

Effects of CH-19 Sweet, a Non-Pungent Cultivar of Red Pepper, on Sympathetic Nervous Activity, Body Temperature, Heart Rate, and Blood Pressure in Humans

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We investigated the changes in autonomic nervous activity, body temperature, blood pressure (BP), and heart rate (HR) after intake of the non-pungent pepper CH-19 Sweet and of hot red pepper in humans to elucidate the mechanisms of diet-induced thermogenesis (DIT) due to CH-19 Sweet. We found that CH-19 Sweet activates the sympathetic nervous system (SNS) and enhances thermogenesis as effectively as hot red pepper, and that the heat loss effect due to CH-19 Sweet is weaker than that due to hot red pepper. Furthermore, we found that intake of CH-19 Sweet does not affect systolic BP or HR, while hot red pepper transiently elevates them. These results indicate that DIT due to CH-19 Sweet can be induced *via* the activation of SNS as well as hot red pepper, but that the changes in BP, HR, and heat loss effect are different between these peppers.

Key words: capsiate; capsaicin; humans; autonomic nervous system; heat loss

Hot red pepper is a typical traditional food that happens to increase diet-induced thermogenesis (DIT).^{1–3)} It contains pungent ingredients called capsaicinoids, and one of the major capsaicinoids in hot red pepper is capsaicin.⁴⁾ Capsaicin accelerates energy expenditure and suppresses body fat accumulation by activating the adrenal sympathetic efferent nerve in rats,^{5–7)} but it causes potent irritation, and so ingestion of hot red pepper at sufficient volumes to suppress body fat accumulation is difficult for people who are not used to eating it.

Recently, Yazawa *et al.* have reported success in

breeding CH-19 Sweet,⁸⁾ a new, non-pungent type of red pepper. CH-19 Sweet increases oxygen consumption and raises core body temperature and surface temperature in humans,⁹⁾ but because CH-19 Sweet has little pungency,¹⁰⁾ humans can ingest it without difficulty. Hence it is possible that CH-19 Sweet is a preferable nutritional application, better than hot red pepper.

CH-19 Sweet contains only very slight amounts of capsaicinoids.⁸⁾ Instead, capsinoids, non-pungent members of the capsaicin analog, are present in large quantities.^{10,11)} One of the major capsinoids in CH-19 Sweet is capsiate,¹¹⁾ and the similarity of the structure of capsiate to that of capsaicin led us to expect that it might have a similar physiological effect in raising energy expenditure. The results of our previous research based on this idea indicate that a single capsiate administration activates energy expenditure and catecholamine secretion and increases core body temperature. Repeated capsiate administration for two weeks suppressed body fat accumulation in mice as effectively as capsaicin.^{12,13)} Hence the enhancement of DIT due to CH-19 Sweet was thought to be induced by the capsiate in it.

Although capsiate in CH-19 Sweet induces thermogenesis the same way as capsaicin in mice, few details have been determined about DIT due to CH-19 Sweet specifically in humans. To elucidate the mechanisms of DIT due to CH-19 Sweet, we examined whether CH-19 Sweet activates the autonomic nervous system in humans, and compared the mechanisms of DIT due to CH-19 Sweet to those due to hot red pepper. CH-19 Sweet was found to activate the sympathetic nervous system (SNS) and to elevate body temperature without

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Abbreviations: BP, blood pressure; HR, heart rate; DIT, diet-induced thermogenesis; SNS, sympathetic nervous system; LFC, low-frequency component; HFC, high-frequency component; TRPV1, transient receptor potential vanilloid 1

affecting blood pressure (BP) or heart rate (HR). Although hot red pepper was also found to activate the SNS and to elevate body temperature, hot red pepper elevated BP and HR.

Materials and Methods

Subjects. Informed consent was obtained from all subjects according to the guidelines established by the Helsinki Declaration. The Medical Ethics Committee of the Japanese Society of Nutrition and Food Science approved this study. Data were collected from healthy, normotensive Japanese volunteers, 5 males and 7 females, ranging in age from 22 to 25 years (mean, 23.4 years), including habitual caffeine consumers and excluding smokers.

Materials. In this experiment, we used three peppers: CH-19 Sweet, Cayenne Long Slim, and California Wonder. CH-19 Sweet is a non-pungent cultivar of red pepper and contains capsinoids. Cayenne Long Slim is a pungent cultivar of red pepper and contains capsaicinoids. California Wonder is a non-pungent red pepper cultivar containing neither capsinoids nor capsaicinoids. All of the peppers were cultivated by the Laboratory of Vegetable and Ornamental Horticulture of Kyoto University, Japan. The peppers were frozen and stored at -20°C immediately after harvest.

Experimental design. Measurements were made in a quiet room at about 50% humidity and a temperature of $21 \pm 1^{\circ}\text{C}$. The subjects were required to abstain from alcohol and excessive eating in the days before the experiments. On the days of the experiments, the subjects abstained from hard exercise, and breakfast was restricted to a light meal that did not contain spices, and a beverage that did not include caffeine. The subjects abstained from food and drink for 3 h prior to the experiment. To avoid the influence of circadian rhythm, each measurement was begun between 1100 h and 1130 h.

We measured autonomic nervous response, body temperature, BP, and HR after intake of CH-19 Sweet, Cayenne Long Slim, and California Wonder. The peppers were defrosted with running water, and subjects ingested them with water (37°C , 50 ml). The subjects chewed the peppers 30 times before swallowing them. The peppers were given to the subjects at the rate of 0.1 g/kg body weight. This dose of CH-19 Sweet has been reported to increase oxygen consumption and body temperature in humans.⁹⁾ CH-19 Sweet and Cayenne Long Slim contained capsiate and capsaicin respectively at about 0.1 mg/kg dry weight. The subjects ingested the samples within 2 min. The measurements of autonomic nervous response, body temperature, BP, and HR were carried out simultaneously. Before the measurements, the subjects were instructed to rest about 20 min in the sitting position.

Power spectral analysis and heart rate measurement. In order to evaluate cardiac autonomic nervous activity, we used power spectral analysis of the temporal intervals between heart beats (RR intervals). Power spectral analysis has been used to detect changes in autonomic nervous activity in response to the intake of foods or the inhalation of odors in humans.^{14–17)} Details of the power spectral analysis procedure have been fully described by Moritani *et al.*^{18,19)} A power spectral analysis by fast Fourier transformation was performed on consecutive 256-s time series of the R–R interval data obtained during the test. To evaluate the autonomic nervous system activity of each subject in the present study, we analyzed both low-frequency (LFC, 0.035–0.15 Hz) and high-frequency (HFC, 0.15–0.5 Hz) components, the latter being the respiration-linked component. In general, HFC is associated almost entirely with vagal nervous activity, while LFC is mediated mainly by sympathetic nervous activity and slightly by vagal nervous activity. All subjects breathed in synchrony with a metronome at 15 times/min (0.25 Hz) to ensure that respiratory-linked variations in heart rate did not overlap with low-frequency heart-rate fluctuations (below 0.15 Hz) from other sources.

Body temperature and blood pressure measurements. Body surface temperatures at the forehead and neck were measured as indicators of the heat loss effect with an electronic thermometer (NR-1000; Keyence, Tokyo). BP was measured with a BP monitor (HEM-707, Omron, Kyoto, Japan). The electrodes of the thermometer were attached to the skin under the clothing. The temperature of the tympanic membrane in the ear was taken as an indicator of thermogenesis with an infrared ear thermometer (S-10; Morisita Jintan, Osaka, Japan).

Data presentation. Because basal autonomic nervous activity, body temperature, BP, and HR differ among individuals, the mean value of autonomic nerve system indexes before intake was standardized as 100%, and the mean value of temperature, BP, and HR before intake was set as a baseline value (0°C , 0 mm Hg, and 0 bpm, respectively), and relative values after intake were compared.

Statistical analysis. Data were expressed as means \pm SE. The effects of time, treatment, and time \times treatment were evaluated by two-way repeated measures ANOVA. Furthermore, comparisons of time, treatment, and time \times treatment between the two groups were used in a contrast test. To compare the groups at certain times, one-way ANOVA and *post-hoc* Scheffe tests were used. Statistics were calculated with the Stat View software package (Macintosh Version J 5.0; Abacus Concepts, Berkeley, CA) and the Super ANOVA software package (Macintosh Version 1.11; Abacus Concepts). A probability level of <0.05 was considered to indicate significance.

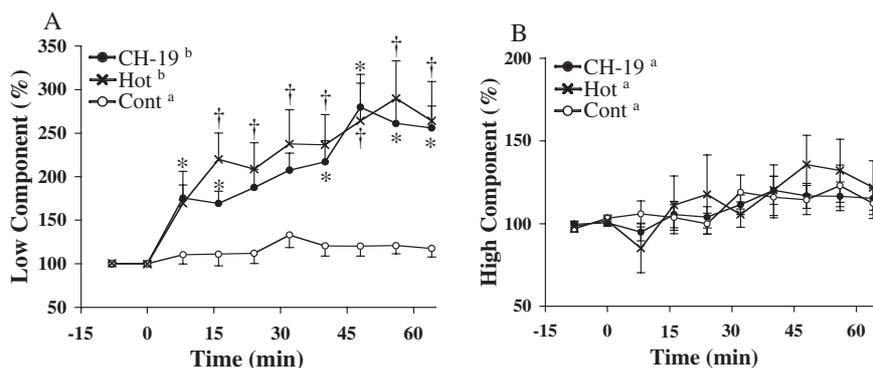


Fig. 1. Effects of Intake of CH-19 Sweet (CH-19), Hot Red Pepper (Hot), and Control Pepper (Cont) on Low-Frequency (LFC, A) and High-Frequency (HFC, B) Components in Humans.

Values are expressed as mean percentages of baseline \pm SE ($n = 8-12$). Groups without a common letter differ overall, $P < 0.001$. A significant difference was apparent at each time point ($P < 0.05$: *CH-19 vs. Cont, †Hot vs. Cont).

Results

Effects of CH-19 Sweet and hot red pepper intake on autonomic nervous activity

Both CH-19 Sweet and hot red pepper (Cayenne Long Slim) significantly increased the subjects' low-frequency component (LFC), which is an indicator of sympathetic nervous activity, as compared to the control pepper (California Wonder) (Fig. 1A). There was no significant difference in the high-frequency component (HFC), an indicator of parasympathetic nervous activity, between groups (Fig. 1B). These results suggest that both CH-19 Sweet and hot red pepper enhance sympathetic nervous activity without affecting parasympathetic nervous activity.

Effects of CH-19 Sweet and hot red pepper intake on thermogenesis, heat loss, systolic blood pressure, and heart rate

We examined the effect of CH-19 Sweet and hot red pepper on body temperature, systolic BP, and HR, which are regulated by the autonomic nervous system. Both CH-19 Sweet and hot red pepper significantly increased tympanic temperature, an indicator of thermogenesis, as compared to the control pepper (Fig. 2A).

Forehead temperature after intake of both CH-19 Sweet and hot red pepper increased significantly in comparison with the control pepper (Fig. 2B); however, the increase in the hot red pepper intake group was about 0.3°C , while that in the CH-19 Sweet intake group was about 0.1°C . The forehead temperature increase was significantly greater after intake of hot red pepper than after CH-19 Sweet. Neck temperature after intake of both CH-19 Sweet and hot red pepper increased significantly in comparison with the control pepper (Fig. 2C); however, the increase in the hot red pepper group was about 0.25°C , while that in the CH-19 Sweet group was about 0.15°C . The neck temperature increase was significantly greater after intake of hot red pepper than after CH-19 Sweet. These results suggest that both

CH-19 Sweet and hot red pepper increase heat loss from the forehead and neck, but that hot red pepper induces heat loss more strongly than CH-19 Sweet.

Significant increases were observed in systolic BP after intake of hot red pepper in comparison with the control pepper and CH-19 Sweet (Fig. 3A). There was no significant difference between CH-19 Sweet and the control pepper. HR changed similarly to systolic BP. HR in the hot red pepper group increased strongly immediately after ingestion. There was a significant increase in HR after intake of hot red pepper in comparison with the control pepper and CH-19 Sweet (Fig. 3B). There was no significant difference between CH-19 Sweet and the control pepper.

Discussion

In the present study, we found that non-pungent CH-19 Sweet activated the SNS and accelerated thermogenesis simultaneously. Hence DIT enhancement due to CH-19 Sweet might be induced by SNS activation. A pharmacological SNS blockade experiment is necessary to validate this possibility. Intragastric and intravenous administration of capsiate individually accelerate catecholamine secretion in animal experiments.^{12,20} Thus, CH-19 Sweet might accelerate catecholamine secretion by activating the SNS in humans.

In this study, we found that hot red pepper also activates the SNS. SNS activation due to hot red pepper (capsaicin) has been reported in several studies,^{17,21,22} and these reports agree with the present results. It has been reported that capsaicin accelerates adrenaline secretion by activating the adrenal sympathetic efferent nerve,⁵ and the increase in energy expenditure due to capsaicin is inhibited by β -adrenergic blockers.⁷ Consequently, it is possible that capsaicin elevates energy expenditure by activating SNS. Iida *et al.* found that capsaicin and capsiate activate the same receptor, transient receptor potential vanilloid 1 (TRPV1), by patch-clamp experiments.²³ We too have reported that

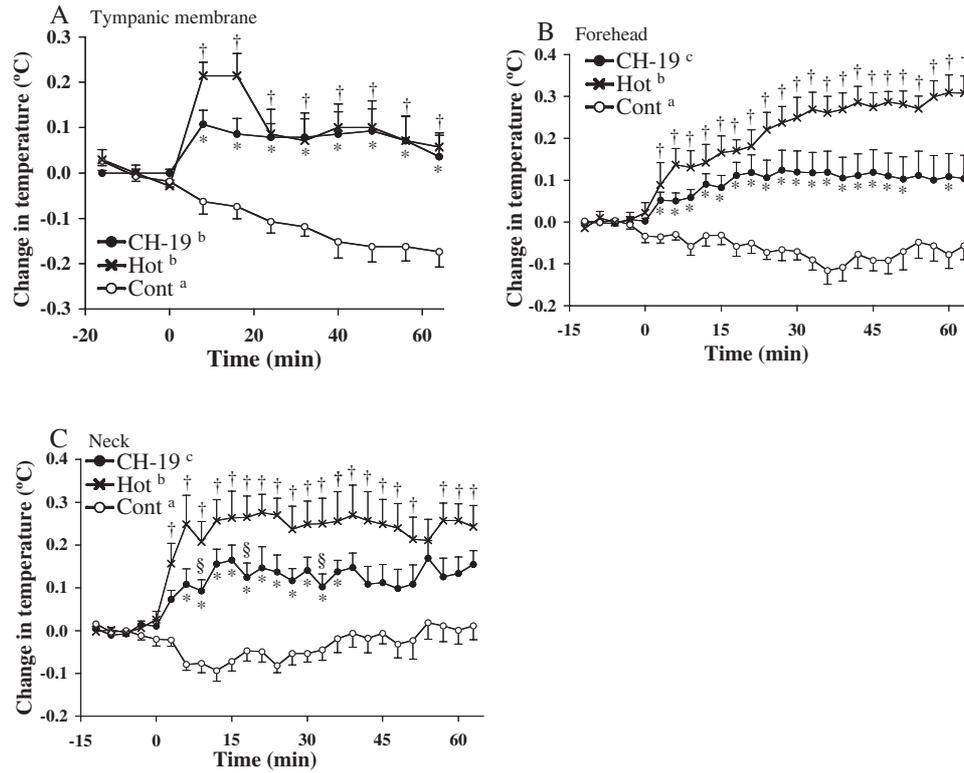


Fig. 2. Effects of Intake of CH-19 Sweet (CH-19), Hot Red Pepper (Hot), and Control Pepper (Cont) on Tympanic Temperature (A), Forehead Temperature (B), and Neck Temperature (C).

Values are expressed as relative values of baseline \pm SE ($n = 8-12$). Groups without a common letter differ overall, $P < 0.05$. A significant difference was apparent at each time point ($P < 0.05$: *CH-19 vs. Cont, †Hot vs. Cont, §CH-19 vs. Hot).

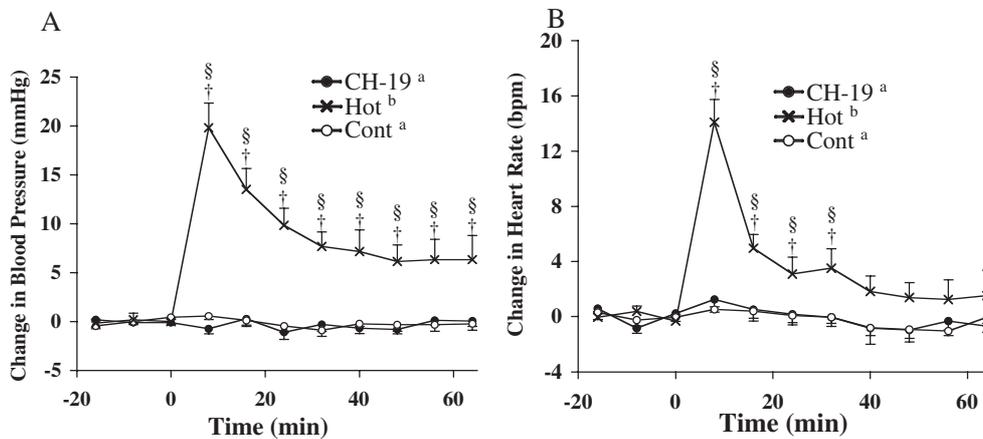


Fig. 3. Effects of Intake of CH-19 Sweet (CH-19), Hot Red Pepper (Hot), and Control Pepper (Cont) on Systolic BP (A) and HR (B).

Values are expressed as relative values of baseline \pm SE ($n = 8-12$). Groups without a common letter differ overall, $P < 0.0001$. A significant difference was apparent at each time point ($P < 0.05$: †Hot vs. Cont, §CH-19 vs. Hot).

the increase in body temperature due to capsiate is inhibited by capsazepine, which is a specific antagonist of TRPV1.¹³ Because capsaicin and capsiate activate the same receptor, the DIT enhancement due to CH-19 Sweet is perhaps also induced by activating the SNS, as with hot red pepper.

In the present study, we found that both CH-19 Sweet

and hot red pepper activate thermogenesis and heat loss simultaneously. We confirmed that CH-19 Sweet elevates the temperature of the tympanic membrane, forehead, and neck in humans.⁹ Kobayashi *et al.* have reported that capsaicin activates thermogenesis and heat loss simultaneously in rats,²⁴ and their results agree with the present study. Moreover, the present results suggest

that CH-19 Sweet and hot red pepper equally activate thermogenesis, but that the heat loss effect due to CH-19 Sweet is weaker than that due to hot red pepper. We have found that capsaicin is present in circulating blood after intragastric administration, while capsiate is not present in mice (unpublished data). This phenomenon might be related to the lower potency of the heat loss effect observed with CH-19 Sweet intake. Osaka *et al.* revealed that the thermogenesis due to capsaicin is controlled by the brainstem, and that the heat loss due to capsaicin is controlled by the forebrain, which includes the hypothalamus.²⁵ It has been suggested that there are mechanisms of signal transduction to the hypothalamus by capsaicin: *via* visceral afferents, *via* vascular afferents, and direct action after penetrating the brain.²⁶ Since capsiate was not detected in circulating blood, it might signal to the hypothalamus solely *via* visceral afferents, resulting in a weak heat loss effect. Signal transduction to the brainstem, which controls thermogenesis, might be the same as between capsiate and capsaicin.

The lower potency of CH-19 Sweet in increasing forehead and neck temperature might be overcome by increasing the amount of CH-19 Sweet intake, because capsiate has been reported to activate TRPV1 with dose dependency.²³ More studies are necessary to determine the dose response effects of CH-19 Sweet in humans.

In the present study, although hot red pepper accelerated BP and HR, CH-19 Sweet did not. There have been several reports that capsaicin elevates BP and HR,^{25,27} and these reports agree with the present results. CH-19 Sweet did not elevate HR although it activated cardiac SNS. Hence it is possible that the HR elevation and the cardiac SNS activation due to hot red pepper in the present results were induced by independent mechanisms. CH-19 Sweet might affect only the activity of cardiac SNS.

Transient increases in HR, BP, and tympanic temperature were observed soon after hot red pepper intake. Since these changes were not observed with CH-19 Sweet intake, and the increases appeared immediately after hot red pepper intake, the increases might be related to pungency. We have observed transient increases in HR, BP, and tympanic temperature in the case of chewing and spitting out hot red pepper (unpublished data). These results also suggest that pungency is related to transient increases in HR, BP, and tympanic temperature. However, since we have also observed mild increases in HR and BP in the case of swallowing hot red pepper by capsule (unpublished data), hot red pepper is thought to increase HR and BP not only by pungency, but in addition by an unknown mechanism. Because capsiate activates TRPV1 as well as capsaicin, differences in mechanism besides the receptor appear to affect the changes in HR and BP. As mentioned above, differences in pungency, metabolism, and chemical characteristics between capsiate and capsaicin might be involved in the changes in HR and

BP. More study is needed to elucidate the effects of the capsinoids in CH-19 Sweet on HR and BP in animal experiments.

In summary, the results of this study indicate (i) that CH-19 Sweet activates SNS and accelerates DIT simultaneously without affecting BP or HR; (ii) that CH-19 Sweet elevates thermogenesis as effectively as hot red pepper, but that the heat loss effect due to CH-19 Sweet is weaker than that due to hot red pepper; and (iii) that hot red pepper also activates SNS and accelerates DIT simultaneously, which transiently elevates BP and HR. Hence the increase in DIT due to CH-19 Sweet might be induced *via* activation of the SNS. Further study is needed to elucidate why differences in changes in, HR, BP, and the heat loss effect occur between CH-19 Sweet and hot red pepper intake.

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