

Skin sympathetic neuroeffector response is attenuated dose-dependently by systemic prostaglandin E1 injection in humans

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Abstract

To clarify the effects of prostaglandin E1 (PGE1) on the vasoconstrictive responses, we compared the correlation between the amplitude of integrated skin sympathetic nerve activity (SSNA) and per cent reduction in skin blood flow (SBF) before and after the infusion of lipo PGE1 and placebo (bolus one-shot infusion, single blind study), and constant rate infusion of PGE1 (10 and 50 ng kg⁻¹ min⁻¹ by infusion pump, dose-dependency study) in ten healthy men. SSNA was recorded microneurographically from the median nerve simultaneously with SBF by laser Doppler flowmetry at the index fingertip. The measurement was conducted 30 min after injection of lipo PGE1 or placebo, and during the drip infusion of 10 and 50 ng kg⁻¹ min⁻¹ of PGE1 with maneuvers to enhance SSNA. The resting and activated skin blood flow were not significantly different between 10 ng lipo PGE1 and placebo administration, and between baseline and 10, 50 ng kg⁻¹ min⁻¹ of PGE1 injection. The vascular response, defined as the slope of regression line between logarithm of amplitude of integrated SSNA bursts and the reduction in SBF, was significantly suppressed by injection of lipo PGE1 as compared with that by placebo. It was also decreased dose-dependently by the constant rate infusion of PGE1 (10 and 50 ng kg⁻¹ min⁻¹). We concluded that the intravenous injection of PGE1 attenuates vasoconstrictive responses to SSNA, and analysis of the relations between SSNA and vasoconstrictive response, i.e. the neuroeffector response, is suggested to be an important tool to assess the drug effect. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

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Effectiveness of vasodilator agents in humans is difficult to evaluate. Prostaglandin E1 (PGE1) has been shown to be a potent vasodilator [8], and has been utilized in the treatment of arteriosclerosis obliterans [7], erectile dysfunction [4,8,9], blood pressure control during general anesthesia [3], and treatment of pulmonary hypertension in lung-transplant patients [12,14], while infusion of PGE1 in healthy humans does not necessarily induce cutaneous vasodilatation or hypotension [16]. The reason for the lack of apparent vasodilatation or hypotension is unknown; however, compensation by enhanced vasoconstrictive skin sympathetic nerve activity might be one of the contributory factors for this phenomenon.

Recent advances in electrophysiological techniques have

made it possible to record vasoconstrictive skin sympathetic nerve activity directly [10,11]. We have previously shown that this activity is closely related to sweat expulsion and peripheral skin blood flow (SBF) reduction with a certain latency [6], and hypothesized that it may be possible to evaluate vasodilators by analyzing the altered relationship between this vasoconstrictive sympathetic nerve activity and SBF reduction [6].

In the present study, we examined how this potent vasodilator alters the vasoconstrictive action of sympathetic nerve activity in healthy humans.

Ten healthy male medical students (age, 21 ± 2 years; height, 168 ± 2 cm; weight, 64 ± 2 kg; mean ± SE) served as subjects. All subjects were assessed as healthy without cardiovascular, diabetic, renal, or any connective tissue diseases. None of the subjects has the habit of smoking, alcohol, or any recreational drugs. Each subject gave their informed consent after a complete explanation of the testing

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procedures in a written form. The protocol was approved by the Committee of Human Research, Research Institute of Environmental Medicine, Nagoya University.

The subjects were required to lie on a bed in a dark and quiet room at an ambient temperature of 25°C. Skin sympathetic nerve activity (SSNA) innervating to the palm and fingertips of the thumb, index and middle fingers was recorded microneurographically. A tungsten microelectrode with a tip diameter of 1 μm , and impedance of 3–5 M Ω was inserted into the skin fascicle of the median nerve. The criteria for identification of the nerve activity were described elsewhere [10]. Briefly, the nerve 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 deep breathing.

The nerve action potentials were fed into a preamplifier ($\times 20\,000$, Kohno Instrument, 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 SSNAs were simultaneously monitored on a loud speaker. Nerve signals were discriminated to determine the 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). The ventilated capsule method (Kenz-Perspiro, Suzuken, Nagoya) and laser Doppler flowmetry (ALF 21, Advance, Tokyo) were employed to differentiate the SSNA burst into sudomotor or vasoconstrictor nerve activity with the probes at the finger tips ipsilateral to microneurography. All data were stored in a multichannel FM tape recorder (Sony-Magnescape KS-616U). In the blind study, one-shot injection of lipo prostaglandin E1 (PGE1), a slow releasing PGE1, and placebo was compared. In the dose-dependency study, a scalp needle catheter was inserted into the cubital vein, which was connected to an infusion pump (Terumo, Tokyo) for infusion of PGE1 at a constant rate.

After the subjects rested in a relaxed state for >30 min, baseline data were collected for 30 min. Activating maneuvers, i.e. mental arithmetic, sudden deep inspiration, sound

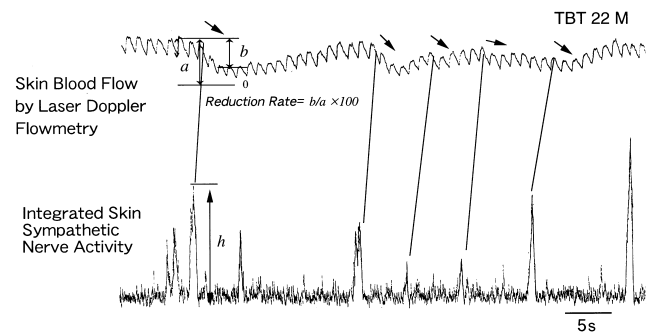


Fig. 1. Relationship of skin sympathetic nerve bursts and skin blood flow reduction. Reduction of skin blood flow was observed after SSNA bursts with specific latency.

stimulation by firing a starting pistol, and electrical stimulation of the tibial nerve at the medial retromalleolar region were loaded to activate the SSNA bursts. Since PGE1 loses its activity after passing through the lung, PGE1 enveloped in lipo-microspheres (lipo PGE1) was employed to observe the differences between the active and placebo agents due to its capability of slow release. One-shot injection of lipo PGE1 or placebo was performed on separate days, and activating maneuvers were loaded again 60 min after injection to compare the effects of PGE1 in the resting state (single blind study). On a separate day, the subjects received intravenous injection of PGE1 at a dose of 10 $\text{ng kg}^{-1} \text{min}^{-1}$, and the activating maneuvers were again loaded to induce SSNA bursts. After more than 60 min of rest, PGE1 injection was increased to a dose of 50 $\text{ng kg}^{-1} \text{min}^{-1}$ followed by the activating maneuvers (dose-dependence study) to obtain a constant rate of infusion. The recovery measurement was performed after >60 min of resting supine position.

The height of integrated vasoconstrictive bursts (SSNA amplitude) and correspondent reduction in SBF were plotted, and the correlation coefficients between two parameters were compared. The reduction in SBF was calculated as $(1 - (\text{SBF after stimulation})/(\text{SBF before stimulation})) \times 100$ (Fig. 1). As for the comparison of tympanic temperature and SSNA, the averaged tympanic temperature for 1 min and per cent increase or decrease in total SSNA (sum of the areas under the integrated SSNA trace) in the same period (1 min) was plotted to analyze the correlation between the core temperature and SSNA. The

Table 1

Changes in mean blood pressure, heart rate, skin temperature, tympanic temperature, SBF and SSNA burst rate

	Baseline	Prostaglandin E1 10 ng/kg/min	Prostaglandin E1 50 ng/kg/min	Recovery
Mean blood pressure (mmHg)	75 \pm 10	75 \pm 11	74 \pm 10	77 \pm 10
Heart rate (beats/min)	61 \pm 6	64 \pm 6	71 \pm 8	68 \pm 8
Skin temperature ($^{\circ}\text{C}$)	29 \pm 4	29 \pm 4	29 \pm 4	29 \pm 4
Core temperature ($^{\circ}\text{C}$)	36.56 \pm 0.46	36.53 \pm 0.49	36.46 \pm 0.46	36.45 \pm 0.49
Skin blood flow (ml/min/100 g)	7.8 \pm 3.4	8.5 \pm 4.1	8.6 \pm 4.9	7.6 \pm 4.0
Skin sympathetic nerve activity (%)	100	112 \pm 21	142 \pm 37 ^a	123 \pm 31

^a $P < 0.05$ vs baseline.

results are expressed as means \pm SE, and coefficients of regression lines were analyzed. Repeated measures analysis of variance was employed to evaluate the effects of PGE1 infusion, and P -values <0.05 were considered significant.

The changes in mean blood pressure, heart rate, skin temperature, tympanic temperature, SBF and SSNA burst rate are shown in Table 1. No significant changes were observed in mean blood pressure, heart rate, skin temperature, or core temperature measured as tympanic temperature during infusion of 10 and 50 ng kg⁻¹ min⁻¹ of PGE. When tympanic temperature and SSNA were compared over a one-min period, a significant negative correlation was observed between core temperature and per cent change in SSNA in all subjects.

The SSNA burst amplitude was logarithmically distributed, and so the logarithms of amplitude of SSNA bursts and SBF reductions were analyzed, i.e. the intercept A and the slope B of (SBF reduction) = A + B \times log (amplitude of SSNA burst) were determined in each subject. The slope B here signifies the vascular response toward sympathetic neural stimulation. In the single blind study, the per cent changes in slopes were calculated in each subject before and after administration of 10 μ g of lipo PGE1 or placebo. The averaged SBF in resting state and during activating maneuvers exhibited no significant changes following injection of either lipo PGE1 or placebo. On the other hand, the logarithmic regression line between the SSNA amplitude (the amplitude of maximum SSNA burst discharge was standardized as 100) and reduction in SBF (slope B) was shifted downward by injection of lipo PGE1 (Fig. 2). The vascular response was significantly suppressed after lipo PGE1 injection, while it did not change significantly after placebo (34.9 \pm 1.2 to 35.3 \pm 1.1 ml min⁻¹ (100 g⁻¹) (SSNA amplitude)⁻¹ by placebo, 35.2 \pm 1.1 to 13.4 \pm 0.8 ml min⁻¹ (100 g⁻¹) (SSNA amplitude)⁻¹ by lipo PGE1, $F = 66.4$, $P < 0.001$, Fig. 3A). In the dose-dependency study, the logarithmic regression line between SSNA and reduction in SBF was shifted significantly by infusion of 10 ng kg⁻¹ min⁻¹ and

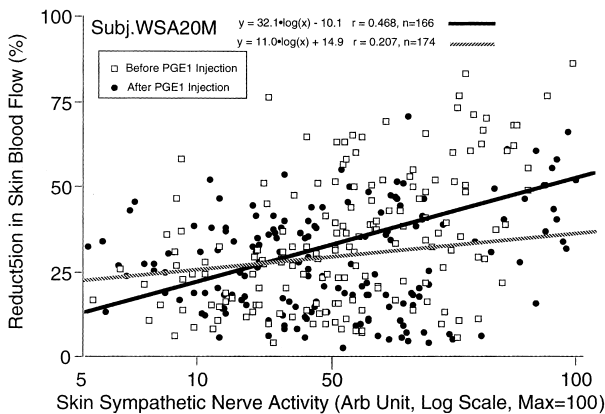


Fig. 2. Semi-logarithmic plots taking maximum SSNA burst as 100 showing the changes in the slopes of regression lines before (\square) and after (\bullet) injection of lipo PGE1. The slope of the regression line was decreased after injection of lipo PGE1.

further shift was observed following administration of 50 ng kg⁻¹ min⁻¹ of PGE1 (Fig. 4). The slope B in each subject was compared during PGE1 infusion, and was significantly decreased by 10 and 50 ng kg⁻¹ min⁻¹ infusion of PGE1 (Fig. 3B). There was a significant decrease in vascular response from the baseline (37.1 \pm 1.2) to 27.5 \pm 1.3 by 10 ng kg⁻¹ min⁻¹ and to 15.2 \pm 0.8 ml min⁻¹ (100 g⁻¹) (log(SSNA amplitude))⁻¹ by infusion of 50 ng kg⁻¹ min⁻¹ PGE1.

The present study revealed that there was a significant difference in the effector response to sympathetic vasoconstrictive stimulation between lipo PGE1 and placebo injection in a single blind study, and the vasoconstrictive response was attenuated dose-dependently by infusion of prostaglandin E1, a potent vasodilator. On the other hand, the average SBF was unchanged during activating maneuvers, and the per cent reduction in SBF was also comparable after administration of PGE1. Significant differences were also observed in core temperature rise and enhancement of resting skin sympathetic nerve activity.

In the present study, enhancement of SSNA by PGE1 without SBF change indicated that vasodilative action was compensated by activation of vasoconstrictive SSNA. This enhancement would be induced by the core temperature

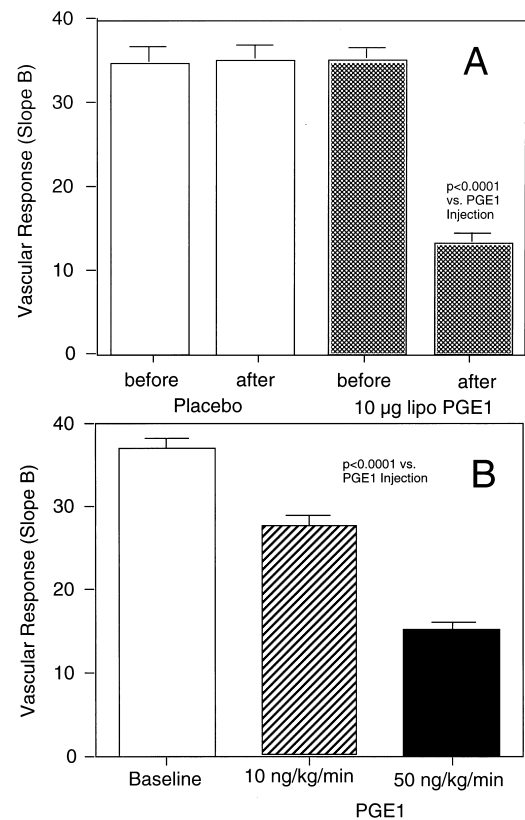


Fig. 3. Changes in vascular response by infusion of PGE1. The vascular response was significantly suppressed by infusion of 10 ng of lipo PGE1, while it was not affected by placebo (A). The vascular response was also attenuated by infusion of PGE1 in a dose-dependent manner.

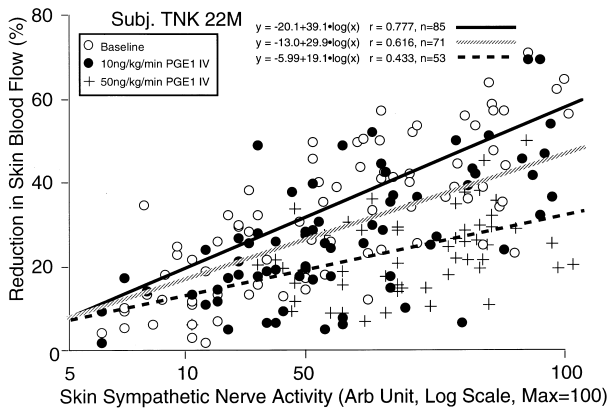


Fig. 4. Semi-logarithmic plots taking maximum SSNA burst as 100 showing the dose-dependent suppression in the slopes of regression by the infusion of PGE1. The regression lines between amplitude of skin sympathetic nerve activity (arbitrary units) and reduction in skin blood flow (%) were shown at baseline (control) level (○), when PGE1 was infused at 10 ng kg⁻¹ min⁻¹ (●), and at 50 ng kg⁻¹ min⁻¹ (+). The slope of the regression line was decreased dose-dependently by the injection of PGE1.

drop through vasodilatation-induced heat loss. Thus, PGE1 caused no changes in the traditional parameters, e.g. skin temperature or skin blood flow, although it attenuated the neuroeffector response of vasoconstrictive sympathetic nerve activity to SBF reduction, as shown by a significant difference between lipo PGE1 and placebo infusion in the single blind study, and the dose-dependent changes in the slopes of regression lines between sympathetic nerve activity and SBF reduction.

The peripheral skin blood flow has generally been measured by venous occlusion plethysmography, and this method has been well established in many studies [13]. However, SBF can be more accurately measured by laser Doppler flowmetry [2]. We have previously reported the temporal and spatial relationship between SSNA and SBF by laser Doppler flowmetry, and logarithmic relationship between the two [5,6]. The results of the present study indicated that this method to evaluate the altered relations between SSNA and SBF reduction may be utilized for the assessment of drugs that modulate neuroeffector responses, which could only be achieved by analyzing the relationships between amplitude of vasoconstrictive sympathetic nerve activity and vascular responses.

SSNA also contains sudomotor nerve activity [1,15], that could not be assessed in the present study due to the failure of sweat rate determination. It might be a limitation of the present study, and differentiation of sudomotor and vasoconstrictor nerve bursts might provide a better correlation in regression analysis, however, since we could obtain fairly well and significant results, we assumed the analysis would be beneficial. The possibility of utilizing the effector response of the sympathetic nerve activity to the sweating should be projected in the future studies.

In conclusion, the intravenous injection of PGE1 attenuates vasoconstrictive responses to SSNA, and it has been suggested that analysis of the relationships between skin sympathetic nerve activity and reduction in skin blood flow provides a new crew to assess the modulation of neuroeffector responses.

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