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Alterations of Heart Rate Variability upon β3-Adrenergic Receptor Polymorphism and Combined Capsaicin, Sesamin, and L-Carnitine in Humans

Ki Ok. Shin[1,3], Hyun Jun. Kim[2] and Sung Hwun. Kang[4*]

[1]*Laboratory of Applied Physiology, Graduate School of Human and Environmental Studies, Kyoto University, Kyoto, Japan*
[2]*Laboratory of Exercise Physiology, Department of Physical Education, Pusan National University, Korea*
[3]*Research Institute of Physical Education & Sport Science, Pusan National University, Korea*
[4]*Department of Pharmacology, Medical Sciences Research Institute, College of Medicine, Dong-A University, Korea*

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We investigated whether 1) the combined capsaicin (75 mg), sesamin (30 mg), and L-carnitine (900 mg) (CCSC) ingestion enhances autonomic nervous system (ANS) activities including thermogenic sympathetic activity as energy metabolic modulator, 2) β_3-AR polymorphism of each subject influences with ANS activity. Seven healthy males (22.0±0.5 yr) volunteered for this study. The cardiac autonomic nervous activities evaluated by means of heart rate variability of power spectral analysis were continuously measured during 5 min every 30 min for total 120 min resting condition with CCSC or placebo oral administration chosen at random. The results indicated that, there are not Arp/Arg^{64} variants of the β_3-AR genotypes in our subjects. There were not also significant differences in heart rate during rest between both trials. The difference of ANS activity did not reach the statistical significance between both trials. However, the significant improvement showed TOTAL power, HF component, and the indices of SNS and PNS activities before and at 30 min after CCSC ingestion ($p<0.05$, respectively). In conclusions, although each component of combined CCSC is associated with lipolysis and/or fat oxidation, the combined CCSC consumption is not influenced in stimulation of thermogenic sympathetic activity as modulator of energy metabolism. In rather, our results suggested that CCSC ingestion improves the balance of both SNS and PNS activities. Therefore, it will be considered many combined nutrient components for ergogenic and/or lipolysis effects as well as genetic variants affecting ANS activity in further studies.

Key words : Autonomic nervous system, heart rate variability, β3-AR, combined capsaicin, sesamin, L-carnitine

Introduction

Recently many people have been interested in the beneficial effects of physical activity and food components-induced thermogenesis for reducing the risk of diseases such as obesity, cardiac heart attack, stroke, hyperlipidemia, and diabetes mellitus. Various food ingredients such as coffee, capsaicin, green tea, and herb tea are believed to affect cardiac autonomic nervous system (ANS) activity and other physiological functions [7,8]. Capsaicin is the major pungent principle in various species of capsicum fruits such as hot chili peppers and has long been globally used as an ingredient of spices, preservatives and medicines [31]. There are many animal studies demonstrating that capsaicin activates the sympathetic nervous system (SNS) activity associated with thermogenesis. Watanabe et al. [35] have investigated neurophysiologic 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. In our human study, capsaicin has also been reported to increase the thermogenesis and activation of the SNS in young women for 30 min after the meal of capsaicin-containing yellow curry sauce [21]. Capsaicin has reported to reduce perirenal adipose tissue weight and serum triglyceride concentration due to the enhancement of energy metabolism in rats [17].

The biological actions of sesamin, one of the most abundant lignans existing in sesame seed and oil have been reported: antioxidant [27], anticarcinogenand [11], blood pressure lowering [20], and serum lipid lowering [1] in experimental animals and humans. In addition, dietary sesamin reduces hepatic concentrations of triglycerol [12], although temporally increasing phospholipid levels accompany liver hypertrophy [9,12]. It is therefore suggested that

*Corresponding author
Tel : +82-51-240-2930, Fax : +82-51-240-2930
E-mail : 94psycho@naver.com

these physiological activities of sesamin feedings might contribute to improve human health.

Carnitine (L-3-hydroxytrimethylaminobutanoate) is a naturally occurring substance that can be synthesized for energy metabolism in mammals from the essential amino acids lysine and methionine [4]. L-carnitine is essential for the transport of long chain fatty acids across the mitochondrial membrane for subsequent fat degradation and energy production [33]. The previous study has been suggested that L-carnitine supplementation can influence lipid metabolism and can also effect body composition [15]. To the best of our knowledge, however, no data regarding physiological effects of combined capsaicin (75 mg), sesamin (30 mg), and L-carnitine (900 mg) (CCSC) upon human ANS activity are currently known.

Cardiac ANS activity plays an important role in the homeostasis 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. It is now possible to explore the functioning of the ANS reliably and non-invasively using comprehensive and functional analysis of HRV. Because it is an ease-to-use and patient-friendly method, HRV spectral analysis has gained popularity in broad applications as a functional indicator of the ANS [6,23,32]. In addition, HRV power spectral analysis lightens the burden imposed on subjects during an experiment, unlike invasive measurement, i.e., plasma catecholamine concentration and muscle sympathetic nerve activity. It also offers a practical and valuable approach to evaluating the sympatho-vagal activity in gynecological research [13,22,28]. 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) [17,19], which may be partly attributable to the difficulties in adequately assessing the sympathetic function modulating energy metabolism in humans.

To consider genetic factors related to thermogenesis, signaling via the β_3-adrenergic receptor (β_3-AR) has been implicated in uncoupling protein 1 (UCP1) activation as β_3-specific agonists enhance energy expenditure and exhibit potent antiobesity effects in rodents [25,30]. In humans, Trp64Arg sequence variation in the β_3-AR has been associated with a lower metabolic resting rate and earlier onset of non-insulin-dependent diabetes mellitus in Pima Indians [34] or abdominal obesity and resistance to insulin [36] or an increased capacity to gain weight [5] in other populations.

Therefore, the aim of the present study was to evaluate 1) ANS activity, particularly the thermogenic sympathetic function as a modulator of energy metabolism in response to CCSC nutrient aid, 2) the influence of ANS activity on β_3-AR variants of each subject.

Methods

Subjects

Seven healthy male (22.0±0.5 yr, 173.9±2.5 cm, 61.5±1.6 kg, %fat 12.6±1.9%, and BMI 20.4±0.8 kg/m^2) estimated by bio-impedance method, mean±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 written 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 ANS activity was measured before, and during 5 min on every 30 min at rest for 120 min after consuming CCSC supplement or placebo with 100 ml of water. Each subject came to the laboratory two times for consuming the different tablets each other day.

Table 1. Physical characteristics of the subjects

Subject (N)	Age (yr)	Height (cm)	Weight (kg)	BMI (kg/m^2)	Fat (%)
7	22.0±0.5	173.9±2.5	61.5±1.6	20.4±0.8	12.6±1.9

Values represent mean±SE
BMI: body mass index

The electrocardiogram (ECG) R-R interval or inter-beat interval of heart rate is determined by the net effect of sympathetic and parasympathetic input. The 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 various physiological conditions [23,26]. 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 sec time series of R-R interval data obtained during the test [2].

Fig. 1 represents a computer output from a subject shows the raw ECG R-R interval during experimental period. 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), total power (0.007-0.5 Hz, TOTAL), and indices of the global PNS and SNS activity by integrating the spectrum for the respective bandwidth. The mean heart rate of each 512 sec 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 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.

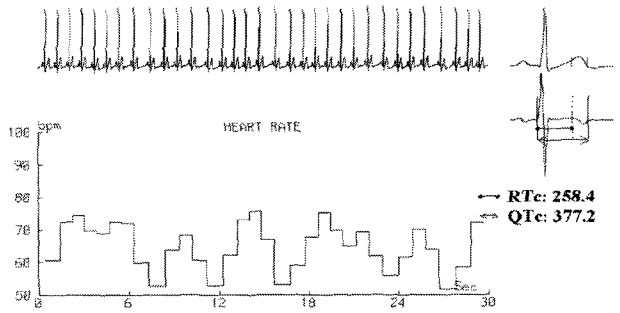

Fig. 1. A computer output from a subject shows the raw ECG R-R interval during experimental period.

The subjects rested for at least 30 min before the start of the experiment. The order of CCSC 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 MvaI polymorphism of β_3-AR gene, which detects the $Trp^{64}Arg$ variant, was determined using PCR-restriction fragment length polymorphism analysis according to our previously reported method [29]. The PCR primers were 5'-CCAATA CCGCCAACACACCAGT-3' (forward) and 5'-AGGAGTCC CATCACCAGGTC-3' (reverse), which flank the whole exon 1 of the β_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.

Statistical analysis

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 two-way ANOVA with repeated measurement. P values<0.05 were considered to be statistically significant. Data are expressed as mean±SE.

Table 2. Distribution of genotype defined by the β_3-AR gene in 7 healthy college males

	Trp/Arg^{64} variant of β_3-AR
Trp/Trp (TT)	2 (28.6)
Trp/Arg (TC)	5 (71.4)
Arg/Arg (CC)	0

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

Results

Distributions of genotype

The distribution of the genotypes defined by the Trp/Arg^{64} variant of the β_3-AR gene in the present study is presented in Table 2. In the present study, there are no Arp/ Arg^{64} variants of the β3-AR genotypes in our subjects.

Power spectral changes

Fig. 2 presents the alterations of ANS activities after consumption of CCSC or placebo (CON) during experimental periods assessed with HRV power spectral analysis in healthy college males. In the present study, ECG R-R interval power spectral results showed markedly different responses in terms of the spectral TOTAL power, representing over-all ANS activity, HF power associated with PNS activity, and indices of SNS and PNS activity. However, there were significant differences between both groups upon ANS activities as well as VLF and LF power components within CCSC group.

In alterations of ANS activities of the present study, TOTAL power increased significantly at 30-min in comparison to before CCSC treat (2837.1±982.2 vs. 4381.4±1098.0 ms^2, $p<0.05$) (Fig. 2, A). Similarly, HF power components improved significantly at 30 min more that before CCSC ingestion (1805.7±819.4 vs. 3397.1±1114.1 ms^2, $p<0.05$) (Fig. 2, B). Moreover, the SNS and PNS index was significant difference between pre and at 30 min in CCSC group, respectively (SNS: 1.15±0.66 vs. 0.47±0.25, PNS: 0.61±0.12 vs. 0.74±0.09, $p<0.05$) (Fig. 2, C-D).

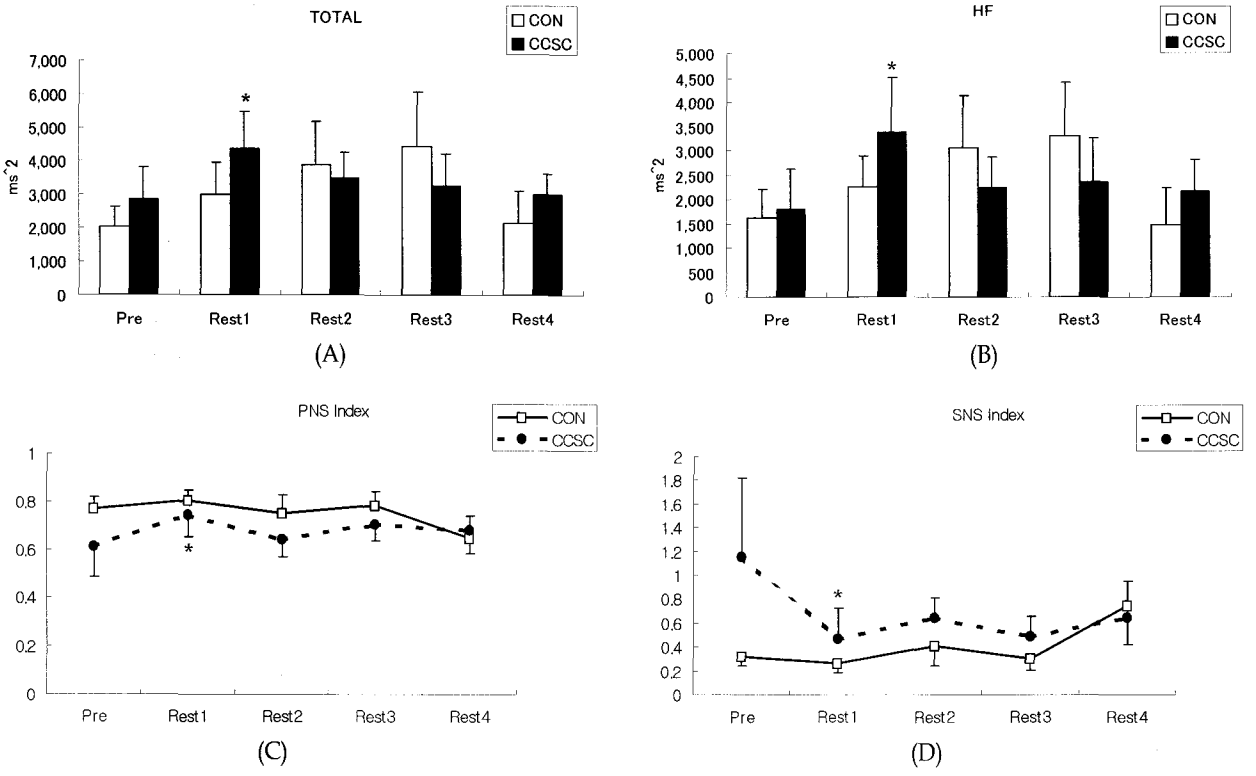

Fig. 2. A-D. Alterations of cardiac autonomic nervous system activity after ingestion of combined capsaicin, sesamin, L-carnitine (CCSC) or placebo (CON) at rest assessed with using heart rate variability power spectral analysis in healthy young men. There were not significant differences on autonomic nervous activity at rest between CCSC and CON trials at any point. There were significant improvements in TOTAL power, HF component, and indices of SNS and PNS activities before and at 30 min after CCSC ingestion. TOTAL, total power of the spectrum; HF, high frequency component; LF, low frequency component.n Values represent mean±SE, *: pre vs. 30 min after CCSC ingestion, $p<0.05$.

Discussion

The main finding of this study was that CCSC ingestion showed significant enhancement of cardiac ANS activities, particularly the TOTAL power, HF component, and indices of SNS and PNS activities of HRV during test period. However, no significant difference was found in VLF and LF components. We have expected the improvement of thermogenic sympathetic nervous activity related to energy metabolism, i.e., fax oxidation from combined test ingestion. However, we are failed to find those results in this experiment.

It has been demonstrated the effect of each component of CCSC on various beneficial physiological activities, particularly fat oxidation for lipolysis. One of the CSSC components, test-meals enriched with capsaicin also increased both energy expenditure and lipid oxidation in human studies [31,33]. According to the recent study of Yoshioka et al. [37], energy expenditure (EE) 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. Second of those, sesamin has been shown to decrease the serum level of cholesterol, particularly of LDL-cholesterol, a risk factor for atherosclerosis in human [10]. It is also apparent that the sesamin preparation exerts strong influences on lipid metabolism, and the alteration of hepatic fatty acid metabolism can account for the serum lipid-lowering effect of the lignan in rats [1]. The last component of CSSC, carnitine has been shown to stimulate fatty acid oxidation in vascular endothelial cells [14]. In the previous study, Müller et al [24] have reported for the first time an increase in fatty acid oxidation after L-carnitine supplementation of 3 g/d for 10 day in healthy adults without L-carnitine deficiency.

As explained with above, each component of the CCSC has been reported the beneficial physiological activities. This study was designed to further examine the influence of CCSC supplementation on cardiac thermogenic sympathetic activity using non-invasive HRV power spectral analysis during rest period. In the present study, we observed significant increase in over-all ANS activity (TOTAL) and globally sympathetic and parasympathetic activities (indices of SNS and PNS) after the administration of CCSC ingestion, indicating the potential ANS enhancing affects. However, there was not change of thermogenic sympathetic activity after CCSC ingestion. These non-significant differences among trials might have been due to the fact that 1) HRV power values have a wide inter-individual variation, and 2) the CCSC components might influence the adverse effect on thermogenesis activity, although each nutritious component might report the improving effect of lipolysis associated with thermogenic sympathetic activity. In these reasons, despite the SNS responsiveness to thermogenic stimuli such as CCSC ingestion, there was not significant difference on thermogenic sympathetic activity.

In the present study, we used non-invasive HRV power spectral analysis in order to investigate the effect of CCSC ingestion on the thermogenic SNS activity in healthy young subjects. 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 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 [18]. 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 [27]. 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 [4,33]. 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 the present study were also derived from a small number of subjects, the interpretation of the results must be carefully considered until a larger scale study confirms the present findings. Nevertheless, no studies, at least to our knowledge, have performed to investigate the effect of CCSC supplement on cardiac ANS activity in humans. In this point of view, the present study would provide valuable results about car-

diac ANS activity.

In conclusions, although each components of combined CCSC is associated with lipolysis and/or fat oxidation, the combined CCSC consumption is not influenced in stimulation of thermogenic sympathetic activity as modulator of energy metabolism. In rather, our results suggest that they improve the balance of both SNS and PNS activities. Therefore, it will be considered combined nutrient components for ergogenic and/or lipolysis effects as well as genetic variants affecting ANS activity in further studies.

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초록 : 복합 캡사이신, 세사인, 그리고 카르니틴과 베타3 유전자 다형에 대한 심박수 변이성의 영향

신기옥[1,3] · 김현준[2] · 강성훈[4*]
([1]교토대학교 인간환경학연구과 대학원 응용생리학 실험실, [2]부산대학교 체육교육학과 운동생리학 실험실, [3]부산대학교 스포츠과학 연구소, [4]동아대학교 의과대학 약리학교실)

본 연구의 목적은 1) 캡사이신(75 mg), 세사민(30 mg), 그리고 카르니틴(900 mg) 복합성분(CCSC)이 에너지 대사조절자로서 열발생 교감신경활동과 관련된 자율신경활동을 향상시키는지, 2) 본 연구의 대상자들의 β_3-AR 유전자 다양성이 자율신경활동에 영향을 주는지를 조사하였다. 7명의 대상자(24.7±1.8세)가 이 실험에 자발적으로 참여하였다. 심박수변이성 파워스펙트랄 분석에 의해 평가된 심장 자율신경활동은 CCSC 섭취 전과 후 총 120분간 매 30분마다 5분간 측정하였으며, CCSC 또는 위약(CON)그룹은 무작위로 대상자에서 섭취되었다. 본 연구의 결과에서, 총 대상자중, β_3-AR 유전자CC 타입을 가진 대상자는 없었다. 두 그룹간의 안정시 심박수에서는 유의한 차이가 없었다. 자율신경활동에서도 그룹간 차이는 없었으나, CCSC그룹에서 섭취전과 섭취 후 30분에서 총자율신경활동(TOTAL power), 부교감신경활동(PNS power), 그리고 교감·부교감 신경활동지수에서 유의한 차이를 보였다($p<0.05$, respectively). 이상의 결과로서, 비록 각각의 성분들은 지방분해와 관련이 있다 할지라도CCSC의 섭취는 열생산 교감신경 자극에 영향을 주지 않았으며, 오히려 양 교감·부교감신경활동의 향상과 관련이 있다는 것을 시사하였다. 따라서 미래의 연구에서는 ANS 활동에 영향을 주는 유전적 다양성뿐만 아니라 운동능력 향상 보조물 그리고/또는 지방분해 효과를 위한 더 많은 복합 영양 성분이 연구되어야 할 것이다.