Effects of Capsaicin-containing Yellow Curry Sauce on Sympathetic Nervous System Activity and Diet-induced Thermogenesis in Lean and Obese Young Women

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Summary The present study was designed to investigate the effect of capsaicin, a pungent component of red pepper, on the sympathetic nervous system (SNS) activity and energy metabolism in 16 age- and height-matched lean and obese young women. The sympato-vagal activities were assessed by means of spectral analysis of heart rate variability (HRV) during the resting condition and after the meal (2,016kJ) with capsaicin (3mg). Energy expenditure was also measured under the two conditions. There was no significant difference in any of the parameters of the HRV between the obese and control groups at rest. After the capsaicin diet, however, the very low frequency component (0.007–0.035Hz) associated with thermogenesis (315.8±78.0 vs. 814.8±211.7ms²Hz⁻¹, p<0.05) as well as its responsiveness (delta changes: 14.6±104.4 vs. 369.2±121.7ms²Hz⁻¹, p<0.05) were significantly lower in the obese than the control group. Energy expenditure was significantly increased in the control group after the meal (5,574.7±221.2 to 6,114.7±239.0kJ day⁻¹; p<0.01), but no such significant thermogenic response was detected in the obese group despite nearly identical lean body mass of the control group. Our data indicate that regardless of the resting level of sympatho-vagal activities, the reduced sympathetic responsiveness to physiological perturbation such as a capsaicin diet, which may cause impaired diet-induced thermogenesis and further weight gain, could be an important etiological factor leading to obesity in young women.

Key Words capsaicin, sympathetic nervous system activity, heart rate variability, diet-induced thermogenesis, obesity

Capsaicin is the major pungent principle in various species of Capsicum fruits such as hot chilli peppers and has long been globally used as an ingredient of spices, preservatives and medicines (1).

The physiological effects of capsaicin have been extensively reviewed in previous animal studies. It has been shown that dietary supplementation of capsaicin in high fat diets lowered the perirenal adipose tissue weight and serum triglyceride concentration in rats due to enhancement of energy metabolism (2, 3). Watanabe et al. (4, 5) have investigated neurophysiological functions of capsaicin and have demonstrated that capsaicin increases energy metabolism by catecholamine secretion from the adrenal medulla through sympathetic activation via the central nervous system. The sympatho-thermogenic effect of capsaicin has also been demonstrated in humans. According to the recent study of Yoshioka et al. (6), energy expenditure increased immediately after the meal containing red pepper; whereas this enhancement of energy metabolism by a red-pepper diet was inhibited after the administration of β-adrenergic blocker, propranolol.

The sympathetic nervous system (SNS) and adrenal medulla combine to form the sympathoadrenal system, which is one of the important regulators of a number of physiological processes. Since the coordination of energy homeostasis is particularly dependent on the normal functioning of the sympathoadrenal system, alterations in the SNS activity are widely believed to contribute to the pathophysiology of obesity (7, 8). Whereas, no consensus has been made among investigators as to the predominant sympathetic abnormality (an increase or decrease) (9, 10), which may be partly attributable to the difficulties in adequately assessing the sympathetic function modulating energy metabolism in humans.

The electrocardiogram (ECG) R-R interval, or interbeat interval of heart rate is determined by the net effect of sympathetic and parasympathetic input. Heart rate variability (HRV) power spectral analysis has been proved as a reliable non-invasive method and has pro-
vided a comprehensive quantitative and qualitative evaluation of neuroautonomic function under various physiological conditions (11-15). In general, the high-frequencies (>0.15 Hz) of HRV are associated with almost entirely vagal nerve activity and low-frequencies (<0.15 Hz) of HRV might be mediated by both vagal and SNS activities (16-18). The frequencies much lower than 0.1 Hz have been thought to reflect thermoregulatory fluctuations in vasomotor tone (19, 20). We have recently demonstrated that very low (VLO) frequency components (0.007-0.035 Hz) were selectively increased against thermogenic perturbation such as acute cold exposure and mixed-food ingestion (21, 22). This finding suggests the possibility of evaluating the SNS activities associated with energy metabolic regulation by means of HRV spectral analysis in humans.

Although disagreement still exists regarding the resting level of the SNS activity, reduced sympathetic response to external physiological stimulation such as glucose ingestion has been found in the obese population (23-25). Because of its strong sympahto-thermogenic effect, investigating capsaicin-induced SNS activity and metabolic change may provide further information as to the sympathetic abnormality in human obesity. To the best of our knowledge, however, no data regarding the physiological effects of capsaicin in obese individuals are currently available.

Therefore, the aim of the present study was to evaluate thermogenic sympathetic function in response to capsaicin-containing spicy food by means of HRV power spectral analysis, as well as to investigate the magnitude of diet-induced thermogenesis in age- and height-matched lean and obese young women.

### METHODS

**Subjects.** Eight lean and eight obese young women volunteered to participate in this study. The two groups were matched in age and height. The percentage of body fat and lean body mass was determined by means of dual-energy X-ray absorptiometry (Hologic QDR = 1000). Descriptive characteristics of the subjects are presented in Table 1.

The study protocol was approved by the Committee on Ethics of Kyoto University Graduate School. All subjects were carefully instructed about the study and all gave their written informed consent to participate in the study. The subjects completed a standardized health questionnaire for past medical history, medication, lifestyle, diet, smoking habits, alcohol consumption, and physical activity. The subjects were non-smokers in good health and had no personal or family history of diabetes mellitus, cardiovascular disease, or other metabolic diseases. All subjects were weight stable at the time of the study with no more than a two-kg weight loss or gain over the six months before the study. Each subject was instructed to avoid any food or beverages containing alcohol or caffeine after 9:00 p.m. of the day preceding the study.

**Experimental procedure.** Subjects came to the laboratory at 9:00 a.m., and all experiments were performed in the morning. The room was temperature controlled (23-24°C) and quiet with minimization of arousal stimuli. The subjects were instrumented with ECG electrodes and then rested for at least 30 min before the beginning of the experiment.

After the resting period, CM5 lead ECG and gas exchange measurements were performed using an Aero-monitor AE 280 (Minato Medical Science) were continuously recorded while the subject remained seated in a comfortable chair for 10 min. The subject then ingested rice with spicy yellow curry sauce containing 3 mg capsaicin over a ten-minute period. The amount of capsaicin used in this study was about 10 times greater than one involved in a retort pouch of regular curry sauce on the market. The experimental meal composition was as follows: 60% carbohydrate, 30% fat and 10% protein as energy, respectively. The energy content of the meal was 2,016 kJ. It should be noted that based on the results of our preliminary research including capsaicin dose response experiments and previous studies (6, 26-28), the amount of capsaicin and energy content of the experimental meal were decided. Thus, the same absolute caloric load rather than a relative one was provided to both lean and obese subjects as a thermogenic perturbation although there was a significant difference in body weight between the two groups.

Immediately after the meal was ingested, the ECG and gas exchange measurements were performed continuously for 30 min. During resting and postprandial conditions, all subjects breathed in synchrony with a metronome at 15 times·min⁻¹ (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.

**R-R spectral analysis.** Our R-R interval power spectral analysis procedures have been fully described elsewhere (12–14, 21). Briefly, analog output of the ECG monitor (Life Scope, Nihon Kohden) was digitized via a 13-bit analog-to-digital converter (Trans Era HTB 410) at a sampling rate of 1,000 Hz. The digitized ECG signal was differentiated, and the resultant QRS spikes and the intervals of the impulses (R-R intervals) were stored sequentially on a hard disk for later analyses (12, 13).

Before R-R spectral analysis was performed, the stored R-R interval data were displayed and aligned se-

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### Table 1. Physical characteristics of subjects

<table>
<thead>
<tr>
<th></th>
<th>Control (n=8)</th>
<th>Obese (n=8)</th>
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<tbody>
<tr>
<td>Age (year)</td>
<td>19.6 ± 0.26</td>
<td>20.1 ± 0.40</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163.1 ± 1.39</td>
<td>160.5 ± 1.46</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>56.1 ± 2.15</td>
<td>74.3 ± 2.47**</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>21.0 ± 0.57</td>
<td>28.8 ± 1.01**</td>
</tr>
<tr>
<td>% fat (%)</td>
<td>16.1 ± 0.58</td>
<td>36.4 ± 1.36**</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>9.1 ± 0.58</td>
<td>27.2 ± 1.67**</td>
</tr>
<tr>
<td>Lean body mass (kg)</td>
<td>47.0 ± 1.71</td>
<td>47.1 ± 1.34</td>
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Values are means ±SE. Control vs. Obese: **p<0.01.
Effects of Capsaicin on Autonomic Nervous System and Thermogenesis in Women

The effects of capsaicin on the autonomic nervous system (ANS) were studied in a group of women to evaluate the impact on thermogenesis. Sequentially to obtain equally-spaced samples with an effective sampling frequency of 2 Hz (29) and displayed on a computer screen for visual inspection. Then, the DC component and trend were completely eliminated by digital filtering for the band-pass between 0.007 and 0.5 Hz. The high-pass filtering at 0.007 Hz was chosen to include the frequency components associated with thermogenic functions of the autonomic nervous system (ANS) (21, 22). The root mean square value of R-R interval was calculated as representing the average amplitude. After passing through the Hamming-type data window, power spectral analysis by means of a fast Fourier transform was performed on consecutive 512-s time series of R-R interval data obtained during the test. To evaluate ANS activity in each subject of the present study, we analyzed very low frequency (0.007–0.035 Hz, VLO), low frequency (0.035–0.15 Hz, LO), high vagal component (0.15–0.5 Hz, HI) and total power (0.007–0.5 Hz, TOTAL) by integrating the spectrum for the respective band width. Since our previous studies (21, 22) have shown that VLO frequency component reflects the SNS activity related to energy metabolic regulation, we defined VLO and VLO divided by TOTAL (VLO/TOTAL) as the absolute and relative thermogenic SNS activities, respectively (21). The mean heart rate of each 512-s segment was also calculated together with standard deviation.

It has been shown that physiological factors such as age might influence HRV (30). No significant difference was, however, found in physical characteristics or clinical features between the lean and obese groups, except for body weight and body fat content, which are associated with an obese state. Thus, the components of HRV spectral analysis were not normalized with any of the physiological parameters in the present study.

Calculation of energy expenditure. Energy expenditure (EE) was determined from the oxygen (O₂) consumption and respiratory quotient (RQ) calculated as the ratio of carbon dioxide (CO₂) produced to O₂ consumed by using the formula: EE (kcal·min⁻¹) = \(4.686 + [(RQ - 0.707) \times 0.293] \times 0.361 \times VO₂\), where 4.686 kcal·L⁻¹ is the energy value of 1 liter O₂ at a nonprotein RQ of 0.707; RQ is the measured respiratory quotient; 0.707 is the RQ when only fat is oxidized; 0.293 is the difference between the RQ for carbohydrate and fat oxidation; 0.361 is the difference in energy value of a liter of oxygen between an RQ of 1 and that of 0.707; and VO₂ (L·min⁻¹) is the rate of oxygen consumption at STPD conditions (31). Energy expenditure expressed as kcal·min⁻¹ was then converted to that as kJ·day⁻¹ (1 kcal = 4.2 kJ).

Statistical analyses. All statistical analyses were performed using a commercial software package (SPSS version 7.5 for Windows, SPSS Inc., Illinois). Statistical differences between groups were assessed using Student’s unpaired t-test. A paired t-test was performed to compare before and after food ingestion within a respective group. p values <0.05 were considered to be statistically significant. Data are expressed as mean±SE.

RESULTS

Figure 1 represents typical sets of raw R-R interval and the corresponding power spectral data obtained from the control and obese subjects, respectively, during the resting and postprandial conditions. R-R variability and frequency components in the power spectra did not seem to differ in the obese and the control subjects during the resting condition. After the ingestion of the capsaicin diet, the VLO frequency component related to the thermogenic SNS activity predominantly increased in

![Fig. 1. Examples of ECG R–R interval changes and the corresponding power spectra for a control subject and an obese subject during the resting and after the capsaicin diet.](image-url)
the control group; whereas, this VLO frequency component remained unchanged in the obese subjects.

Figure 2 represents group data with respect to the R–R spectral parameters (TOTAL, VLO, LO, and VLO/TOTAL) obtained from 8 control and 8 obese subjects during the resting and postprandial conditions. TOTAL, VLO and LO tended to be lower in the obese group compared to the control group during the resting condition; however, no significant difference was found in any of the parameters of HR variability (TOTAL, VLO, LO, HI and VLO/TOTAL) between the control and obese groups.

After the capsaicin diet, heart rate increased significantly both in the control (57±3.3 to 62±3.5 bpm, p<0.01) and the obese groups (67±2.8 to 72±2.8 bpm, p<0.01). HI frequency component related to PNS activity did not show any significant change in either group. As Fig. 2 shows, the control group demonstrated a significant increase in TOTAL (2,896.8±851.7 to 3,547.4±988.1 ms², p<0.05), VLO (445.6±188.0 to 814.8±211.7 ms², p<0.01), LO (611.1±149.1 to 894.0±174.8 ms², p<0.01) and VLO/TOTAL (0.17±0.05 vs. 0.26±0.03, p<0.05) after the diet. These findings suggest that capsaicin enhances the global ANS activity, which may be predominantly attributable to the significant increase in the thermogenic sympathetic nerve activities. In the obese group, however, these four parameters did not significantly increase in response to the capsaicin diet. Moreover, during the postprandial condition, the obese group demonstrated significantly lower TOTAL (1,563.4±269.6 vs. 3,547.4±988.1 ms², p<0.05), VLO (315.8±78.0 vs. 814.8±211.7 ms², p<0.05) and LO (419.7±61.5 vs. 894.0±174.8 ms², p<0.05) frequency components as well as markedly reduced responsiveness in the VLO frequency component (delta changes from resting to postprandial conditions: 14.6±104.4 vs. 369.2±121.7 ms², p<0.05) as compared to the control group.

Energy expenditure was significantly increased in the control group after the capsaicin diet (5,574.7±221.2 to 6,114.7±239.0 kJ·day⁻¹; p<0.01); however, no such significant thermogenic change was found in the obese group during the postprandial condition (6,191.8±274.3 to 6,531.8±337.3 kJ·day⁻¹; NS). RO tended to increase in the control group after the capsaicin diet; however no significant difference was detected in RQ between the resting and postprandial conditions in the two groups.

**DISCUSSION**

The present study provides new information regarding physiological effects of capsaicin on the SNS activity and diet-induced thermogenesis in lean and obese young women. Our data demonstrate that despite the nearly identical resting sympatho-vagal activities, obese young women possess much reduced sympathetic responsiveness to capsaicin-containing spicy food, as well as a lower capacity to enhance energy metabolism after food ingestion.

It has been shown that the thermogenic action of capsaicin on energy metabolism is neurophysiologically modulated. Briefly, capsaicin stimulates primary afferent neurons (32), which are transmitted to the spinal cord. Adrenal sympathetic efferent nerve activity is
then enhanced through the excitation of the central nervous system, which causes marked catecholamine secretion from the adrenal medulla (5, 33). Pharmacological blockade experiments have suggested that catecholamines secreted into the blood react with β-adrenergic receptors in peripheral organs, which enhance energy metabolism and consequently increase body heat production (3, 6, 33).

In the present study, we used HRV power spectral analysis in order to investigate the enhancing effect of capsaicin on the SNS activity in lean and obese young women. In contrast with other techniques such as catecholamine assay and microneurography, measurement of the HRV integrates pre-synaptic and post-synaptic end-organ response, thus providing a more comprehensive quantitative and qualitative evaluation of neuroautonomic function. Concerning the thermogenic component of the SNS activity, Landsberg and Young (34) demonstrated that capsaicholine turnover within cardiac tissue fluctuated with thermogenic stimulation such as cold exposure, fasting and overfeeding. This finding indicates that the cardiac SNS activity could precisely reflect autonomic events that affect energy metabolism elsewhere in the body. A recent study has shown that metabolic changes after glucose ingestion are associated with a predominant sympathetic activity in cardiac sympatho-vagal balance evaluated by HRV spectral analysis (24). In their study, the validity of HRV spectral analysis was confirmed by the measurement of plasma catecholamine concentration: a strong positive correlation was found between changes of HRV and plasma norepinephrine concentration in response to glucose ingestion. We have recently conducted a pharmacological experiment to explore further the relationship between HRV and thermoregulation and have found that complete autonomic blockade causes the abolishment of heart rate fluctuations and significant reduction of energy expenditure (11, 21, 22). Furthermore, we have identified the VLO frequency component and have demonstrated that this frequency component of HRV selectively increased against external thermogenic perturbation such as acute cold exposure and food intake in non-obese healthy volunteers (21, 22). With all these facts taken into account, the VLO frequency component of HRV integrates pre-synaptic and post-synaptic end-organ response, thus providing a more comprehensive quantitative and qualitative evaluation of neuroautonomic function.

In contrast, this effect of capsaicin was not detected in the obese young women in the present study: thermogenic SNS activity as well as its responsiveness after the capsaicin diet was markedly reduced in the obese subjects despite the similar level of ANS activity of the lean subjects at rest. Concerning energy expenditure after the meal, no significant increase was found in the obese group although lean body mass was almost identical to that in the control group. It has been shown that neonatal (5) and adult (33) capsaicin pretreatment inhibited capsaicin-induced adrenal catecholamine secretion in anesthetized rats. According to the results of the health questionnaire, however, our subjects did not have a long-term dietary history of eating spices such as chilli or hot red peppers. Prior to participation in this study, some of them reported a strong distaste for extremely spicy foods, preferring instead, mildly spicy food. Thus, we assume that daily dietary habit or taste sensitivity to capsaicin did not affect the data obtained in the present investigation.

Reduced sympathetic response to food ingestion has been reported in previous studies. Bazelmans et al. (23) reported a decreased stimulation of norepinephrine appearance in obese subjects in response to overfeeding. Spraul et al. (25) have also found a negative correlation between the percentage of body fat and the increase in the muscle sympathetic nerve activity (MSNA) in response to glucose ingestion while fasting; MSNA correlated positively with body fat. A previous study of Paolillo et al. (24) using HRV spectral analysis has shown that the rise in the sympathetic nerve activity after glucose ingestion negatively correlated with body fat content, whereas it positively correlated with glucose-induced thermogenesis and glucose uptake. Recent research in our laboratory (22) has demonstrated that the VLO frequency component of HRV was markedly reduced in obese young women after mixed-food ingestion. The methodology such as experimental designs, selection of subjects and measurements for ANS are not always the same as that used in the present study; however, our findings support these previous investigations and reinforce the finding that the altered specific sympathetic function related to thermogenic capacity may be a significant sign reflecting the autonomic state in human obesity.

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In conclusion, we examined the effect of capsaicin on the SNS activity and energy metabolism in age- and height-matched lean and obese young women. The underlying physiological mechanism of SNS activity modulating energy metabolism and its association with obesity remains elusive in humans. Results found in the present study, however, indicate that regardless of the resting level of the ANS activity, the reduced sympathetic responsiveness to thermogenic perturbation such as that found in the capsaicin diet, which may cause impaired diet-induced thermogenesis and further weight gain, could be an important etiological factor leading to obesity in young women.

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