Mechanism of vasoconstriction in the rat's tail when warmed locally

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SAKURADA, SOHTARO, OSAMU SHIDO, AND TETSUO NAGASAKA. *Mechanism of vasoconstriction in the rat's tail when warmed locally.* J. Appl. Physiol. 71(5): 1758–1763, 1991.—The vascular response of the tail to local warming was investigated in urethan-anesthetized rats whose colonic temperature was maintained at 39.5°C with an intravenous thermode at an ambient temperature of 23°C. The tail, covered with thin latex tubing, was immersed in temperature-controlled water initially kept at 35°C. The tail was warmed by raising the water bath temperature from 35 to 44°C at a constant rate. Tail blood flow (BF), mean arterial blood pressure (BP), and tail skin temperature (T_{sk}) were measured before and during the local warming. Tail vascular conductance (VC) was computed as 100 × tail BF/BP. When T_{sk} exceeded 37°C, tail BF and VC significantly decreased from the levels at T_{sk} of 35°C, and significant reductions in tail BF and VC occurred until T_{sk} reached 42°C. Surgical deafferentation of the tail, chemical sympathectomy with 6-hydroxydopamine (100 mg/kg), and α-blockade with phentolamine (7 or 40.1–45.5 mg/kg) or phenoxybenzamine (5 mg/kg) failed to stop the decrease in tail BF and VC during the local warming. These results suggest that a reflex via the central nervous system and the α-adrenergic sympathetic nervous system is not indispensable for heat-induced vasoconstriction (HIVC). It is therefore assumed that, at least in the rat's tail, HIVC predominantly originates from a local vascular response to high temperature.

skin blood flow; spinal cordotomy; vascular conductance; α-adrenergic blockade; chemical sympathectomy; temperature

CUTANEOUS VESSELS in the distal skin area strongly dilate with warm stimulation on the skin or the central thermoreceptors, allowing a very high blood flow through the vessels to transfer heat accumulated in the body to the environment. When this region of the skin is warmed locally to temperatures above core temperature, however, vasoconstriction takes place and blood flow decreases (heat-induced vasoconstriction, HIVC). This reduction in cutaneous blood flow has been observed in human fingers (12, 13), the hindlimbs of sheep (5), and the tails of rats (20) and red kangaroos (17). Because the phenomenon clearly occurred in hyperthermic subjects and was obscure in normothermic ones (5, 13, 20), the HIVC has been interpreted as a physiological response to reduce heat gain at high local skin temperatures (12, 17). Hales et al. (5) have measured partitional blood flow through cutaneous capillaries and arteriovenous anastomoses (AVAs) in the hindlimbs of sheep during local warming and indicated that AVAs are a vascular component responsible for this characteristic HIVC.

Hirata et al. (6) have reported that, in human subjects, the reduction of finger blood flow closely relates to an increase in thermal sensation on the hand warmed locally. Nagasaka et al. (14) have shown that HIVC is evoked through increased sympathetic outflow to the resistance vessels of the finger. Moreover, Nagasaka et al. (15) observed that finger blood flow decreased simultaneously in the control hand that was not subjected to local warming, although the magnitude of the finger vasoconstriction was significantly less. These reports suggest that, at least partly, HIVC is reflexly mediated by the sympathetic nerves after perception of local thermal sensation in the central nervous system. It has been reported that local temperature also has distinct effects on the sensitivity of vascular smooth muscle to norepinephrine (8) and on vascular contractility (22). Therefore the contribution of local mechanisms to this HIVC is also suggested, but until now there have been no detailed investigations on this issue. In the present study, we attempted to examine how local mechanisms are responsible for the induction of HIVC in the tails of anesthetized rats.

METHODS

Animals and preparations. Male Wistar rats (Std:Wistar/ST), initially weighing 330–440 g, were used. Before the experiment, they were individually housed in a wire mesh cage and provided laboratory rat chow and tap water ad libitum at an ambient temperature of 24 ± 1°C with a light-dark cycle of 12:12 h (light on at 0600). Twenty-four hours before the experiment, a chemical sympathectomy was performed in five rats (CSX group) through an intraperitoneal injection with 6-hydroxydopamine hydrobromide (6-OHDA, Research Biochemicals) at a dose of 100 mg/kg (16). On the day of measurement, all rats including CSX rats were anesthetized with urethan (1 g/kg ip) and underwent an operation. An intravascular thermode (0.7 mm diam) made of a polyethylene tube with double lumen was inserted 10 cm into the inferior vena cava via the left femoral vein. A polyethylene catheter (0.7 mm diam) filled with heparinized saline (500 IU/ml) was inserted into the right common carotid artery to measure mean arterial blood pressure (BP). Another catheter filled with sterile saline was introduced into the right jugular vein for drug administration. In another five rats, the film terminale was dissected at the level of L3 to interrupt thermal input from the tail (SPD group).

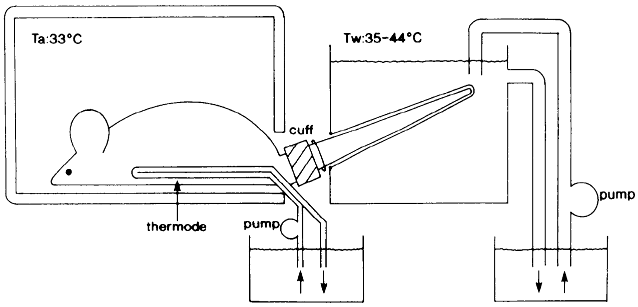

FIG. 1. Apparatus used in the present study. T_a, ambient temperature; T_w, water temperature.

After surgery, the rat was transferred to an apparatus shown in Fig. 1. The whole body except for the tail was placed in a small insulated chamber (20 × 15 × 25 cm) in which inner temperature was maintained at 33°C. The tail, covered with a blind thin latex tubing and protruding through a hole on a wall of the chamber, was immersed in a temperature-controlled water bath. To facilitate venous drainage, the tail was held on a board tilted at an angle of 12.5°. The water temperature (T_w) around the tail was initially kept at 35°C, and colonic temperature (T_{co}) was maintained at ~39.5°C with the intravenous thermode perfused with cool water at an adequate rate using a peristaltic pump. This specific T_{co} was chosen because of our preliminary observation showing that temperature of ~39.5°C produced a sufficiently constant tail BF. If necessary, additional anesthetic was injected intraperitoneally.

Procedures and measurements. After equilibrium was made in variables, phentolamine (40.1–45.5 mg/kg, Ciba-Gigy Japan, Hyogo), dissolved in sterile saline, was injected intravenously via the jugular catheter in five rats (α-BK group). In a few rats, phentolamine (7 mg/kg) or phenoxybenzamine (Research Biochemicals; 5 mg/kg) was injected. The control, SPD, and CSX groups received sterile saline as a vehicle instead of the α-adrenergic antagonists. The volume of saline injected was ~1.5 ml/animal in each group. When T_{co}, BP, and tail BF had been stabilized again, measurements commenced. After a 5-min control period, T_w was raised to 44°C in 20 min at a constant rate of 0.45°C/min.

Tail BF was measured by venous occlusion plethysmography using a temperature-compensated mercury-in-Silastic strain gauge (7, 25). The strain gauge was wound once or twice around the tail 2 cm from the radix of the tail. An occlusion cuff (1.5 cm wide) was placed at the proximal end of the tail and inflated to 40 mmHg four times every minute by switch activation of solenoid valves connected to a pressurized air tank. The changes in tail circumference were recorded on a potentiometer (SP-H6P, Riken Denshi, Tokyo), and tail BF at a standard tail volume (100 ml) was calculated.

T_{co} was measured with a thermocouple covered with a polyethylene tube inserted 6 cm into the colon. Tail skin temperature (T_{sk}) and T_w were also measured with the other thermocouples. BP was monitored with a pressure transducer (MPU-0.5, Orientec, Tokyo) via the arterial catheter. All variables except tail BF were continuously recorded on potentiometers (SP-H6P, Riken Denshi) and digitized every 30 s with a digitizer connected to a personal computer (PC9801vm, NEC, Tokyo).

After termination of the experiment, the completion of the deafferentation in the SPD group and the effect of phentolamine and phenoxybenzamine in the α-BK group were checked. The tails of SPD rats were pinched after recovery from the anesthesia. When a rat responded to the stimulus, the data for the rat were discarded from the results. The α-BK rats were quickly cooled down while T_w was kept constant, and the changes in tail BF were observed. If tail BF decreased greatly, we did not consider the data available.

Data analysis and statistics. Tail vascular conductance (VC) was calculated as 100 × tail BF/BP. The results are presented as means ± SE, and the statistical evaluation of mean values across time was performed with one-way analysis of variance (ANOVA) and paired Student's t test. The difference of mean values among groups was assessed with Scheffé's multiple comparison tests after one-way ANOVA. The level of significance was taken as $P < 0.05$.

RESULTS

Figure 2 shows an example of changes in tail BF, T_{co}, and T_{sk} in a control rat. At T_{sk} below 36°C, tail BF remained at higher levels and hardly changed. When T_{sk} reached 36°C, tail BF started to decrease and reached the minimum levels thereafter. This marked reduction in tail

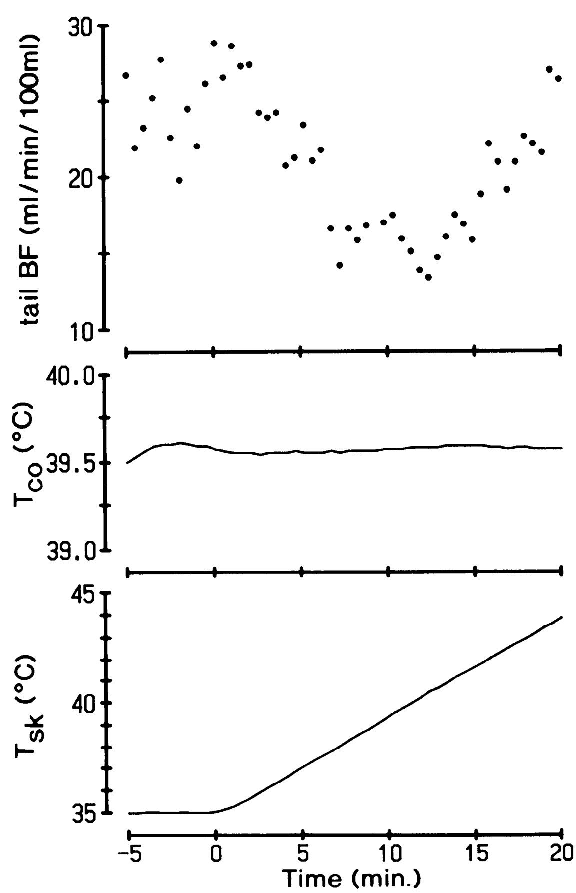

FIG. 2. Representative changes in tail blood flow (BF) and colonic temperature (T_{co}) before (*time 0*) and during tail warming. Values are means of values measured every 30 s.

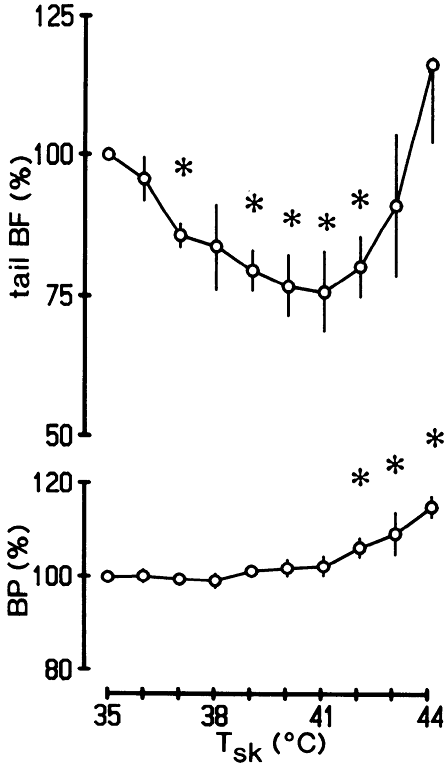

FIG. 3. Mean %changes in tail BF and blood pressure (BP) as a function of skin temperature (T_{sk}) in control group. Values are means ± SE. *Significantly different from values at T_{sk} of 35°C.

BF continued for 10 min. When T_{sk} exceeded 42°C, tail BF started to increase and returned gradually to the levels at T_{sk} of 35°C. T_{co} remained at the same level throughout the experiment. Figure 3 shows the mean percent changes in tail BF and BP as a function of T_{sk} in the control group, in which 100% corresponded to the mean value at T_{sk} of 35°C. Similar to the data shown in Fig. 2, tail BF, almost constant at T_{sk} <36°C, decreased significantly when T_{sk} was raised beyond 37°C. The level of tail BF became the lowest at T_{sk} of 41°C. Further tail warming increased tail BF, and at T_{sk} of 44°C tail BF surpassed the control level (NS). Mean BP at T_{sk} of 35°C was 102.0 ± 9.2 mmHg in this group and was maintained until T_{sk} reached 41°C. When T_{sk} was raised beyond 42°C, however, BP rose significantly.

In the SPD and CSX groups, tail BF also decreased at T_{sk} between 38 and 43°C (Fig. 4). The mean BP at T_{sk} of 35°C for the SPD and CSX groups was 79.2 ± 6.7 and 74.6 ± 5.5 mmHg, respectively. The spinal nerve dissection stopped the significant rise in BP at T_{sk} >43°C, as observed by comparison with the control rats. The α-adrenergic blockade after intravenous phentolamine or phenoxybenzamine had little effect on the reduction of tail BF during the tail warming. Tail BF started to decrease at T_{sk} of 38°C and maintained significantly lower levels to nearly the end of the experiment (Fig. 4). Mean BP at T_{sk} of 35°C in the α-BK rats (51.4 ± 2.1 mmHg) was significantly lower than that of the control group. The intravenous injections of α-blockers also interfered with the rise in BP at T_{sk} beyond 43°C, as clearly observed by comparison with the control group.

The changes in tail BF can be physically modified by a change in perfusion pressure in the region and do not necessarily indicate change in vasomotor activity in the vessels. To eliminate such an effect, tail VC was calculated. Figure 5 illustrates the changes in tail VC plotted against T_{sk} in the control, SPD, CSX, and α-BK groups. In all groups, tail VC started to decrease at T_{sk} between 37 and 38°C, and the reductions were persistent until T_{sk} reached 42–43°C, suggesting the occurrence of vasoconstriction in the rat's tail warmed locally. The magnitude of the reduction of tail VC did not differ among the groups at any T_{sk} tested.

DISCUSSION

Local HIVC has been observed in skin areas where abundant AVAs exist (5, 12, 13, 20). Hales et al. (5) have directly measured BF in the hindlimb AVAs of sheep and indicated that they are the vascular component responsible for HIVC. There are also rich AVAs in the rat's tail (4), and HIVC could be expected. Raman et al. (20) have reported a reduction in BF in the rat's tail when warmed locally. However, because the perfusion pressure had not been measured, no direct evidence of HIVC was available. The present results clearly showed a reduction in the VC of a tail warmed locally and confirmed the existence of HIVC in rats. In most cases, the tail vasoconstriction started at T_{sk} of ~37°C and lasted until T_{sk} reached ~42°C. The observation concerning the temperature range of the occurrence in HIVC is consistent with previous reports of the hindlimbs of sheep (5) and human fingers (12, 13).

There are several reports suggesting the mechanism of HIVC in the fingers of human subjects. According to the observations made by Nagasaka et al. (15), a slight vasoconstriction simultaneously occurred in the fingers of the contralateral hand immersed in water kept at a constant temperature of 35°C, while the other hand was warmed to a temperature higher than body core temperature. Hirata et al. (6) have observed that the magnitude of finger vasoconstriction was closely related to a dynamic response of local thermal sensation and that HIVC could be suppressed when the subjects concentrated on mental calculation. From these results, they proposed that the perception of local thermal sensations in the higher levels of the central nervous system was involved in the mechanism of HIVC. In the present study, however, HIVC was still observed in the tails of rats under anesthesia. Moreover, the interruption of sensory input from the tail by surgical deafferentation failed to stop the induction of HIVC in the tail (Fig. 4), indicating that HIVC can occur without perception of local thermal sensation.

Temperature has been shown to have distinct effects on the contractility of isolated blood vessels in response to electrical stimulation and exogenous norepinephrine (NE). In canine superficial (saphenous and mesenteric) veins, contractions sensitive to electrical stimulation were attenuated by raising T_w from 35 to 42°C but were augmented in the deep (femoral) vein (22). In an isolated rat tail artery, sensitivity to NE was maximal at T_w of 32–34°C and was reduced at 42°C (23). This effect of temperature on contractility was due to a change in NE release from the sympathetic nerve endings (1) and the affinity of α-adrenoreceptors (8). If sympathetic dis-

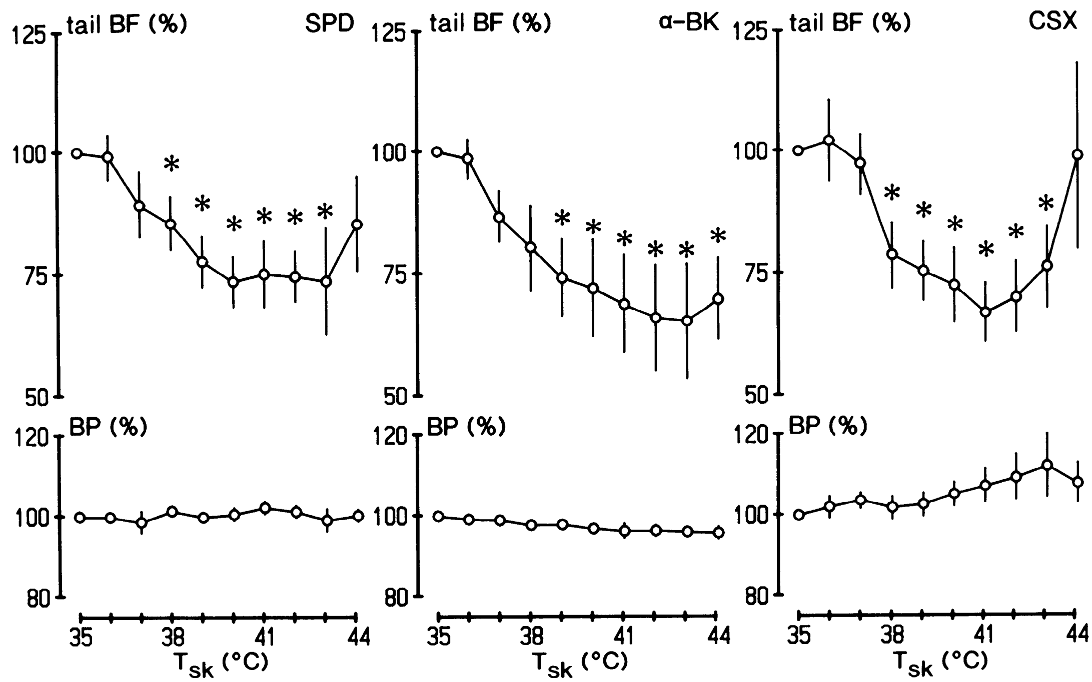

FIG. 4. Mean %changes in tail BF and BP as a function of T_{sk} in surgically deafferented (SPD), α-adrenergically blocked (α-BK), and chemically sympathectomized rat (CSX) groups. Values are means ± SE. *Significantly different from values at T_{sk} of 35°C.

charge to the vessels does not change during local warming, therefore, the regional vasomotion can differ according to the local temperature through modulation of adrenergic neurotransmission. Generally, contractile response to electrical stimulation and exogenous NE may be reduced through warming in the cutaneous vessels and act inconsistently with HIVC, but if high skin temperature evokes some reflexes to increase sympathetic activity and the release of NE in the warmed area, vasoconstriction may be observed. Nagasaka et al. (14) observed such an increase in skin sympathetic discharge when fingers were vasoconstricted with warming. O'Leary et al. (18) have observed that, in the rat's tail, sympathetic nerve stimulation after a complete α-adrenergic receptor blockade failed to produce any change in tail VC and concluded that the rise in tail VC during whole body warming is brought about solely by the withdrawal of vasoconstrictor nerve activity. Thus, if the α-adrenergic system were completely blocked, participation of a sympathetic system in vasoconstriction could be excluded at least in the rat's tail. To check the role of sympathetic nerves in this HIVC, we performed a chemical sympathectomy with 6-OHDA, which depresses NE stored in the sympathetic nerve terminals (19), and applied sufficient doses of α-antagonists to the rats (18). Even after these treatments, HIVC occurred consistently, as observed in the control rats (Figs. 4 and 5), indicating that participation of the α-adrenergic sympathetic nervous system is not indispensable in the production of HIVC.

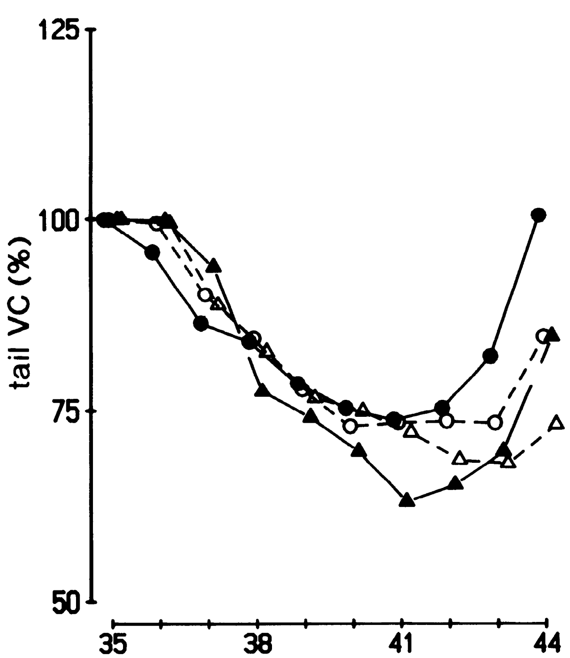

FIG. 5. Mean %changes in tail vascular conductance (VC) as a function of T_{sk} in control (●), SPD (○), CSX (▲), and α-BK (△) groups. Values are means; SEs not shown for clarity.

Vanhoutte and Lorenz (22) have studied the effects of temperature on the reactivity of isolated vein strips in dogs. Although the manipulation of temperature was rather rough, their results clearly showed that raising the bath temperature from 37 to 43°C resulted in an increase in basal isometric tension of saphenous and mesenteric vein strips and an increase in the spontaneous activity of mesenteric vein strips, whereas lowering the temperature from 37 to 29°C reduced the spontaneous activity of the mesenteric vein. Elkhawad et al. (2) have reported that tone in the isolated facial vein of desert camels increased significantly by increasing the bath temperature from 30 to 45°C. McMeeken and Bel (10) have reported that, in hyperthermic dogs, warming the blood from 40 to 44°C by means of an extracorporeal circuit increased femoral vascular resistance, which was not prevented by a sympathetic blockade. The temperature range within which vascular smooth muscle tension or vascular resistance rises seems to be comparable to that within which HIVC can be observed in several species of mammals (5, 12, 13). Although to date we have no available information concerning temperature-dependent changes in the cutaneous vascular tone of rats, it is reasonable to assume that the HIVC originates from a myogenic vascular response in the smooth muscles of the arteriole warmed locally.

A local reflex, named "axon reflex" or "axon response" (9), has been proposed as a cutaneous vasomotor control mechanism in the flare component of the triple response and in cold-induced cutaneous vasodilation. The reflex has been shown to be mediated by several neuropeptides such as substance P, vasoactive intestinal polypeptide, and neurokinin A (3). These vasoactive neuropeptides usually cause cutaneous vasodilation, however, and we do not know whether the axon reflex contributes to a vasoconstriction as strong as that observed in HIVC.

HIVC does not seem to be consistently observed in the distal skin area in mammals. Hales et al. (5) have observed HIVC in sheep when the core temperature was clamped 0.5–1.5°C above the individual's core temperature but not when it was maintained at 0.5°C below. In the rat's tail (20), HIVC was observed when T_{co} was raised to ~39°C but not when it remained at 37°C. Nagasaka et al. (13) have reported that, in human subjects, vasoconstriction of the finger heated locally was induced in the warm state but not in the cool state. Several studies have been inconsistent concerning HIVC in normothermic subjects. Webb-Peploe et al. (24) have reported that, in a vascular isolated canine hindleg that was cross-perfused at a constant flow, local cooling of one leg from 47 to 17°C caused the lateral saphenous vein to constrict. Raman and Vanhuyse (21) reported that finger BF increased when the finger was warmed locally from 20 to 40°C. All these results suggest that HIVC is distinctly observed only when the subjects are hyperthermic. As proposed by Nagasaka et al. (13), cutaneous vessels might act to reduce heat transfer from a hot environment into the body when body heat content has already been increased.

In the control rats, BP rose significantly when T_{sk} exceeded 42°C. Because such changes in BP were not observed in the SPD, CSX, or α-BK groups, the rise in BP at an extremely high T_{sk} may be reflexively mediated by the α-adrenergic sympathetic nervous system after perception of a local thermal sensation. Skin temperature >42°C seems rather high, and a further rise in temperature would stimulate heat nociceptors (26), which could result in the flight response.

When T_{sk} exceeded 42°C, tail VC started to rise (Fig. 5). The changes were consistent in all the groups tested. When local temperature rises to the level of potential tissue damage, an increase in the local BF may be of advantage to cool down the tissue, inasmuch as arterial blood temperature is quite a bit lower than the warmed tissue temperature. The vasodilation observed at T_{sk} of 43–44°C may be the result of a tissue-protecting mechanism rather than the thermoregulatory response.

In summary, VC in the tail of anesthetized rats decreased when the tail was warmed to 37–42°C. This fall in VC was consistent even after surgical deafferentation of the tail, chemical sympathectomy, and the pretreatment of α-antagonists. Thus a direct constrictor effect of high temperature on the tail vessels is the mechanism for decreasing tail BF; however, as observed in human fingers, the constrictor response may also include a central vasomotor mechanism when the animals are in unanesthetized conditions.

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