, and induces generalized vasoconstriction to reduce heat loss from the skin, which was indicated by generalized vasoconstriction by cold saline infusion (Snell, 1954). The present study confirmed that this was mediated through sympathoexcitation to the skin. However, no significant correlation was observed between the magnitude of reduction in T_{ty} and the capability to activate vasoconstrictors, whereas correlation was shown in our previous generalized cooling study (Sawasaki et al., 2001). These findings indicate that the decrease rate, rather than the magnitude of the drop in core temperature, may contribute to the capability to activate vasoconstrictors. Since the observed initial drop in T_{ty} was so small that the subjects could not detect it, we assume that this secondary response is one of the negative feed forward regulations that control human core temperature before it changes significantly.

4.2. Secondary response

We observed a significant positive correlation between the capability to activate vasoconstrictors and the increase rate of the core temperature (Fig. 2D), which indicated that a greater activation of vasoconstrictors is associated with a greater increase in core temperature. This is consistent with a previous study showing a significant positive correlation between the activation rate of vasoconstrictors and core temperature rise during localized cooling (Sawasaki et al., 2001). Since thermoregulatory vasoconstriction is also known to reduce heat loss and to impair core cooling (Sessler et al., 1990, 1992; Kurz et al., 1995a,b; Sessler, 2000), the T_{ty} rise may be due to decreased heat loss to the environment through sympathoexcitation-induced vasoconstriction. Moreover, the capability to activate vasoconstrictors was inversely related to the time delay from vasoconstrictor activation to the T_{ty} rise (Fig. 2B), showing that the greater the vasoconstrictor activates, the shorter the onset of the T_{ty} rise. These results indicate that the capability to control vasoconstrictor is one of the most important processes for maintaining core temperature in human thermoregulatory function. The delay from vasoconstrictor activation to the T_{ty} increase was calculated as 11 min, which is also compatible with the previous result of 10 min on average (Sawasaki et al., 2001). These phenomena suggest that it takes approximately 11 min for sympathetic activation to be reflected in the core temperature.

Sweating at the sole of the foot (glabrous skin) is considered to be mental sweating (Ogawa, 1975; Kuno, 1956; Kerslake, 1972), and that at the hairy skin is thought

to represent thermal sweating (Nakayama and Takagi, 1959; Sugeno et al., 1990). The sudomotor nerve activity in the peroneal nerve was enhanced with the increase in core temperature, but there was no sweating response in the hairy skin, since T_{ty} did not exceed the pre-heated value.

In conclusion, human thermoregulatory function is largely dependent on the suppression and activation capability of vasoconstrictor, although there are large interindividual differences in the time course of responses to local heating of the sole. Further analyses of the interrelations between sudomotor and vasoconstrictor nerve activities in maintaining the core temperature should be projected in future studies.

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