Capsaicin activates heat loss and heat production simultaneously and independently in rats

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Kobayashi, Akiko, Toshimasa Osaka, Yoshio Namba, Shuji Inoue, Tai Hee Lee, and Shuichi Kimura. Capsaicin activates heat loss and heat production simultaneously and independently in rats. Am. J. Physiol. 275 (Regulatory Integrative Comp. Physiol. 44): R92–R98, 1998.—Subcutaneous administration of capsaicin (5 mg/kg) immediately increased the temperature of the tail skin (Tsk) for 2 h in urethan-anesthetized rats, suggesting an increase in heat loss. O2 consumption, an index of heat production, also immediately increased after the capsaicin injection, and this increase lasted for >10 h. Colonic temperature (Tco) decreased within 1 h after the injection, and this decrease was followed by a long-lasting hyperthermic period. Adrenal demedullation largely attenuated the capsaicin-induced increase in O2 consumption, and sympathetic denervation of the interscapular brown adipose tissue partly attenuated the increase in O2 consumption. However, capsaicin-induced heat loss was normal in these rats. In rats with cutaneous vasodilation maximized by warming and administration of hexamethonium, capsaicin did not further increase Tsk but normally increased within 1 h after the injection, and this decrease was followed by a long-lasting hyperthermic period. Adrenal demedullation largely attenuated the capsaicin-induced increase in O2 consumption, and sympathetic denervation of the interscapular brown adipose tissue partly attenuated the increase in O2 consumption. However, capsaicin-induced heat loss was normal in these rats. In rats with cutaneous vasodilation maximized by warming and administration of hexamethonium, capsaicin did not further increase Tsk but normally increased within 1 h after the injection, and this decrease was followed by a long-lasting hyperthermic period. Adrenal demedullation largely attenuated the capsaicin-induced increase in O2 consumption, and sympathetic denervation of the interscapular brown adipose tissue partly attenuated the increase in O2 consumption. However, capsaicin-induced heat loss was normal in these rats.

Body temperature regulation; oxygen consumption; brown adipose tissue; adrenal gland

Capsaicin, the pungent ingredient of red pepper, elicits a warm sensation at its threshold concentration and produces a burning pain at higher concentrations. The receptors of capsaicin are located mainly on primary sensory neurons in the dorsal root, trigeminal, and nodose ganglia (25). Capsaicin-sensitive neurons respond to warmth and noxious sensory stimuli, including heat, mechanical, and chemonociceptive signals (27). They transmit these signals to the central nervous system and are critically involved in the pain system. Therefore, the actions of capsaicin have resulted in considerable interest in the use of capsaicin or capsaicin analogs for pain therapy (6). Moreover, capsaicin has unique thermoregulatory actions.

Intracerebral or subcutaneous administration of capsaicin induces a fall in body temperature accompanied by heat loss responses such as cutaneous vasodilation (13, 15, 26, 29). However, administration of a high dose of capsaicin makes animals insensitive to the hypothermic effect of a subsequent injection, a phenomenon known as capsaicin desensitization (15, 26, 29). An injection of capsaicin (1–50 mg/kg sc) elicited a dose-dependent fall in body temperature for 2–5 h followed by a hyperthermic phase lasting for 1–2 days (26). In this dose range a larger amount of injected capsaicin induced a higher hyperthermic response and a larger degree of desensitization. Therefore, it has been speculated that the prolonged hyperthermic effect observed 1–2 days after the capsaicin treatment is linked to the process of desensitization of warm receptors and that the early increase in body temperature represents a regulatory response to the hypothermia (26).

On the other hand, it has been reported that systemic administration of capsaicin immediately increases O2 consumption, indicating stimulation of heat production (17). The response was suggested to be mediated by enhanced adrenal sympathetic activity through catecholamine secretion from the adrenal medulla (30, 31). Catecholamine secretion also increased immediately after capsaicin administration (31). Therefore, it seems difficult to explain the capsaicin-induced increase in heat production by the regulatory response to the hypothermia or by the desensitization.

From the physiological viewpoint of body temperature regulation, heat loss and heat production work in the opposite direction and usually do not facilitate simultaneously. For example, animals exposed to a cold environment activate heat production and inhibit heat loss to keep body temperature stable. Therefore, it seems paradoxical that capsaicin simultaneously induces heat loss and heat production. However, the relationship between heat loss and heat production induced by capsaicin has not been examined. To clarify this relationship, we simultaneously recorded O2 consumption, an index of heat production, tail skin temperature (Tsk), an index of heat loss response, and colonic temperature (Tco). Moreover, to determine the causal relationship between heat loss and heat production, we prevented changes in heat loss or heat production in rats before administration of capsaicin: Adrenal-demedullated rats were used to attenuate the capsaicin-induced heat production, and warmed and hexamethonium-treated rats were used to minimize the change in capsaicin-induced heat loss.

Although capsaicin stimulates adrenal catecholamine release, the major anatomic localization of thermogenesis is unknown. The site of thermogenesis by ephedrine has been identified as skeletal muscle in humans (2). Brown adipose tissue (BAT) is the site of regulatory nonshivering thermogenesis (8) and of diet-induced thermogenesis (21) in rodents. The liver is also the main site of diet-induced thermogenesis in cafeteria-fed rats (18). Thus we measured the change in the
temperature of muscle, interscapular BAT (IBAT), and liver after capsaicin injection to determine the site of heat production. The participation of BAT in capsaicin-induced thermogenesis was also assessed by cutting of the sympathetic nerves innervating IBAT.

METHODS

Animals and drugs. Male Wistar rats, weighing 250–300 g, were housed in a room maintained at an ambient temperature of 24 ± 1°C with a 12:12-h light-dark cycle. They had free access to standard chow diet and water.

Just before the experiments the rats were anesthetized with urethane (1.5 g/kg) and kept on a heating pad to maintain their body temperature at ~36–37°C during the experiment, unless otherwise noted. Capsaicin (98% purity, Sigma Chemical) was dissolved in saline containing 10% ethanol and 10% Tween 80 and injected at 5 mg/kg sc with a volume of 1 ml/kg. This dose was reported to be adequate to show the initial hypothermic and subsequent hyperthermic response in rats (26). Each rat received a single injection of capsaicin. Stable recordings were obtained for ≥2 h before administration of capsaicin. Control rats received the same amount of vehicle solution.

Temperature and O2 consumption measurements. Tco was measured with a thermistor (XN-64 probe, Technol Seven, Yokohama, Japan) inserted 6 cm beyond the anus. Tsk was measured with a small thermistor (XK-67 probe, Technol Seven) attached to the dorsal base of the tail. Temperatures of IBAT, liver, and muscle were measured with other XK-67 probes placed below the IBAT pad, between liver lobes, and into the femoral muscle of the left leg, respectively. The temperature was continuously monitored and recorded every 10 min. O2 consumption was measured by an open-circuit method. Briefly, the head of a test rat was covered with a cylindrical hood (45 mm long, 30 mm diameter) that was continuously ventilated at a constant rate of 1.0 l/min. The difference in O2 concentration between inflow and outflow air was measured with an O2 analyzer (model LC700E, Toyo). O2 consumption was recorded at 1-min intervals. The results were expressed in terms of metabolic mass (kg0.75).

Adrenal demedullation. Bilateral adrenal demedullation was done under anesthesia with ketamine (50 mg/kg ip) and isoflurane (1%) in air at 6 wk of age. After demedullation the animals received the antibiotic benzylpenicillin (50,000 IU/kg im) and were used for experiments 1–4 wk later. At the end of experiments, blood was collected for catecholamine analysis. Rats with plasma epinephrine concentration ≥0.05 ng/ml were excluded, inasmuch as they were considered to represent failed adrenal demedullation.

IBAT denervation. Rats were anesthetized with pentobarbital sodium (50 mg/kg ip) 4–5 days before the experiments. Five intercostal nerves on each side were cut bilaterally to surgically denervate IBAT. The incision was closed with surgical silk, and the rats then received benzylpenicillin.

Capsaicin desensitization. For capsaicin desensitization, rats received increasing doses (15, 30, and 60 mg/kg sc) of capsaicin on 3 consecutive days, and experiments were done within 1 wk.

Hexamethonium treatment. The temperature of the heating pad was increased to maintain a Tsk of 33–34°C, and hexamethonium dichloride (5 mg/kg ip) was administered 15 min before the capsaicin injection to block the transmission of autonomic ganglia. These procedures were done to maximize the cutaneous vasodilation before the administration of capsaicin.

Statistical analysis. Values are means ± SE at 10-min intervals. O2 consumption was analyzed at 1-min intervals, but SE is shown at 10-min time points for clarity. Tco and O2 after the capsaicin injection were evaluated by Friedman’s repeated-measures ANOVA. Dunnett’s test was used for multiple comparisons. Changes in organ temperature were compared by one-way repeated-measures ANOVA followed by Tukey’s test for multiple comparisons. Differences between two groups were compared by the Mann-Whitney test. Statistical significance was defined by P < 0.05.

RESULTS

O2 consumption immediately and significantly increased above the baseline value at 6 min after capsaicin injection, and the increase continued and reached a peak of 17.2 ± 0.4 ml·min⁻¹·kg⁻⁰·⁷⁵ (n = 8) at 50 min (Fig. 1, top). The significant increase continued for >10 h. Contrary to the increase in O2 consumption, Tco immediately decreased; the decrease continued for 10–90 min (average decrease = 0.37 ± 0.09°C at 40 min) after the injection (Fig. 1, middle), and Tco subsequently increased beyond the baseline level from 120 to 430 min. Tsk significantly increased at 10 min after the injection, and the increase continued and reached a peak of 3.12 ± 0.45°C at 50 min (Fig. 1, bottom). Tsk returned to the baseline level within 120 min. Administration of vehicle solution alone (n = 6) had no effect on O2 consumption, Tco, or Tsk (Fig. 1, thin lines).

Adrenal-demedullated rats showed a baseline O2 consumption similar to that of intact rats. Although they showed slightly increased O2 consumption at 10 min after the capsaicin injection, the increase reached a peak of only 15.0 ± 0.7 ml·min⁻¹·kg⁻⁰·⁷⁵ (n = 5) at 60 min (Fig. 2, top); it was significantly smaller than that of intact rats. Tsk increased by 3.60 ± 0.67°C (Fig. 2, bottom), which was similar to that of intact rats, resulting in a fall of Tco by 0.76 ± 0.21°C (Fig. 2, middle); however, Tco did not subsequently increase above the baseline.

In rats maintained with Tsk at 33–34°C by warming and hexamethonium administration, no further rises in Tsk were induced by capsaicin (Fig. 3, bottom). However, O2 consumption immediately increased with a time course similar to that of intact rats and reached a peak of 18.7 ± 0.6 ml·min⁻¹·kg⁻⁰·⁷⁵ (n = 5) at 35 min (Fig. 3, top). The increase was 14.2 ± 1.0% above the baseline and comparable to that found in intact rats. Tco gradually rose without a hypothermic period and maximally increased by 0.64 ± 0.08°C (Fig. 3, middle). O2 consumption did not increase above the baseline (Fig. 4, top) in capsaicin-desensitized rats (n = 4), although the baseline O2 consumption, Tsk, and Tco were similar to those of intact rats. Tco did not change after capsaicin injection (Fig. 4, middle). A small increase in Tsk was observed, but it was not statistically significant (Fig. 4, bottom).

In rats with IBAT denervation, O2 consumption immediately increased after the injection and reached a peak of 16.4 ± 0.5 ml·min⁻¹·kg⁻⁰·⁷⁵ (n = 4) at 60 min. No difference was observed in the initial increase between intact and IBAT-denervated rats. However, O2 consumption of denervated rats rapidly returned to the
Baseline level, and subsequently it was significantly lower than that of intact rats from 240 to 450 min (Fig. 5, top).

A biphasic temperature change in three organs (IBAT, muscle, and liver) occurred in parallel with that of Tco after capsaicin administration in intact rats, and changes in these temperatures showed no difference (data not shown). To exaggerate the differences in organ temperature, we recorded temperatures in rats in which capsaicin-induced heat loss was minimized by warming and hexamethonium administration. Changes in the temperature of these organs were almost identical during the first 3 h after the capsaicin injection (Fig. 5, bottom). Thereafter, the increase in IBAT temperature was significantly higher than in the liver at 240–570 min and that in the muscle at 280–570 min (Fig. 5, bottom).

**DISCUSSION**

Capsaicin-induced heat loss and heat production. In the present study we confirmed previous results showing that capsaicin induced a prompt reduction in body temperature (Tco), which was followed by a prolonged

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**Fig. 1.** O2 consumption, colonic temperature (Tco), and skin temperature (Tsk) after capsaicin (5 mg/kg sc, thick lines; n = 8) or vehicle injection (thin lines; n = 6) in intact rats. Capsaicin induced a simultaneous increase in O2 consumption and Tsk. Tco initially decreased, and the decrease was followed by a long-lasting hyperthermic period. Arrow, time of drug injection. *Significantly different from baseline at time 0 in capsaicin-treated rats (P < 0.05). Vehicle injection had no effect on O2 consumption or temperature.

**Fig. 2.** Attenuation of capsaicin-induced thermogenesis in adrenal-demedullated rats (n = 5). Note normal increase in Tsk and monophasic decrease in Tco. Arrow, capsaicin injection. *Significantly different from preinjection value. †Significant difference between intact and adrenal-demedullated rats (P < 0.05).
elevation of body temperature (26). The increase in heat loss accompanied by cutaneous vasodilation after the capsaicin injection, as indicated by the rise in Tsk, probably accounts for the decrease in Tco. However, capsaicin simultaneously increased O2 consumption, indicating activation of heat production. The increase in Tsk stopped within 2 h after the injection, whereas the increase in O2 consumption lasted for >10 h. Accordingly, the biphasic Tco response induced by capsaicin can be explained by the sum of heat loss and heat production: the effect of heat loss predominated during the initial 2 h, and that of heat production emerged after the end of heat loss. Thus our results show that hyperthermia is not a regulatory response to the hypothermia, nor is it the result of desensitization of warm receptors.

Watanabe et al. (31) showed that capsaicin enhanced adrenal sympathetic nerve activity and catecholamine secretion from the adrenal medulla. They also showed that pretreatment with a β-blocker, propranolol, prevented the capsaicin-induced increase in O2 consumption (17). Consistent with their results, the capsaicin-
induced increase in O$_2$ consumption was remarkably attenuated in adrenal-demedullated rats in the present study. Therefore, the capsaicin-induced heat production was mainly mediated by catecholamine release from the adrenal medulla. The adrenal-demedullated rats showed the transient hypothermia accompanied by a rise in $T_{sk}$ but did not show the subsequent hyperthermia. The results demonstrated that capsaicin effectively induced heat loss in these rats and that heat production was not affected by the capsaicin-induced heat loss and hypothermia. Similarly, the increase in $T_{sk}$ was not caused by the increase in heat production.

Cutaneous vasodilation is an important thermoregulatory response against hyperthermia in a hot environment. Large increases in tail blood flow in rats occur via reduction in sympathetic vasoconstrictor tone of the skin (20). To prevent the capsaicin-induced change in cutaneous vasomotor tone, we maximized vasodilation by warming and administration of a ganglion blocker, hexamethonium. This procedure increased $T_{sk}$ to a steady level of 33–34°C, and administration of capsaicin did not further increase $T_{sk}$ in these rats. In this condition, the capsaicin-induced heat production did occur to the extent similar to that in intact rats, showing stimulation of heat production without heat loss. Consequently, the body temperature gradually rose without the hypothermic period. The results demonstrated that heat production was not caused by the hypothermia.

Two independent systems for body temperature regulation. Capsaicin simultaneously increased heat loss and heat production, and suppression of one response did not affect the other. These results suggest that capsaicin activated two independent systems that regulate heat loss and heat production. Under physiological conditions, it is assumed that systems responsible for heat loss and heat production have reciprocal inhibition (3, 5). This assumption is based on the fact that heat loss and heat production do not overlap in the normal body temperature regulation. However, the present results demonstrate that capsaicin stimulates the systems regulating heat loss and heat production simultaneously and independently, such that they have no reciprocal inhibition.

Activation of the capsaicin-sensitive warm receptor probably accounts for the heat loss responses and hypothermia. What kind of sensory neurons participate in the heat production? Rats treated with large doses of capsaicin showed impaired heat defense responses, whereas the cold defense responses remained unchanged (14, 28). Specific cold fibers were not influenced by capsaicin desensitization (11). These findings suggested that large doses of capsaicin impair peripheral and central warm receptors but do not affect specific cold receptors. In the present study, desensitized rats did not increase $O_2$ consumption after capsaicin injection. Thus capsaicin-induced heat production is not attributable to the activation of specific cold receptors. Therefore, capsaicin-induced heat production may have a physiological significance in a system other than temperature regulation. Capsaicin excited nociceptive fibers that are sensitive to mechanoheat and mechanocold in the skin (23) and in the cornea (9). Cutaneous noxious stimuli reflexly enhanced adrenal sympathetic nerve activity and catecholamine secretion. Stimulation of the nociceptors and pain system also facilitates the production of corticotropin-releasing factor. Intracerebroventricular administration of corticotropin-releasing factor produces prolonged elevation of plasma concentration of catecholamine and increases $O_2$ consumption (4). Thus the pain-and-stress system may cause the activation of heat production, although "stress hyperthermia" has usually been observed after...
exposure to a psychological, rather than a physical, stressor (19, 24).

Two different capsaicin receptors were found in the perfused hindlimb preparation: one stimulates and the other inhibits O2 consumption (7). Thus we speculate that nociceptors and warm-sensitive fibers may have different receptors, although we have no evidence.

Sites for capsaicin-induced thermogenesis. Changes in temperatures of IBAT, muscle, and liver were almost identical within 3 h after capsaicin administration. The results suggest that these tissues equally contributed to the thermogenesis or that tissues other than these are responsible for the thermogenesis. However, IBAT denervation attenuated the capsaicin-induced increase in O2 consumption in a period when changes in IBAT temperature were higher than those of liver and muscle. Thus the results suggest that capsaicin-induced heat production occurred partly in IBAT via sympathetic nerves. The issue of the heat production site by capsaicin requires further investigation.

Perspectives

Body temperature is frequently considered to be regulated around a hypothetical “set point” (10). Displacement of the set point is generally used for an explanation of the regulatory changes in body temperature. For example, fever can be explained by an elevation of the set point, resulting in an increase in heat production and a decrease in heat loss. However, the present study demonstrates simultaneous and independent activation of heat loss and heat production. Thus the results cannot be ascribed to changes in a single set point.

The apparent set temperatures of various autonomic effector responses, such as shivering, vasomotor, and sweating, are not identical (12). Satinoff (22) and Kanosue et al. (16) summarized their observations showing separate and independent circuits from the thermal detectors to the autonomic or motor effectors. There is a possibility that the temperature regulation system does not have a particular set point as a thermostat. The set point probably reflects a consequence of dynamic balance of multiple thermoregulatory responses. Moreover, although they suggested the synergistic control of body temperature by the multiple parallel circuits, the present results showed that the system could behave paradoxically. The physiological significance and neural mechanisms of the present observations are open questions.

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