

# Alterations of Human Autonomic Nervous System Activity on Capsaicin Ingestion, and Variants of UCP1 and $\beta_3$ -adrenergic Receptor Polymorphism

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We investigated whether 1) capsaicin ingestion (100 mg) enhances autonomic nervous system (ANS) activities associated with thermogenic sympathetic activity as energy metabolic modulator, 2) UCP1 and  $\beta_3$ -AR variants of each subjects influence with ANS activity. Eight healthy males ( $24.7 \pm 1.8$  yr) volunteered for this study. The cardiac autonomic nervous activities evaluated by means of heart rate variability of power spectral analysis and energy metabolism were continuously measured during 5-min rest for total 90-min resting condition with placebo or capsaicin oral administration chosen at random. The results indicated that there were no significant differences in heart rate during rest between both trials. Autonomic nervous activity increased in capsaicin tablet trial, but the difference did not reach the statistical significance. Capsaicin, however, induced significantly lower respiratory gas exchange ratio at Test3 (CAP:  $0.80 \pm 0.02$  vs.  $0.85 \pm 0.02$ ), means  $\pm$  SE,  $p < 0.05$ ). In conclusion, it may be suggested the capsaicin consumption as a valuable supplement for the treatment of individual with hyperlipidemia and/or obesity by improving lipolysis. Further studies will also be considered genetic variants such as UCP1 and/or  $\beta_3$ -AR associated with obesity.

**Key words** -- Autonomic nervous system, heart rate variability power spectral analysis, UCP1,  $\beta_3$ -AR, capsaicin

## Introduction

Various food ingredients such as caffeine, green tea, and chicken essence, have affected animal physiological homeostasis. Especially, capsaicin is a spicy component of hot red peppers, which are widely used as an important spice for enhancing the palatability of food, and also utilized as a medicine for developing counter-irritation [34]. Capsaicin has reported to reduce perirenal adipose tissue weight and serum triglyceride concentration due to enhancement of energy metabolism in rats [14]. According to the recent study of Yoshioka et al. [37], 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  $\beta$ -adrenergic blocker, propranolol. To the best of our knowledge, however, no data regarding physiological effects of capsaicin tablets upon human autonomic nervous system (ANS) activity are currently available.

Cardiac ANS activity plays an important role in the ho-

meostasis maintenance under diverse physiological and psychological environments. The ANS activity may be mediated by regain of parasympathetic nervous system (PNS) activity and withdrawal of sympathetic nervous system (SNS) activity by heart rate variability (HRV) power spectrum analysis at rest. The SNS activity 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 [3], alterations in the SNS activity are widely believed to contribute to the pathophysiology of obesity. Otherwise, no consensus has been made among investigators as to the predominant sympathetic abnormality (an increase or decrease) [19,38], 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 inter-beat interval of heart rate is determined by the net effect of sympathetic and parasympathetic input. HRV power spectral analysis has been proved as a reliable non-invasive method and has provided a comprehensive quantitative and qualitative evaluation of neuroautonomic function under vari-

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ous physiological conditions [22,23,26]. 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 [1,2,27]. The frequencies much lower than 0.1 Hz have been thought to reflect thermoregulatory fluctuations in vasomotor tone [13,15]. We have recently demonstrated that very low (VLF) frequency components (0.007-0.035 Hz) were selectively increased against thermogenic perturbation such as acute cold exposure and mixed- food ingestion [20,21]. This finding suggests the possibility of evaluating the SNS activities associated with energy metabolic regulation by means of HRV spectral analysis in humans.

To consider genetic factors related to thermogenesis, uncoupling protein-1 (UCP1) is expressed exclusively in brown adipose tissue (BAT) [5,18] and is a key moderator of the thermogenic function of BAT in humans [16]. UCP1 expression and activity is regulated by the SNS [4,29] and signaling via the  $\beta_3$ -adrenergic receptor ( $\beta_3$ -AR) has been implicated in UCP1 activation as  $\beta_3$ -specific agonists enhance energy expenditure and exhibit potent antiobesity effects in rodents [24,33]. In humans, Trp64Arg sequence variation in the  $\beta_3$ -AR has been associated with a lower metabolic resting rate and earlier onset of non-insulin-dependent diabetes mellitus in Pima Indians [35] or abdominal obesity and resistance to insulin [36] or an increased capacity to gain weight [7] in other populations.

These observations were supported by recent studies including our own [31,32] showing an additive effect of the  $\beta_3$ -AR Trp64Arg variant with a Bcl I polymorphism in the 5' -region of the UCP1 gene on reduced ANS activities and weight gain in obese subjects [8]. In addition, in obese subjects, the same UCP1 polymorphism was associated with lower weight loss during a low calorie diet [10].

Therefore, the aim of the present study was to evaluate 1) ANS activity, particularly the thermogenic sympathetic function associated with energy metabolism in response to capsaicin tablets (100 mg), 2) the influence of ANS activity on genotype of each subject.

## Materials and Methods

### Subjects

Eight healthy male ( $24.7 \pm 1.8$  yr.,  $171.8 \pm 3.2$  cm.,  $64.2 \pm 1.0$  kg, and %fat  $14.9 \pm 1.1\%$  estimated by bio-impedance method, mean  $\pm$  SE) students from Kyoto University volunteered for this experiment. All experimental procedures

were explained in detail to each subject who then signed a statement of informed consent. The institutional Review Board of Kyoto University Graduate School approved the experiment for Use of Human Subjects. The physical characteristics of all subjects are presented in Table 1.

### Experimental Procedures

Subjects came to the laboratory at 8:00 a.m. after eating breakfast before at least 2 hr they arrived at the laboratory for two different occasions in which autonomic nervous system activity was measured before, and every 30 min for total 90 minutes after consuming 2 tablets of capsaicin (100 mg) or placebo with 100 ml of water. Each subject came to the laboratory two times for consuming the different tablets each other day.

Our R-R interval power spectral analysis procedures have been fully described elsewhere. Briefly, analog output of the ECG monitor (Life Scope, Nihon Kohden) was digitized via a 13-bit analog-to-digital converter (Trans Era HTB 420) at a sampling rate of 1024 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.

Before R-R spectral analysis was performed, the stored R-R interval data were displayed and aligned sequentially to obtain equally-spaced samples with an effective sampling frequency of 2 Hz 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 low-pass filtering at 0.007 Hz was chosen to include the frequency components associated with thermogenic functions of the ANS. The root mean square value (RMS) 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 then performed on consecutive 512-s time series of R-R interval data obtained during the test [1].

Fig. 1 represents typical sets of raw R-R intervals and

Table 1. Physical characteristics of the subjects

Subject (N)	Age (yr)	Height (cm)	Weight (kg)	BMI ( $\text{kg}/\text{m}^2$ )	fat (%)
8	$24.7 \pm 1.8$	$171.8 \pm 3.2$	$64.2 \pm 1.0$	$21.9 \pm 0.7$	$14.9 \pm 1.1$

Values represent means (SE).

BMI: body mass index

the corresponding power spectral analysis. To evaluate ANS activity in each subject of the present study, we analyzed very low frequency (0.007-0.035 Hz, VLF), low frequency (0.035-0.15 Hz, LF), high vagal component (0.15-0.5 Hz, HF) and total power (0.007-0.5 Hz, TOTAL) by integrating the spectrum for the respective bandwidth. The mean heart rate of each 512-s segment was also calculated together with standard error.

Subjects were requested to avoid any medication for one week prior to the study and were kept on their usual diet. Each subject was instructed to avoid any food or beverages containing alcohol or caffeine or capsaicin after 9:00 p.m. of the day preceding the study. The room was temperature controlled (23-24°C) and quiet with minimization of arousal stimuli. The subjects rested for at least 30 minutes before the start of the experiment. The order of capsaicin or placebo tablets was chosen at random.

### Genetic analysis

A noninvasive genotyping sampling method has been implemented for collecting buccal mucosa cells using buccal swab brushes. After the phenol-extraction procedure, 0.2 to 2 µg of DNA per subject was obtained. The BclI polymorphism of UCP1 gene, which detects the A-G point variant at position -3826 base pair (bp) in the 5' -flanking domain, was determined by polymerase chain reaction (PCR) restriction fragment length polymorphism analysis according to the method proposed by Cassard-Doulcier et al. [6]. The PCR primers were 5' -CTTGGGTAGTGACAAA

G-TAT-3' (forward) and 5' -CCAAAGGGTCAGATTC-TAC-3' (reverse). Genomic DNA (100 ng) in a total volume of 20 µl was used for PCR. The PCR was performed by initial denaturation at 94°C for 5-min, 30 cycles at 94°C for 30-sec, 55°C for 30-sec, 72°C for 30-sec, and a final extension at 72°C for 10-min. We then incubated 5 µl of the PCR product for 1 hr with 10 U of BclI at 37°C in a final volume of 10 µl without further purification. The samples were then run on a 3.0% agarose gel, stained with ethidium bromide, and analyzed under UV light. In the presence of the polymorphism, the restriction site for BclI is lost; therefore, the allele of this polymorphism corresponds to the 470 bp-undigested bands.

The MvaI polymorphism of  $\beta_3$ -AR gene, which detects the Trp<sup>64</sup>Arg variant, was determined using PCR-restriction fragment length polymorphism analysis according to our previously reported method [30]. The PCR primers were 5' -CCAATACCGCCAACACACCAGT-3' (forward) and 5' -AGGAGTCCCATCACCAGGTC-3' (reverse), which flank the whole exon 1 of the  $\beta_3$ -AR gene. Genomic DNA (100 ng) in a total volume of 20 µl was used for PCR. The PCR was performed by initial denaturation at 94°C for 5-min, 30 cycles at 94°C for 30-sec, 67°C for 30-sec, 72°C for 30-sec, and a final extension at 72°C for 10-min. We then incubated 5 µl of the PCR product for 1 hr with 10 U of MvaI at 37°C in a final volume of 10 µl without further purification. The samples were then run on a 3.0% agarose gel, stained with ethidium bromide, and analyzed under UV light. In the presence of the polymorphism, the restriction site for MvaI is lost; therefore, the allele of this polymorphism corresponds to the 158 bp-undigested bands.

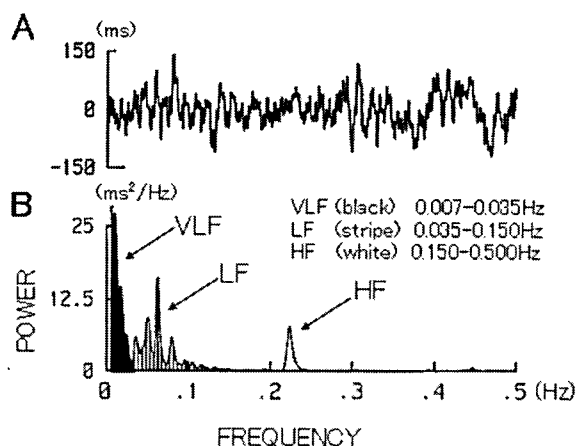


Fig. 1. A typical set of ECG R-R interval changes and corresponding power spectrum analysis. Very low (VLF), Low (LF), and High (HF) frequency components represented by the black area, stripe area, and white area, respectively.

### Statistical analyses

All statistical analyses were performed using a commercial software package (SPSS version 11.5 for Windows, SPSS inc., Illinois). Statistical differences between treatments were assessed using Student's paired t-test. P values < 0.05 were considered to be statistically significant. Data are expressed as mean  $\pm$  SE.

## Results

### Distribution of Genotypes

The distribution of the genotypes defined by the -3826 A→G polymorphism of UCP1 gene and the Trp/Arg<sup>64</sup> variant of the  $\beta_3$ -AR gene in the present study is presented in Table 2. Previous genetic studies regarding the -3826 A→G

Table 2. Distribution of genotype defined by the -3826 A→G nucleotide variant of the UCP1 promoter gene and the β<sub>3</sub>-AR gene in 8 healthy college males.

Trp/Arg <sup>64</sup> variant of β <sub>3</sub> -AR	A→G variant of the UCP1		
	AA	AG	GG
Trp/Trp (TT)	0	1 (12.5)	2 (25.0)
Trp/Arg (TC)	2 (25.0)	2 (25.0)	1 (12.5)
Arg/Arg (CC)	0	0	0

Values represent the number of subjects (percentage). Abbreviation: AA, TT, wild type; AG, TC, heterozygous alleles; GG, CC, homozygous alleles.

polymorphism of UCP1 clearly indicated that GG homozygotes demonstrated an increased tendency to gain weight over time [11]. In the present study, three subjects of all subjects were having GG homozygous carriers of the A→G UCP1 variant (37.5%). However, there are no Trp/Arg<sup>64</sup> variants of the β<sub>3</sub>-AR gene in homozygous carriers of the A→G UCP1 variant.

**Heart Rate Changes**

Fig. 2 represents resting heart rate (HR) change after consuming the respected tablets with 100 ml of water. HR did not show any significant changes in two experimental treatments.

**Power Spectral Changes**

Fig. 3 presents the alterations of activity in ANS activities after consumption of capsaicin (CAP) or placebo (CON) during experimental periods assessed with HRV power spectral analysis in healthy college males. ECG R-R interval power spectral results showed markedly different responses in terms of the spectral TOTAL power, representing over-all ANS activity, VLF power associated with SNS thermogenic component and LF power containing the sympatho-vagal

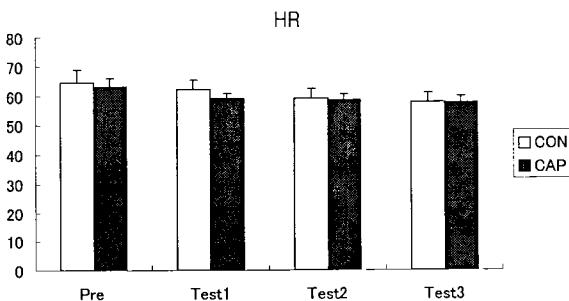


Fig. 2. Alterations of heart rate after consumption of capsaicin (CAP) or placebo (CON) trial at rest. Values represent means ± SE.

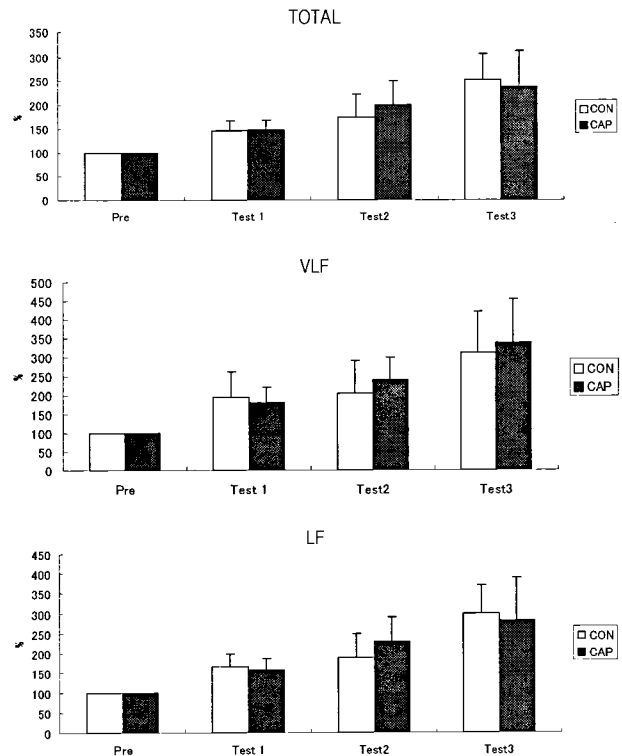


Fig. 3. Changes of activity in the autonomic nervous system after ingestion of capsaicin tablets (CAP) or placebo (CON) at rest assessed with using heart rate variability power spectral analysis in healthy young men. There were not significant differences on autonomic nervous activity at rest in capsaicin and placebo trials at any point. TOTAL total power of the spectrum, VLF very low frequency component of the spectrum, LF low-frequency component of the spectrum. The value of each placebo trial was standardized as 100%. Values represent means ± SE.

component, respectively.

In alterations of ANS activities of the present study, TOTAL power increased progressively after capsaicin and placebo tablet treatments. Similarly VLF and LF power components increased after both experiment treatments. Although there were statistically significant differences due possibly to the small number of subjects, the markedly augmented response in VLF power seemed to continue at least for 90-min after capsaicin tablets intake, suggesting the increased thermogenic effects.

**Metabolic Responses to Capsaicin**

Fig. 4 shows the changes in respiratory gas exchange ration (RQ) after consumption of CAP or CON at resting condition. In the present study, RQ values in CAP trial were significantly lower than those in CON trial (Test2:

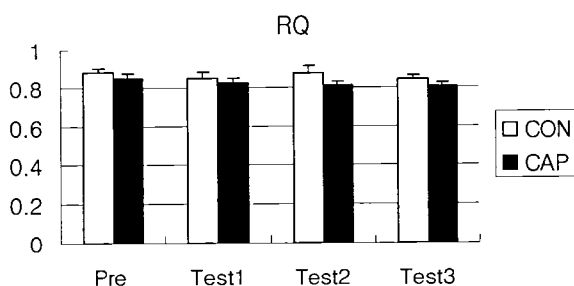


Fig. 4. The Changes of respiratory gas exchange ratio (RQ) after ingestion of capsaicin tablets (CAP) or placebo tablets (CON) at rest in healthy young men. There were not significantly differences on autonomic nervous activity at rest in capsaicin and placebo trials. The RQ values of capsaicin were significantly lower 60-min and 90-min at rest. Values represent means  $\pm$  SE., \* : CON vs. CAP,  $p < 0.05$ .

0.81  $\pm$  0.02 vs. 0.87  $\pm$  0.04, Test3: 0.80  $\pm$  0.02 vs. 0.85  $\pm$  0.02, CAP vs. CON trial, means  $\pm$  SE.,  $p < 0.05$ ).

## Discussion

The main finding of this study was that capsaicin intake in this study showed lower RQ value during test period and progressively increased SNS activity, particularly the TOTAL power, VLF, and LF frequency components of HRV. However, no significant difference was found in SNS activities. Although no significant differences of SNS activities, lower RQ values in CAP trial suggest that consumption of capsaicin increases fat oxidation enhancing lipolysis. In human studies, test-meals enriched with capsaicin also increased both energy expenditure and lipid oxidation [21,37]. From this point of view, the result of the present study is in accordance with these previous studies. However, no studies regarding the effects of capsaicin extract tablets on autonomic nervous system activity were found. These non-significant differences among trials might have been due to the fact that 1) HRV power values have a wide inter-individual variation, 2) the amounts of capsaicin used in this study may lower than that of other studies, and 3) genotype of each subject varies. In the present study, the subjects with GG allele gene type have 37.5% among all subjects. In these reasons, despite the SNS responsiveness to thermogenic stimuli such as capsaicin intake, there were not significant differences on SNS activities.

As a key contributor to the regulation of energy balance mitochondrial UCP1 in  $\beta_3$ -AR is generally assumed to play an important role in body weight regulation in rodents

and humans [9,12,25,32]. The relationship between UCP1 polymorphism and human obesity has been supported [9,11]. However, we observed a quite marked increase in TOTAL, VLF and LF frequency components for 90 minutes after the administration of two capsaicin tablets, indicating the potent SNS enhancing effects.

In the present study, we used HRV power spectral analysis in order to investigate the effect of capsaicin tablets on the SNS activity in healthy young subjects. In contrast with other techniques such as catecholamine assay and micro-neurography, measurement of the HRV integrates pre-synaptic and post-synaptic end-organ response, thus providing a more comprehensive quantitative and qualitative evaluation of neuro-autonomic function.

Concerning thermogenic component of the SNS activity, it has been shown that catecholamine turnover within cardiac tissue correlates strongly with autonomic effects that affect energy metabolism elsewhere in the body [17]. 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 [28]. In their study, the validity of HRV spectral analysis was confirmed by the measurement of plasma catecholamine concentration. In our previous study, we identified the VLF frequency component and 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 [20,21]. With all these facts taken into account, the VLF frequency components are thought to reflect more precisely the SNS activity modulating energy metabolism and possibly the sympatho-thermogenic effect of capsaicin tablets in humans.

However, because the results of this present study were also derived from a small number of subjects and just non-invasive measures, the interpretation of the results must be carefully considered until a larger scale study confirms the present findings. Nevertheless, only no studies, at least to our knowledge, have performed to investigate the effect of food components in humans. In this point of view, this present study would provide valuable results, although no significant differences on cardiac SNS activity.

In conclusions, we demonstrated that the orally administration of capsaicin tablets may be enhancing the activity of fat oxidation. Therefore the results of the study suggest that capsaicin consumption may markedly increase SNS ac-

tivity, particular the thermogenic SNS activity associated with energy metabolism as a valuable supplement for the treatment of individual with hyperlipidemia and/or obesity by improving lipolysis. Further studies will also be considered such as UCP1 and/or  $\beta_3$ -AR associated with obesity.

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## 초록 : 캡사이신 섭취와 UCP1 과 $\beta_3$ - adrenergic Receptor Polymorphism의 다양성에 대한 자율 신경활동의 변화

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본 연구의 목적은 1) 캡사이신 섭취 (100 mg) 가 에너지 대사 조절자로서 열발생 교감신경활동과 관련된 자율 신경활동을 향상시키는지, 2) 본 연구의 대상자들의 UCP1 과  $\beta_3$ -AR 유전자 다양성이 자율신경활동에 영향을 주는지를 조사한 것이다. 8명의 대상자 (24.7 ± 1.8세) 가 이 실험에 자발적으로 참여하였다. 심박수변이성 파워 스펙트럼 분석에 의해 평가된 심장자율신경활동과 에너지 대사는 총 90분간 매 30분마다 5분간 측정하였으며, 캡사이신 또는 위약 그룹은 무작위로 대상자에서 섭취되었다. 본 연구의 결과에서, 두 그룹간의 안정시 심박수에서는 유의한 차이가 없었다. 자율신경활동은 캡사이신 그룹에서 증가하였으나, 통계적으로 유의한 차이는 없었다. 총 대상자중, UCP1의 GG유전자 타입을 가진 대상자는 37.5% 였다. 그러나 캡사이신 그룹은 Test3에서 측정시 호흡교환율이 유의하게 낮았다 (CAP: 0.80 ± 0.02 vs. CON: 0.85 ± 0.02, means ± SE, p<0.05). 이상의 결과로서, 캡사이신 (100 mg) 의 섭취는 지방분해를 향상시킴으로서 비만 과/또는 고지혈증을 가진 개개인에서 유의한 성분임을 시사할 수 있다. 또한 자율신경에 대한 비만과 관련된 UCP1 과/또는  $\beta_3$ -AR 과 같은 유전자 다양성은 앞으로의 연구에 고려되어야 할 것이다.