

Research article

Capsaicin supplementation fails to modulate autonomic and cardiac electrophysiologic activity during exercise in the obese: with variants of UCP2 and UCP3 polymorphism

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Abstract

We investigated the effects of capsaicin supplementation (150mg) on alterations of autonomic nervous system (ANS) activity associated with adverse effects of cardiac depolarization-repolarization intervals during aerobic exercise in obese humans. Nine obese males (26.1 ± 1.5 yrs) volunteered between study designed. The cardiac ANS activities evaluated by means of heart rate variability of power spectral analysis and cardiac QT interval were continuously measured during 5-min rest and 30-min exercise at 50% of maximal ventilation threshold (50%VTmax) on stationary ergometer with placebo (CON) or capsaicin (CAP) oral administration chosen at random. The uncoupling protein (UCP) 2 and UCP 3 genetic variants of the subjects were analyzed by noninvasive genotyping method from collecting buccal mucosa cells. The results indicated that there were no significant differences in cardiac ANS activities during rest and exercise between CON and CAP trials. Although no significant difference, A/A allele of UCP2 polymorphism showed a reduced sympathetic nervous system (SNS) index activity compared to G/G + G/A allele during exercise intervention in our subjects. On the other hand, the data on cardiac QT interval showed no significant difference, indicating that oral administration of capsaicin did not cause any adverse effect on cardiac depolarization-repolarization. In conclusion, our results suggest that capsaicin supplementation 1 h before exercise intervention has no effect on cardiac ANS activities and cardiac electrical stability during exercise in obese individuals. Further studies should also consider genetic variants for exercise efficacy against obesity.

Key words: Heart rate variability power spectral analysis, cardiac depolarization-repolarization interval, uncoupling protein, capsaicin, exercise.

Introduction

Obesity is highly prevalent in the world and caused public health problems related to the risk of cardiovascular disease, complication of diabetes mellitus, hypertension, and other chronic diseases. However, the causes of human obesity are still unclear because of various reasons such as physiological, environmental, and genetic factors. As one of causes of human obesity, recently Bray (1991) has proposed that obesity is associated with a reduction of sympathetic nervous system activity. The previous studies (Matsumoto et al., 1999; 2000; 2001) have also indicated that human obesity was associated with significantly lower cardiac autonomic nervous system (ANS) activity,

especially sympathetic nervous system (SNS) activity against thermogenic perturbations at resting condition. Moreover, obesity development may result from the genetic variations (Kopelman, 2000). Among genetic factors related to obesity, uncoupling protein (UCP) 2 is widely expressed in white adipose tissue, skeletal muscle, pancreatic islets, and the central nervous system (Dalgaard et al., 2001; Saleh et al., 2002). The disruption of UCP2 gene reduced fat free acid (Yanovsk et al., 2002) and exercise efficiency (Buemann et al., 2001). UCP3 is a mitochondrial anion carrier protein with a highly selective expression in skeletal muscle, a major site of thermogenesis in humans (Hesselink et al., 2003). The dysfunction of UCP3 decreases energy expenditure and increases the propensity to store fat (Saltzman and Roberts, 1995). In contrast, increased expression of UCP3 is related to an increase in the metabolic rate during sleeping and reduced body mass index (BMI) (Schrauwen et al., 1999). In this point of view, UCP2 and UCP3 may play a central role as etiological factors of obesity development.

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 (Suzuki and Iwai, 1984). There are many animal studies demonstrating that capsaicin activates the SNS activity associated with thermogenesis. Watanabe et al. (1988a; 1988b) investigated neurophysiologic functions of capsaicin and demonstrated that capsaicin increased energy metabolism via catecholamine secretion from the adrenal medulla. Ohnuki et al. (2001) have also reported that the SNS activity of rats on capsaicin supplementation was enhanced at rest. The previous human study demonstrated that capsaicin increased thermogenesis and activated the SNS in young women, but not obese individuals for 30-min after capsaicin supplement in diet meal (Matsumoto et al., 2000). However, it is unknown, at least to our knowledge, whether capsaicin stimulation before aerobic exercise might improve cardiac ANS activity in obese individuals.

A prolonged cardiac heart rate-adjusted QT interval (QTc) is associated with a risk for increased cardiovascular mortality in patients with cardiac disease (Algra et al., 1991) and healthy populations (Dekker et al., 1994; Schouten et al., 1991). The QT interval is the time required to complete myocardial depolarization and repolarization period. It has been suggested that QTc prolongation may be a consequence of an unfavorable balance

between sympathetic and parasympathetic nervous activity. In our previous study (Ue et al., 2000), we measured cardiac depolarization-repolarization interval and performed the analysis of electrocardiogram (ECG) R-R interval power spectral analysis simultaneously by using CM₅ lead ECG in patients with ischemic heart disease (IHD) and with varying degrees of diabetic autonomic neuropathy. We have reported that the change in sympatho-vagal balance reflects significantly longer corrected activation-recovery interval (ARI) and recovery time (RT). However, it is first time to study, at least to our knowledge, whether the alterations of cardiac ANS activity, especially sympathetic nervous activity by the traditional thermogenic effect of capsaicin ingestion are associated with the cardiac electrical instability during aerobic exercise in the obese.

Accordingly, the aim of this study investigated whether capsaicin supplementation (150mg) modulates the positive alterations of the ANS activity, particularly the SNS activity associated with adverse effects of cardiac depolarization-repolarization intervals during aerobic exercise in obese humans.

Methods

Subjects

Nine obese young men participated in this study. Our obese subjects were ≥ 25 for BMI criteria on the basis of the guidelines defined by the Japan Society for the Study of Obesity. Their physical characteristics are described in Table 1. They were not taking any medications and had no cardio-vascular and metabolic diseases as checked by university general health screening performed every year. No subject was involved in regular physical activity or smoked. All subjects gave written informed consent to take part in this study. The Institutional Review Board of Kyoto University Graduate School approved the experiment for Use of Human Subjects.

Table 1. Physical characteristics of the subjects (n = 9). Values represent means (\pm SE).

Age (yr)	26.1 (1.5)
Height (m)	1.72 (.02)
Weight (kg)	85.2 (3.8)
BMI (kg·m ⁻²)	28.8(1.2)
Body fat (%)	30.5 (2.0)
VO ₂ max (ml·kg ⁻¹ ·min ⁻¹)	40.8 (2.7)

BMI: body mass index

Determination of VO₂max and VTmax

Prior to the experiment, all subjects came to the laboratory for measuring their body composition and maximal oxygen uptake (VO₂max) on a stationary cycle ergometer (CB-X 1000, NAPS, Japan) to determine their VTmax. VO₂max of each subject was measured using the mixing chamber method (Aero monitor AE 280, Minato Medical Science, Tokyo, Japan). Following warm-up exercise at 30Watt for 3-min, exercise load at a pedaling frequency of 60 rpm was increased 10Watt every minute. The 50%VTmax was also determined according to our previously described procedures (Moritani et al., 1987). The 50%VTmax protocol was adopted according to our previous study (Nishijima et al., 2002) and has been shown to

be a sensitive procedure for evaluating the effects of various foods and nutrients on ANS activity.

Experimental procedures

On the day prior to the experiment, subjects were instructed to refrain from strenuous physical exercise and alcohol. They were also instructed to avoid any spicy food or beverages except water during and after dinner. On the day of the experiment, all experiments were performed in the morning from 7:50 to 11:30 AM to minimize the circadian influence. Subjects were given a simple breakfast (energy content 300 kcal or approximately 1,254 kJ), which is a traditional Japanese food about 3 h before the exercise. This meal contained 10, 20, and 70 % of energy as fat, protein, and carbohydrate, respectively. The subject was placed in an upright seated condition for at least 30-min before the experiment in a room of the temperature of 24–25°C. The ECG data of each subject were recorded for 5-min as baseline data. At rest, all subjects breathed in synchrony with an electric metronome at 15 beats/min (0.25 Hz) to ensure that respiratory-linked variations in heart rate did not overlap with low-frequency heart-rate fluctuations (<0.15 Hz) from other sources. Following the resting protocol subjects ingested placebo (CON) or capsaicin (CAP) supplementation (150 mg, Cerebos Co., Ltd., Taiwan) chosen at random, separated by a week for washing-out. The amount of capsaicin used in this study was the dose of 1.5 times per time ingestion. We also performed the preliminary experiment on CAP supplementation at rest before this study and confirmed to be optimal time for capsaicin effect at 60 and 90-min after ingestion of capsaicin in young healthy humans. Based on these results, our obese subjects ingested CON or CAP supplementation 1 h before the exercise. After 1 h, the subjects performed an aerobic exercise using a stationary cycle ergometer (CB-X 1000, NAPS, Japan) for 30-min at 60 rpm with intensity of 50%VTmax, ranging 60 to 78 Watt for each subject. During exercise, subject could breathe freely as the respiratory rate would easily exceed the 0.25 Hz, so that low frequency components of heart rate variability (HRV) would not be affected by respiration. The ECG data were collected for 30-min during exercise for both trials. Our ECG R-R interval power spectral analysis has been fully described elsewhere (Nagai et al., 2003; Moritani et al., 1993; Matsumoto et al., 1999). The procedures of measurement of cardiac depolarization-repolarization interval have also been fully described elsewhere (Benhorin et al., 1990; Haws and Lux, 1990; Shimizu et al., 1994; Ue et al., 2000).

Genetic analysis

The distribution of the genotypes defined by the -866 G/A polymorphism of UCP2 gene and -55 C/T polymorphism of UCP3 gene in the present study is presented in Table 2. 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 μ g of DNA per subject was obtained. Genotypes were determined with a fluorescence-based allele-specific DNA primer assay system (Toyobo Gene Analysis, Tsuruga, Japan) (Yamada et al., 2002). The analytical measurement of -866 G/A polymorphism of UCP2 gene

and -55 C/T polymorphism of UCP3 gene has been fully described elsewhere (Hamada et al., 2008a, 2008b).

Statistical analysis

All statistical analyses were performed using a commercial software package (SPSS version 11.5 for Windows, SPSS Inc., Chicago, IL). Statistical differences were assessed using two-way ANOVA with repeated measurements for time, treatment, and time \times treatment. When a significant difference was found, Student's paired t-test was used for comparisons between the trials at certain specific times. Student's unpaired t-test was used to compare differences in measurements between wild type + heterozygous type and homozygous type of UCP2 or UCP3 polymorphism, respectively. P values <0.05 were considered to be statistically significant. Data are expressed as mean and standard errors (SE).

Results

Effects of capsaicin on the power spectrum of the R-R intervals

The baseline ANS data of capsaicin (CAP) or placebo (CON) trials were not significantly different (TOTAL

power: CON, $1089.2 \pm 312.6 \text{ ms}^2$, CAP, $1259.7 \pm 345.8 \text{ ms}^2$; LF power: CON, $268.0 \pm 53.2 \text{ ms}^2$, CAP, $393.2 \pm 115.4 \text{ ms}^2$; HF power: CON, $830.2 \pm 281.6 \text{ ms}^2$, CAP, $866.6 \pm 257.3 \text{ ms}^2$; SNS index: CON, 0.42 ± 0.10 , CAP, 0.52 ± 0.16). ECG R-R interval power spectral results also showed that the TOTAL power representing overall ANS activity in both trials did not reach statistical significance during exercise (Figure 1A). In LF power containing the sympatho-vagal component, there were no significant differences in these trials at any points (Figure 1B). The HF power associated with parasympathetic activity, also, was not significantly different between trials (Figure 1C). Moreover, the SNS index presenting the global sympathetic nervous activity was not significantly different during exercise in CON or CAP supplementation (Figure 1D).

Distribution of genotypes

Table 2 shows the distributions of genotypes of our subjects on -866 G/A variant of UCP2 gene and -55 C/T variant of UCP3 gene. In the -866 G/A variant of UCP2 gene, GG allele had an overall frequency of 55.5 %, whereas subjects with the G/A allele and AA allele had frequency of 11.1 % and 33.3 %, respectively. In the -55

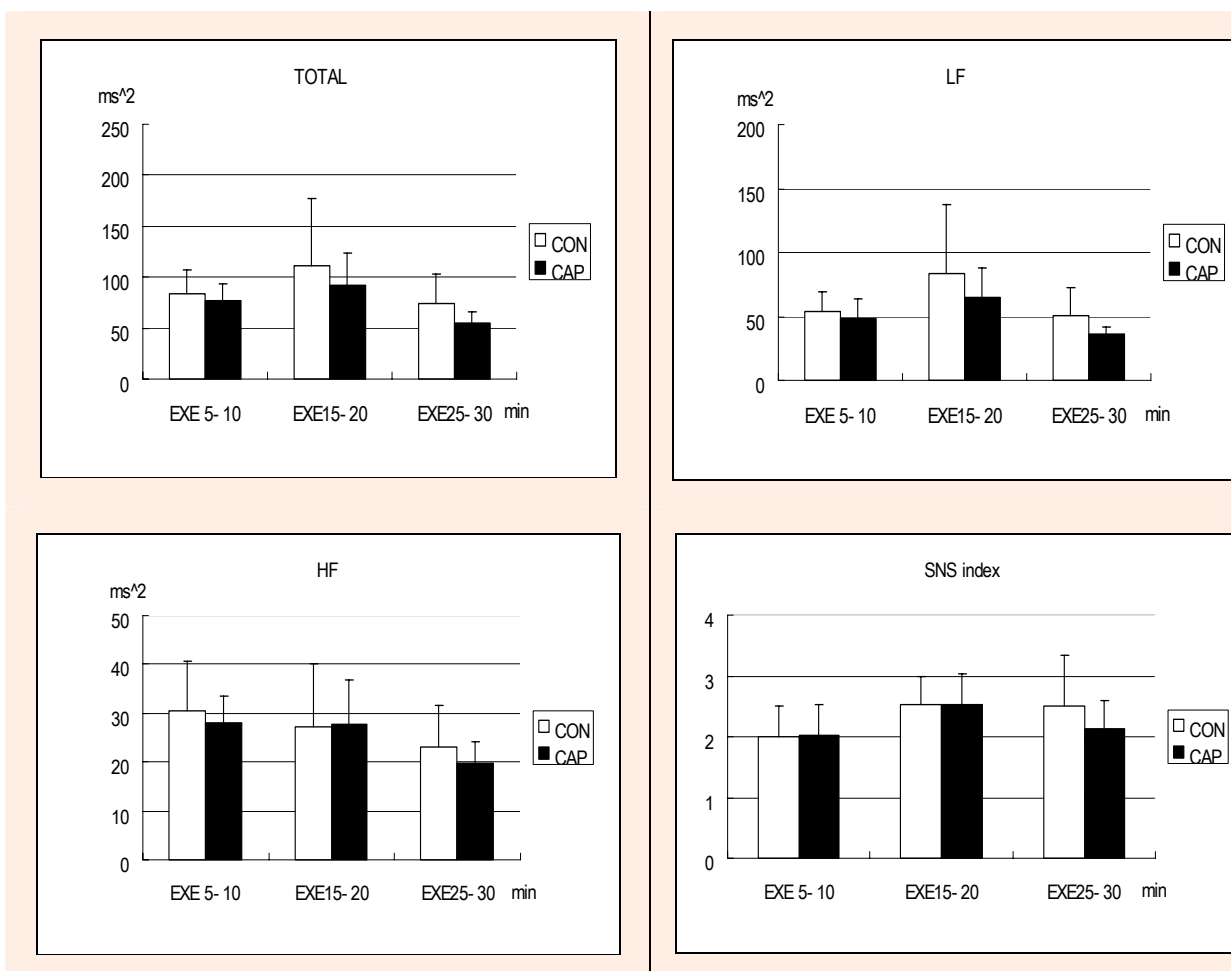


Figure 1A-D. Changes of activity in the autonomic nervous system after ingestion of capsaicin tablets (CAP) or placebo (CON) at rest and during exercise assessed with using heart rate variability power spectral analysis in the obese. There were no significant differences on autonomic nervous activity at rest and during exercise in capsaicin and placebo trials at any point. A (top left); TOTAL = total power of the spectrum, B (top right); LF = low frequency component of the spectrum, C (bottom left); HF = high-frequency component of the spectrum, D (bottom right); SNS = sympathetic nervous activity. The value of each placebo trial was standardized as 100%. Values represent means \pm SE.

Table 2. Distribution of genotype defined by the -866 G/A variant of the UCP2 promoter gene and -55 C/T variant of the UCP3 promoter gene in nine obese men. Values represent the number of subjects (percentage).

	-55 C/T variant of UCP3 gene		
866 G/A variant of UCP2 gene	CC, 3 (33.3)	CT, 4 (44.4)	TT, 2 (22.2)
GG, 5 (55.5)	3 (33.3)	1 (11.1)	1 (11.1)
GA, 1 (11.1)	0	1 (11.1)	0
AA, 3 (33.3)	0	2 (22.2)	1 (11.1)

Abbreviation: GG, CC, wild type; GA, CT, heterozygous alleles; AA, TT, homozygous alleles.

C/T variant of UCP3 gene, subjects with CC allele had frequency of 33.3 %. The CT allele and TT allele had frequency of 44.4 % and 22.2 %, respectively. The subject with GG allele of UCP2 and TT allele of UCP3 has also frequency of 11.1 %. The AA allele with CT allele and AA allele with TT allele in our subject has frequency of 22.2 % and 11.1 %, respectively. Although no significant difference between genotypes of UCP2 polymorphism (no Figure), G/G + G/A allele increased in SNS index compared to AA allele at EXE 15-20 min during the exercise ($p > 0.068$) However, genotypes of UCP3 on SNS index were not different (no Figure).

Cardiac depolarization-repolarization interval

The baseline RTc and QTc data of both trials were not significantly different. Figures 2A-B show the changes of cardiac depolarization-repolarization interval after ingestion of CAP or CON during exercise in our obese subjects. There were no significant differences in RTc and QTc during exercise in both trials.

Discussion

In this study, we investigated whether capsaicin ingestion affects cardiac ANS activity and cardiac QT intervals as well as, for the first time to our knowledge, the association between cardiac ANS activity and variants of UCP2 and UCP3 polymorphisms during aerobic exercise in obese males. The effects of capsaicin on cardiac ANS activities during exercise intervention did not appear statistically significant changes in the present study. Capsaicin stimulates primary afferent neurons (Longhurst et al., 1984), 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 (Watanabe et al., 1988a; 1991). The validity of spectral analysis of HRV has been shown under the resting condition. However, several studies have experienced difficulty in using HRV spectral analysis during non-resting conditions such as dynamic exercise (Arai et al., 1989; Perini et al., 1990; Rimoldi et al., 1992) because of the extremely reduced spectral power associated with increased heart rate. Human ANS activities are also influenced by the individual's psychological, behaviour, environmental, and genetic factors. With these regards, we have tried to minimize the external environment of the subjects affecting cardiac ANS activity during our experiment period as well as analyzed genetic variants of our subjects. In the present study, we found the homozygous allele of UCP2 and UCP3 polymorphisms (33%, 22% frequency, respectively) in our subjects. We indicated the association with the SNS index and GG allele of UCP2, but not UCP3 polymorphism, although no signifi-

cant difference. In this respect, genotypes of UCP2 polymorphism may influence to cardiac ANS activity, particularly sympathetic nervous activity. Furthermore, the results of the present study on cardiac ANS activities strongly support the MONA LISA hypothesis, an acronym for "Most Obesities Known Are Low In Sympathetic Activity" as well as agree with the previous studies (Matsumoto et al., 1999; 2000; 2001).

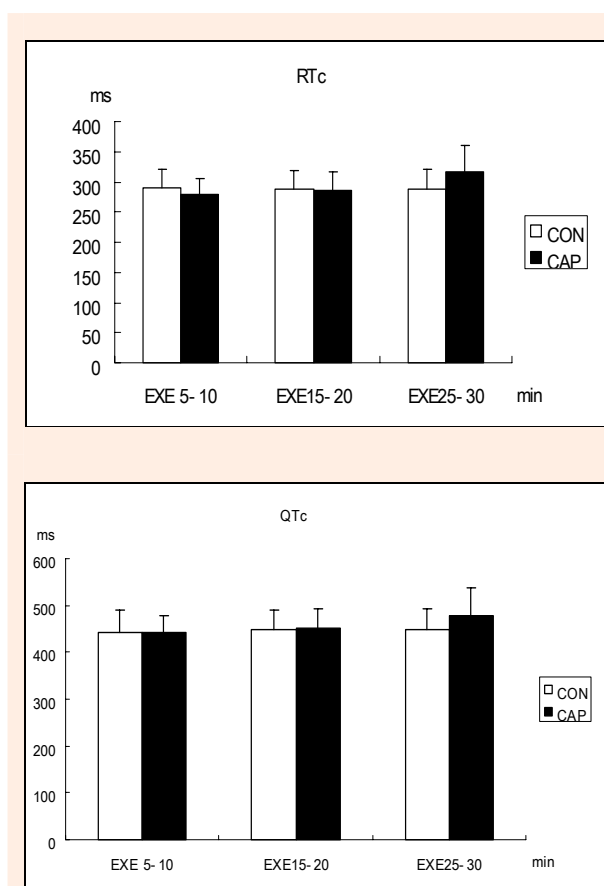


Figure 2A-B. Changes of cardiac depolarization-repolarization interval after ingestion of capsaicin tablets (CAP) or placebo tablets (CON) randomly at rest and during exercise in healthy young men. There were not significantly differences on cardiac depolarization-repolarization interval at rest and during exercise in capsaicin and placebo trials at any point. a RTc corrected activation recovery interval, b QTc corrected QT interval. Values represent means \pm SE.

The ECG QT interval has been classically thought to be the duration of electrical stability. Prolongation of the QT interval has been shown in various cardiac diseases (Schwartz and Wolf, 1978; Schwartz et al., 1993), particularly in patients with ventricular arrhythmias. In our previous study, cardiac depolarization-repolarization

interval was also significantly prolonged in patients with ischemic heart disease and with varying degrees of diabetic autonomic neuropathy in comparison to control subjects (Ue et al., 2000). There is also increasing evidence that a prolonged QTc is predictive of coronary heart disease mortality in healthy populations (Schouten et al., 1991). However, it is often difficult to determine the end of the T wave and to measure the QT interval precisely because of a variety of morphological T wave abnormalities such as bifid, biphasic, or notched T waves (Moss et al., 1985; Schouten et al., 1991; Schwartz et al., 1993). The present study examined the influence of cardiac depolarization-repolarization intervals on ECG by the newly developed method for evaluating the effect of the capsaicin ingestion before exercise. The findings in the current investigation suggest that the ingestion of capsaicin is not associated with a prolongation of cardiac RTc and QTc intervals, nor does it appear to have any adverse effect upon cardiac electrical stability.

On the other hand, because the results of the present study were derived from a limited number of subjects, the results must be carefully interpreted until further studies clarify to predisposition of the present findings. Nevertheless, no studies, at least to our knowledge, are performed to investigate the alterations of cardio-protective functions upon the distribution of UCP2 and UCP3 genotypes and capsaicin supplementation during the exercise in obese individuals.

Conclusion

We showed that capsaicin ingestion 1 h before exercise has not affected the positive alterations of cardiac ANS activity during low intensity exercise corresponding to 50%VTmax in obese individuals. We also suggested that -866 G/A variants of UCP2, but not UCP3 polymorphism may associate with alteration of cardiac ANS activity. Otherwise, capsaicin is not associated with the prolongation of cardiac depolarization-repolarization interval. Therefore, although causing no adverse effects on cardiac electrical stability, our results suggest that capsaicin supplementation has no effect on cardiac ANS activities during exercise intervention in obese subjects. Further studies should also consider genetic variants for exercise efficacy against obesity.

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Key points

- Obese individuals possess reduced cardiac autonomic nervous activities, especially sympathetic nervous activity associated with thermogenesis induced by capsaicin.
- Lower sympathetic nervous activity may associate with -866 G/A variants of UCP2 polymorphism.
- Capsaicin ingestion, however, may consider as a safe nutrient-aid with no adverse effects of cardiac electrical stability.

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