The Combined Effects of Capsaicin, Green Tea Extract and Chicken Essence Tablets on Human Autonomic Nervous System Activity

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Summary The purpose of this study was to investigate whether combined capsaicin, green tea, and chicken essence tablets (CCGC) enhance human autonomic nervous activities (ANS) associated with thermogenic sympathetic activity without any adverse effect on the cardiac depolarization-repolarization period. Six healthy males (25.2±1.7 y) volunteered for this experiment. Autonomic nervous activities were examined 5-min at rest per 30-min for total 1.5 h after consuming chicken or CCGC or placebo tablets at random on separate days. Using heart rate variability power spectral analysis, we assessed human autonomic nervous activities. In comparison to chicken essence or placebo tablets, it was observed that the consumption of CCGC significantly increased human autonomic nervous activities [Total power representing over-all ANS activity; CCGC trial 160.2 (50.0) vs. placebo 92.8 (53.3)%, p<0.05; VLF, very low-frequency power associated with thermogenic sympathetic activity: CCGC trial 235.5 (101.7) vs. chicken 130.5 (52.9)%, p<0.05; LF, low frequency power representing combined sympatho-vagal activity: CCGC trial 199.8 (59.8) vs. placebo 120.6 (49.2)%, p<0.05] at 60-min and 90-min. There were no significant differences in heart rate corrected cardiac recovery time (RTc) or QT interval (QTr). In conclusion, the consumption of CCGC enhances thermogenic sympathetic activity compared to that of chicken essence or placebo tablets. Therefore, these results suggest that combined capsaicin, green tea, and chicken essence tablets may be a beneficial food ingredient improving human autonomic nervous activities, particularly thermogenic sympathetic activity as a modulator of energy metabolism without any adverse effects on cardiac electrical stability.

Key Words thermogenic sympathetic nervous activity, heart rate variability power spectral analysis, cardiac depolarization-repolarization interval, combined chicken essence, capsaicin, green tea extract

Various foods such as coffee, capsaicin, green tea and herb tea are believed to affect autonomic nervous activity and other physiological functions (1–3). Chicken essence and chicken soup are, on the other hand, also widely consumed, particularly in Chinese communities in Southeast Asia, as traditional remedies for several ailments including i) recovery from blood loss during childbirth and menstruation, ii) nutritional supplement for sickness, and iii) enhancement of mental efficiency. Consumption of this chicken essence extract also has been reported to stimulate the metabolic rate by an average of 5% to 12% in human subjects (4, 5). Capsaicin has been reported to reduce perirenal adipose tissue weight and serum triglyceride concentration due to the enhancement of energy metabolism in rats (6). According to the recent study of Yoshioka et al. (7), energy expenditure (EE) increased immediately after a meal containing red pepper, whereas this enhancement of energy metabolism by a red-pepper diet was inhibited after the administration of a β-adrenergic blocker, propranolol. Green tea extract, which is rich in catechins and polyphenols, potentiates sympathetic mediated thermogenesis more than would be expected for its caffeine content alone (8) and has been shown to increase 24-h EE and fat oxidation (9). To the best of our knowledge, however, no data regarding physiological effects of the combined capsaicin, green tea, and chicken essence tablets (CCGC) upon human autonomic nervous system (ANS) activity, particularly thermogenic sympathetic nervous activity as an energy metabolic modulator are currently available.

The activity of the human ANS plays a substantial role in physiological homeostasis. As an important contributor to the regulation of EE, the sympathoadrenal system is widely assumed to play a major role in the pathophysiology of obesity. As well, recent studies have demonstrated that the percentage of body fat (10, 11), changes in body weight and energy storage (12), and glucose-induced thermogenesis (13) were correlated with differences in HRV power spectrum analysis. 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 (14), alterations in SNS activity are widely believed to contribute to the pathophysiology of obesity. No consensus has been made among investigators as to the predominant sympathetic abnormality (an increase or decrease) (15, 16), 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 beat-by-beat 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 a reliable non-invasive method and has provided a comprehensive quantitative and qualitative evaluation of neuroautonomic function under various physiological conditions (17-19). 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 (20-22). The frequencies much lower than 0.1 Hz have been thought to reflect thermoregulatory fluctuations in vasomotor tone (23, 24). We have recently demonstrated that very low frequency (VLF) components (0.007-0.035 Hz) were selectively increased against thermogenic perturbation such as acute cold exposure and mixed-food ingestion (25-28).

This finding suggests the possibility of evaluating the SNS activities associated with energy metabolic regulation by means of HRV spectral analysis in humans.

On the other hand, increased duration of the QT interval on the surface ECG is associated with increased mortality in patients with cardiac disease (29) and in apparently healthy populations (30, 31). QT interval is the time required to complete myocardial depolarization and repolarization. Consequently both ventricular conduction velocity and repolarization influence its length, and the QT duration is an important arrhythmogenic indicator (32). It has been suggested that cardiac heart rate-adjusted QT interval (QTc) prolongation may be a consequence of an unfavorable sympatho-vagal balance. In our previous study (33), we measured the cardiac depolarization-repolarization interval and performed the ECG R-R interval power spectral analysis simultaneously by using a CM5 lead ECG in patients with ischemic heart disease (IHD) and with varying degrees of diabetic autonomic neuropathy. We reported that change in sympatho-vagal balance reflects significantly longer cardiac activation-recovery interval (ARI) and recovery time (RT).

Therefore, the aim of the present study was to evaluate ANS activity, particularly the thermogenic sympathetic function in response to CCGC, which can be taken as a convenient nutritional supplement rather than taking a large quantity of the test food substances, by means of HRV power spectral analysis. We also determined the possible adverse effects of increased thermogenic sympathetic enhancement upon cardiac electrical stability.

### Table 1. Physical characteristics of subjects.

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<tr>
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BMI: body mass index. Values represent means (SE).

### METHODS

#### Subjects.
Six healthy male students from Kyoto University volunteered for this experiment. The physical characteristics of the subjects are described in Table 1. No subjects were taking any medication or smoking. All experimental procedures were explained in detail to each subject who then signed a statement of informed consent. The experiment was approved by the Institutional Review Board of Kyoto University Graduate School for Use of Human Subjects.

#### Experimental procedures.
The subjects came to the laboratory by 8:00 a.m. after eating a simple breakfast at least 2 h before they arrived at the laboratory. Subjects were requested to avoid any medication for 1 wk 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. Each subject came to the laboratory three times to consume three different tablets on separate days. The order of three experimental treatments (CCGC tablets or chicken essence tablets or placebo tablets) was chosen at random. The baseline values of all trials were standardized as 100%, and the relative value of CCGC tablets and chicken essence tablets was compared to that of placebo tablets because integrated values of the basal HRV spectrum differ greatly among individuals. Figure 1 illustrates the typical computer output of raw ECG R-R interval and trigger-averaged signals.

The subject rested for at least 30 min in a seated position in a quiet room of the temperature 23-24°C. ECG data of the subject were then measured by using heart rate variability power spectral analysis for 5-min as baseline data. Then, each subject consumed 2 tablets containing one of the three ingredients: placebo, 400 mg chicken essence, or the CCGC [0.2 mg capsaicin, 312.5 mg green tea extract (25 mg caffeine and 62.5 mg catechins), and 400 mg chicken essence] with 100 mL of water at random. The subject was measured for 5-min every 30-min for a total of 90 min to gain ECG data in the three tablet trials.

Our R-R interval power spectral analysis procedures have been fully described elsewhere (17, 25, 27, 28).
Food Substances and Autonomic Nervous System Activity

![Graph of CCGC Tablets and Heart Rate](image)

**Fig. 1.** A computer output from a subject shows the raw ECG R-R interval, and trigger-averaged signals for determining cardiac depolarization-repolarization intervals, i.e., corrected cardiac recovery time (RTc), and QTc interval at rest.

![Diagram of Myocardial Depolarization-Repolarization Analysis](image)

**Fig. 2.** A schematic representation of myocardial depolarization-repolarization analysis procedures.

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 1.024 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 the 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 1,024-s time series of R-R interval data obtained during the test (20).

To evaluate ANS activity in each subject of the present study, we analyzed very low frequency (0.007–0.03 Hz, VLF), low frequency (0.03–0.15 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. In addition, indices of the SNS and parasympathetic nervous system (PNS) activities were also calculated as the ratio of LF/HF and HF/TOTAL, respectively. The mean heart rate of each 256-s segment was also calculated together with standard error.

Our method for measuring cardiac depolarization-repolarization interval and its physiological rationale have been fully described elsewhere (33–37). Figure 2 shows a schematic representation of myocardial depolarization-repolarization analysis procedures. We used ECG waveform averaging technique using a computer algorithm before calculating cardiac depolarization-repolarization related parameters according to our previous study (33). The points of QRS (the ventricle depolarization) onset, the minimum dV/dt of the QRS and the maximum dV/dt in the ECG T wave were determined automatically by our computer system from CM5 lead ECG. Transmembrane activation time (AT) was defined as the interval between the QRS onset and the maximum dV/dt of the QRS. Likewise, ARI was defined as the interval between the endpoint of AT and the maximum dV/dt in the ST-T (the interval between ECG QRS onset and T wave onset) segment. The ARI and RT time were corrected (ARIC, RTIC) by Bazett's heart rate correction formulae \( QT = QTc \times \sqrt{R-R \text{ interval}} \) according to our previous study (33). Moreover, RT was defined as a sum of AT and ARI and assessed quantitatively the time required for completing cardiac depolarization and repolarization phases instead of evaluating changes in ST-T segment and QT interval.

**Statistical analyses.** All statistical analyses were per-
formed using a commercial software package (SPSS version 11.5 for Windows, SPSS Inc., Illinois). Statistical differences were assessed using two-way analysis of variance (ANOVA) with repeated measurements for time, treatment, and time × treatment. The comparison of three tablet trials at each measurement time was analyzed using Tukey's post hoc test. p values of <0.05 were considered to be statistically significant. Data are expressed as mean (SE).

RESULTS

The effects of chicken essence or placebo or the combined capsaicin, green tea, and chicken essence tablets on autonomic nervous system activity

Heart rate changes. Figure 3 shows the alterations of heart rate for a total of 90 min after consumption of chicken, placebo, and CCGC. Heart rate did not show any significant difference among three experimental treatments [Pre: placebo 56.58 (2.83), chicken 60.23 (2.44), CCGC 59.62 (3.79); at 30-min: placebo 58.00 (2.73), chicken 57.47 (2.71), CCGC 57.73 (2.95); at 60-min: placebo 56.92 (3.15), chicken 56.37 (2.21), CCGC 57.68 (3.18); at 90-min: placebo 57.07 (2.69), chicken 56.68 (2.32), CCGC 56.78 (3.68) beats/min, means (SE), p>0.05].

Power spectral changes. Figure 4 shows a representative sample of ECG R-R interval power spectrum from a subject. Our HRV power spectrum analysis has accurately separated VLF, LF, and HF power components of ANS activities. ECG R-R interval power spectral results showed markedly different responses in terms of the spectral total power, representing over-all ANS activities, VLF power represented with SNS thermogenic component, and LF power containing the sympathovagal component.

Figure 5 shows the group data for the time course changes of autonomic nervous activities after consumption of chicken, placebo, and CCGC. Total power of CCGC was nearly two times higher than that of the placebo trial. The difference was significant at 60-min [CCGC 160.2 (50.0), placebo 92.8 (53.3)%], p<0.05. At 30-min, there was also significant difference in the chicken trial and placebo [chicken 141.1 (49.9), placebo 96 (46.5)%], p<0.05. Furthermore, at 90-min, there were significant differences between the chicken trial and placebo, and CCGC and placebo [chicken 127.5 (21.9), placebo 99.5 (9.9), CCGC 174.1 (50.3), placebo 99.5 (9.9)%], p<0.05, respectively. In VLF power, there was a significant difference between the chicken trial and CCGC trial at 90-min [chicken 130.5 (52.9), CCGC 235.5 (101.7)%], p<0.05. In LF power, the differences were significant at 60-min [CCGC 179.6 (66.0), placebo 100.5 (49.3); chicken trial 109.5 (26.9), CCGC 179.6 (66.0)%], p<0.05 and 90-min [CCGC 199.8 (59.8), placebo 120.6 (49.2); chicken trial 133.7 (43.6), CCGC 199.8 (59.8)%], p<0.05. There was also a significant difference in HF power between CCGC and placebo at 90-min [CCGC 152.5 (52.4), placebo 90.6 (21.5)%], p<0.05.

In the indices of PNS and SNS activity, the PNS index decreased and SNS index increased slowly during the experiment. However, no significant change was found in the indices of PNS and SNS activity. In this study, the significantly augmented response in TOTAL, VLF, and LF powers seemed to continue at least for 1 h after con-

![Fig. 3. Changes in heart rate at rest after consumption of chicken or placebo or CCGC. There were no significant differences in three tablet trials. Values represent means (SE).](image)

![Fig. 4. The representation of an ECG R-R interval power spectrum from a subject. Very low (VLF), low (LF), and high (HF) frequency components are represented by the black, striped, and white area, respectively.](image)
Fig. 5. Changes of activity in the autonomic nervous system after consumption of chicken or placebo or CCGC at rest for total 90-min assessed by using heart rate variability power spectral analysis in healthy males. It showed significant differences for TOTAL, VLF, LF, and HF components of autonomic nervous activities at 60-min and 90-min in chicken or placebo or CCGC tablet trials. However, the difference did not reach statistical significance for PNS or SNS indices. A: TOTAL total power of the spectrum. B: VLF, very low frequency component of the spectrum. C: LF, low frequency component of the spectrum. D: HF, high-frequency component of the spectrum. The baseline value of each trial was standardized as 100%. Values represent means (SE). *p<0.05, **p<0.01.

Fig. 6. Alterations of cardiac depolarization-repolarization interval after consumption of chicken or placebo or CCGC at rest in healthy males. There were no significant differences in cardiac depolarization-repolarization interval at rest among three trials at any point. A: RTc, corrected activation recovery interval. B: QTC, corrected cardiac QT interval. Values represent means (SE).
summing CGCG, suggesting the increased thermogenic effects.

Cardiac depolarization and repolarization interval changes

Figure 6 shows the time course alterations of cardiac depolarization-repolarization interval after consumption of chicken, placebo, and CGCG. There were no significant differences in RTc or QTc at rest for 90 min among three trials at any point.

DISCUSSION

The main finding of this study was that the ingestion of CGCG tablets significantly increased cardiac ANS activities, particularly the TOTAL power, VLF, and LF frequency components of HRV. In our previous study (38), we assessed the respiratory rate and substrate oxidation with the present test tablets. Thus, we have reported that the CGCG tablet ingestion could translate to a positive clinical effect by reducing approximately 460 g of body fat, following 2-wk of supplementation, and the application of this natural health supplement for excess fat regulation should be considered. Therefore, considering our previous results, the present study investigated the effects of CGCG tablet on cardiac ANS activity associated with the modulator of energy metabolism. On the basis of their mechanisms of action, these ingredients such as capsaicin, green tea, and chicken essence, appear to complement each other by acting on the various pathways of the SNS at the cellular and molecular level (38).

The higher thermogenic effects of chicken essence extract reported by Geissler and Boroumand-Naini (4) could be also explained by the different degree of SNS activation through the sensory stimulation triggered by food ingestion, causing a rapid increase in noradrenaline, glucagon, and insulin during the first few minutes of feeding. Orally administered chicken essence extract would not have such sensory stimulation and thus no immediate SNS activation. In human studies, test meals enriched with capsaicin also increased both energy expenditure and lipid oxidation (7, 26). However, to our knowledge, no studies regarding the effects of capsaicin extract tablets on ANS activity were found. Moreover, tea catechins were shown to prolong the effect of norepinephrine-mediated thermogenesis by suppressing catechol O-methyltransferase (COMT) and inhibiting the degradation of norepinephrine at the synaptic cleft (39). Caffeine in green tea extract also prolongs the thermogenic signal of norepinephrine by inhibiting phosphodiesterase-induced degradation of intracellular cyclic AMP (cAMP) (40). Along with these findings, we observed the significant increase in TOTAL, VLF and LF frequency components for total 90 min after the intake of CGCG tablets, indicating the improvement of ANS activities.

In the present study, we used HRV power spectral analysis in order to investigate the combined effect of CGCG on 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 neuro-autonomic function (25–28).

Concerning the 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 (41). 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 (13).

In that study, the validity of HRV spectral analysis was confirmed by the measurement of plasma catecholamine concentration. In our previous study (25), we conducted a pharmacological experiment to explore further the relationship between HRV and thermoregulation and found that complete autonomic blockade caused the abolishment of heart rate fluctuations and significant reduction of energy expenditure. Furthermore, we identified the VLF frequency component, which was selectively increased against external thermogenic perturbation such as acute cold exposure and food intake in non-obese healthy volunteers (25). 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 sympathetic-thermogenic effect of CGCG tablets in humans.

The QT interval on the ECG has been a parameter of variable interest since the advent of electrocardiography (42). This interest was because the prolongation of the QT interval has been shown in various cardiac diseases (43, 44), particularly in patients with ventricular arrhythmias and in healthy populations (45). In our previous study (33), we have also reported that decreased ANS activities in diabetic patients reflect a prolonged cardiac QT interval due to cardiac autonomic dysfunction because of diabetic neuropathy.

In this study, we examined cardiac depolarization-repolarization interval on ECG HRV power spectral analysis by using the newly developed method for investigating the safety of CGCG tablets. Our data suggest that the ingestion of CGCG tablets does not cause such prolongation of cardiac QT interval toward sympatho-vagal balance.

In conclusion, we examined whether the ingestion of CGCG tablets elevates ANS activities, particularly thermogenic sympathetic activity at rest compared to that of chicken or placebo tablets. In this study, the consumption of CGCG tablets at rest in healthy males led to significant autonomic function progression. Our results suggest that CGCG tablets could be a beneficial food substance, which significantly improves ANS activity related to the thermogenic component of the SNS activity as an energy metabolic modulator without any adverse effect in cardiac depolarization and repolarization period in human subjects.
Acknowledgments
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