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ORIGINAL ARTICLE

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Influence of caffeine ingestion on autonomic nervous activity during endurance exercise in humans

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Abstract The effects of caffeine ingestion on the activities of the autonomic nervous system (ANS) during endurance exercise at low intensity were investigated using a power spectrum analysis of heart rate variability. Placebo or caffeine (300 mg) capsules were randomly administered to the subjects. Each subject ingested the samples 2 h before cycling on an ergometer for 30 min at an intensity corresponding to 40%–50% of his ventilatory threshold. The electrocardiogram, blood pressure (BP) and gas exchange parameters were monitored during rest and exercise. The results indicated that there were no significant differences in heart rate and systolic blood pressure between the trials. The spectrum integrated values of the low frequency power and total power components in the caffeine trial were significantly greater than in the placebo trial during exercise, which implied that activities of the ANS were augmented by caffeine. Caffeine also induced enhanced lipid oxidation as shown by the significantly lower respiratory gas exchange ratio and increases in diastolic blood pressure during exercise. The results shed some light upon the relationship between the activity of the ANS, energy metabolism and BP. In conclusion, the results suggest that caffeinated beverages have a potential to be useful supplements to the prescription of exercise for individuals who experience a depressed activity of the ANS. The results also suggest that the experiment protocol used in this study is a sensitive and noninvasive method for evaluating the effects of various foods and nutrients on the activity of the ANS.

Keywords Autonomic nervous system activity · Caffeine · Endurance exercise · Power spectrum analysis

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Introduction

Cardiovascular disease is the leading cause of morbidity and death in Japan (Japan Ministry of Health and Welfare 1999). Depression in cardiac vagal tone is associated with coronary heart disease; it is a critical risk factor for sudden cardiac death (Huikuri et al. 1998). We have demonstrated that the heart rate variability (HRV) of diabetic patients was smaller in comparison with a control group (age-matched healthy people), which was mainly caused by a depression of activity in the cardiac parasympathetic nerve supply (Moritani et al. 1993). Furthermore, we reported that activity in both the sympathetic and parasympathetic nervous systems is reduced as age increases (Oida et al. 1999). Bray (1991) has proposed the MONA LISA hypothesis, an acronym for "Most Obesities kNown Are Low In Sympathetic Activity" indicating that obesity is associated with a relative or absolute reduction in the activity of the thermogenic component of the sympathetic nervous system.

It has been reported that habitual exercise training can prevent age-related chronic heart disease, diabetes, and hypertension (Biewener and Bertram 1994; Farrell et al. 1998) and osteoporosis (Vasankari et al. 1998). Pellizzer et al. (1999) have recently demonstrated that a reduced dietary fat intake increases parasympathetic nerve activity in healthy premenopausal women. Our most recent study (Amano et al. 2001) has also demonstrated a strong possibility that activity in the autonomic nervous system (ANS) can be enhanced by exercise training among previously obese individuals experiencing reduced activity of the ANS.

In this context, the physiological effects of caffeine could be of great clinical importance since caffeine-containing products such as coffee, tea, and chocolate are widely consumed throughout the world. It is well known that caffeine ingestion improves performance during prolonged exercise to exhaustion (Costill et al. 1978; Kovacs et al. 1998), an effect which is due to an increase in circulating free fatty acids (Graham and Spriet 1991). It has already been confirmed by observation of endogenous catecholamine release (Bangsbo et al. 1992; Van-Soeren and Graham 1998; Kalmar and Cafarelli 1999) that caffeine ingestion enhances the activity of the sympathetic nervous system in humans at rest and during exercise.

It is reasonable to assume that the ingestion of caffeine before moderate exercise might enhance both fat oxidation and activity in the ANS. There has been no study, at least to our knowledge, that has investigated the effects of caffeine upon the activity of the ANS with special reference to fat oxidation and blood pressure (BP) responses during exercise at an intensity below the anaerobic threshold.

Methods

Subjects

A group of eight healthy young Japanese men [mean (SEM)] [age 25.5 (0.8) years, body mass 68.3 (1.7) kg, height 172.2 (4.3) cm] participated in this study and their informed consent was obtained according to the guidelines established by the declaration of Helsinki. They were physically active, but none were engaged in regular athletic training. They were habitual users of caffeine and normally consumed less than 500 $mg \cdot day^{-1}$. This study was approved by the Institutional Review Board for Use of Human Subjects at Kyoto University.

Study design

Prior to the start of the experiment, the subjects were given an incremental cycling test on a stationary cycle ergometer (CB-X 1000, NAPS, Japan) to determine their ventilatory thresholds (VT). The intensity of exercise just below that at which metabolic acidosis occurs has been called the AT. Thus, AT can be considered to be an important assessment of the ability of the cardio-respiratory system to supply oxygen at a rate adequate to prevent anaerobiosis in the muscles during exercise. We estimated the AT of each individual using gas exchange parameters, i.e. VT in this study.

Following warm-up exercise at 20 W for 2 min, the ramp exercise test at a pedalling frequency of 60 rpm started with a 10 W increment every minute. The exercise was stopped when one of the following criteria of maximal oxygen uptake was obtained:

1. A plateau or levelling off of oxygen uptake ($\dot{V}O_2$) in spite of the increasing exercise intensity
2. Reaching maximal heart rate (maximal predicted heart rate $\pm 5\%$), or
3. Volitional exhaustion

The VT was then determined according to our previously described procedures (Moritani et al. 1987).

On the day preceding the exercise test, the subjects were instructed to refrain from strenuous physical exercise, tobacco and alcohol. They were instructed not to take any food or beverages except water during the 10 h prior to the commencement of exercise.

The next morning at 2 h and 5 min before the exercise, they consumed a standardized breakfast of boiled rice (energy content 300 kcal or approximately 1,254 kJ), which is a traditional Japanese food. At 2 h before exercise, placebo capsules or caffeine capsules (300 mg of caffeine, Takasago-kohryoh Co., Osaka, Japan) were ingested with 100 ml of water. The amount of caffeine ingested was based on the previous studies (Chad and Quigley 1989), which provided evidence of the effects of caffeine on substrate utilization during mild exercise. The order of the experimental treatments was chosen at random, separated by a week. To avoid the influences of circadian rhythm, each test was made between 0800 and 1100 hours.

After taking the capsules the subjects rested in a sitting position in a quiet and relaxing atmosphere at a temperature of 23–24°C, and the baseline electrocardiogram (ECG), BP, and gas exchange parameters were recorded for 5 min (*rest*). Following this, the subjects cycled for 30 min at an intensity corresponding to 40%–50% of that at the VT of each individual, ranging from 60 to 80 W. Measurements were made at the following times: 5–10 min, 15–20 min and 25–30 min after the start of exercise.

During *rest*, the subjects were instructed to breathe at a frequency of 1 breath every 4 s (0.25 Hz) in synchrony with the sound of an electric metronome, as mentioned in our study (Hibino et al. 1997), so that respiratory-linked HRV would not overlap with fluctuations in low-frequency heart rate. During exercise, the subject was instructed that they could breathe freely as the respiratory rate would easily exceed the 0.25 Hz, so that low frequency HRV frequency components would not be affected by the respiration.

Data acquisition

The ECG was obtained using a CM5 lead. The analogue output of the ECG was connected to an ECG amplifier (Multi-channel Amplifier MEG-6100, Nihon Kohden Co., Japan) and digitized using a 13 bit analogue-to-digital converter (HTB410) at a sampling rate of 1 kHz, using a 0.5 Hz–100 Hz band pass filter at rest and a 1.5 Hz–100 Hz filter during exercise.

The BP was recorded using an automated sphygmomanometer (FINAPRES 2300, Ohmeda, USA) connected to a finger cuff containing a plethysmotransducer. Analogue output of the BP was digitized using a 13 bit analogue-to-digital converter at a sampling rate of 1 kHz. Beat-by-beat systolic blood pressure (BP_s) and diastolic blood pressure (BP_d) values were calculated later using computer software developed in our laboratory.

Measurements of gas exchange parameters were obtained using the mixing chamber method (AE-280S, Minato, Japan). The analogue signals of fractional concentrations of O_2 and CO_2 from the gas analysers and those from the flow transducer were continuously digitized using a 13 bit analogue-to-digital converter at a sampling rate of 50 Hz. The $\dot{V}O_2$, carbon dioxide production, and expired ventilatory volume were calculated every 15 s.

All signals were stored continuously on a computer (DOS/V) for later analysis.

R-R interval power spectrum analysis

The heart acts in a discrete fashion with successive heartbeats leading to a series of fluctuating values of R-R intervals. In recent years, the power spectrum analysis of HRV has been proved to be a reliable non-invasive method to use for the quantitative and qualitative assessment of the activities of the cardiac sympathetic and parasympathetic nervous system in human studies (Matsumoto et al. 1999; Moritani et al. 1993). In general, power spectrum analysis of HRV has shown two major distinct regions of periodicity in R-R intervals: the high frequency, respiration-linked component (HI, greater than 0.15 Hz) and the low frequency component (LO, less than 0.15 Hz). The HI is associated solely with activity in the parasympathetic nervous system while LO reflects mainly activity in the sympathetic nervous system, and partly activity in the vagus (Pomeranz et al. 1985; Pagani et al. 1986).

In the actual analysis, the derived R-R interval time series was aligned in 2 Hz sequences for power spectrum analysis. The DC component and linear trends were completely eliminated by digital filtering for band pass between 0.03–0.5 Hz in rest and 0.03–0.8 Hz during exercise as described elsewhere (Moritani et al. 1993; Oida et al. 1997; Matsumoto et al. 1999, 2000, 2001). After passing through a Hamming-type data window, power spectrum analysis using a fast Fourier transform was performed on consecutive 240 s time series of the data for R-R intervals obtained during the experiments. We analysed LO (0.03–0.15 Hz), HI (at rest: 0.15–0.4 Hz, during exercise: 0.15–0.8 Hz), and total power (TOTAL, at rest: 0.03–0.4 Hz, during exercise: 0.03–0.8 Hz) by integrating the spectrum for the appropriate bandwidth. Because integrated values of the basal spectrum differ greatly among individuals, the value of each placebo trial was standardized as 100%, and the other values were compared to this.

Statistical analyses

All statistical analyses were performed using a commercial software package (SPSS version 7.5 for Windows, SPSS Inc., Chicago, Ill.). The effects of time, treatment and time×treatment were evaluated using 2-way ANOVA for repeated measurements; for comparisons between the trials at certain times, we used Student's paired *t*-test. *P* values of less than 0.05 were considered to be statistically significant. Data are expressed as mean ± SEM.

Results

Effect of caffeine on the power spectrum of the R-R intervals

There were no significant differences in heart rate between the placebo and the caffeine trials at any points [*rest*: placebo 59 (4.25), caffeine 63 (2.6); *5–10 min*: placebo 93 (4.3), caffeine 92 (3.2); *15-20 min*: placebo 95 (4.4), caffeine 94 (3.3); *25–30 min*: placebo 96 (4.3), caffeine 95 (3.0) beats·min^{-1}, $P > 0.05$]. With regard to the integrated values of the spectrum, there were no significant differences between the trials at *rest*, but during the exercise, HI, LO and TOTAL in the caffeine trial were around double those of the placebo trial. The differences were significant at *25–30 min* into the exercise [TOTAL = 194.3 (32.6)%, LO = 194.1 (33.1)%, HI = 230 (59.9)%, $P < 0.05$]. See Fig. 1a, b, and c.

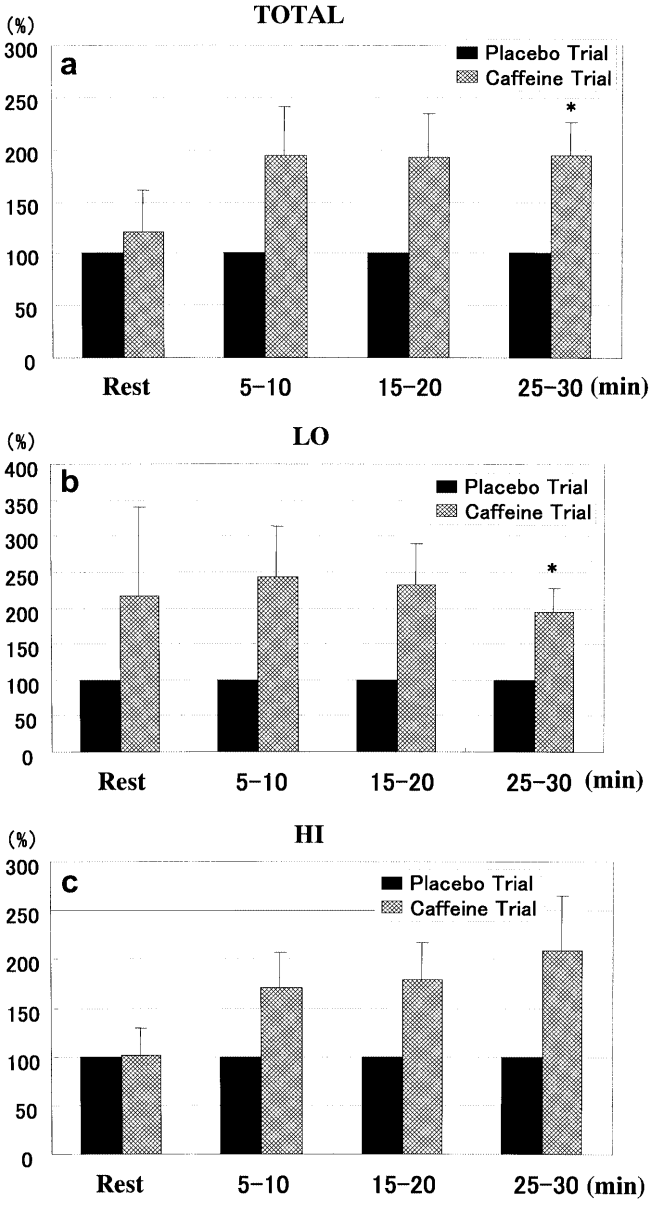

Fig. 1a–c. Changes of activity in the autonomic nervous system following ingestion of capsules containing either caffeine or a placebo, as assessed from a power spectrum analysis of the R-R interval. **a** *TOTAL* Total power of the spectrum, **b** *LO* low frequency component of the spectrum, **c** *HI* high frequency component of the spectrum. Measurements were made at rest (*Rest*), and *5–10* min, *15–20* min and *25–30* min after the start of exercise. The value of each placebo trial was standardized as 100%. Values are means and SEM, $n = 8$. *$P < 0.05$ compared to placebo trial

Effect of caffeine on BP

In Fig. 2a and b the changes in BP_s and BP_d observed during the rest and the exercise period, are shown. At *rest*, there was no significant difference between the trials in respect of BP_s and BP_d. Exercise induced a rise in both BP_s [*5–10 min*: placebo 143 (7.9), caffeine 148 (4.6); *15–20 min*: placebo 149 (8.4), caffeine 153 (6.7); *25–30 min*: placebo 154 (7.8), caffeine 160 (6.6) mmHg, $P > 0.05$] and BP_d [*5–10 min*: placebo 71 (3.9), caffeine 76 (3.1); *15–20 min*: placebo 73 (3.8), caffeine 78 (3.8) mmHg, $P > 0.05$]. At *25–30 min*, a significant caffeine effect on BP_d was observed [placebo 77 (3.7) mmHg, caffeine 83 (3.1) mmHg, $P < 0.05$].

Metabolic response to caffeine

At *rest*, $\dot{V}O_2$ and respiratory gas exchange ratio (*R*) showed no significant difference between the trials [$\dot{V}O_2$: placebo 0.27 (0.03), caffeine 0.24 (0.05) l·min^{-1}; *R*: placebo 0.79 (0.03), caffeine 0.76 (0.02); both $P > 0.05$]. During the exercise period, $\dot{V}O_2$ values were significantly increased ($P < 0.001$) in both trials when compared to the resting condition, e.g. *25–30 min*: placebo

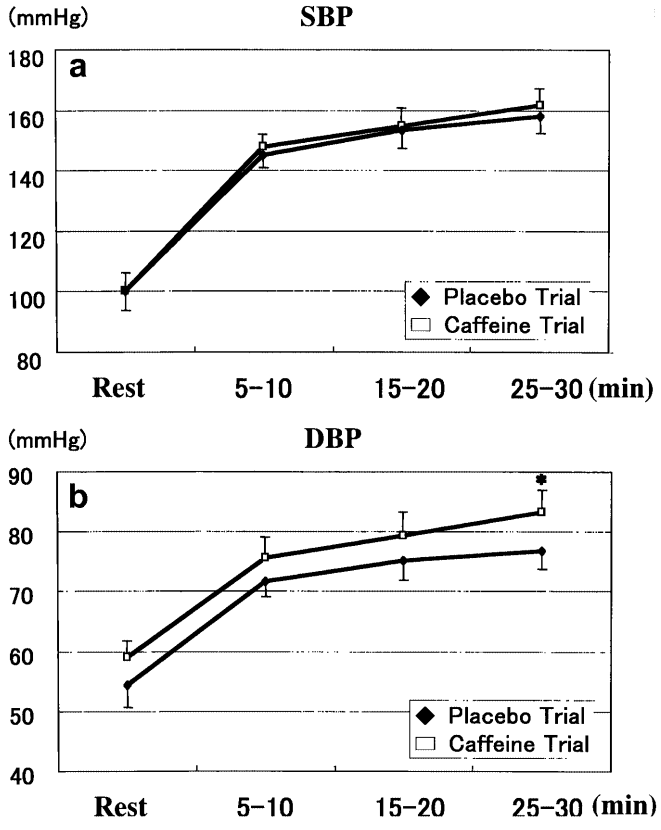

Fig. 2a, b. Changes in blood pressure before and during exercise after ingesting capsules containing either placebo or caffeine. Measurements were made at rest (*Rest*), *5–10* min, *15–20* min and *25–30* min after the start of exercise. **a** Systolic blood pressure (*SBP*), **b** diastolic blood pressure (*DBP*). Values are means and SEM, $n=8$. $^*P<0.05$ compared to placebo trial

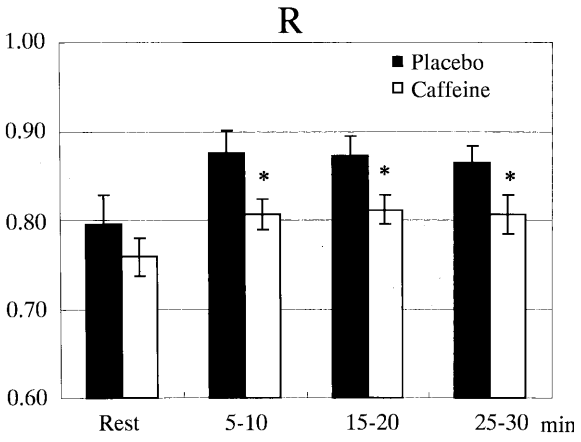

Fig. 3. Changes of respiratory exchange ratio (*R*) before and during exercise after the ingestion of capsules containing either placebo or caffeine. Measurements were made at rest (*Rest*), *5–10* min, *15–20* min and *25–30* min after the start of exercise. Values are means and SEM, $n=8$. $^*P<0.05$ compared to placebo trial

1.04 (0.06), caffeine 1.09 (0.11), but there were no significant group differences in $\dot{V}O_2$ during the exercise period. On the other hand, *R* values in the caffeine trial were significantly lower than those in the placebo trial during the exercise [*5–10 min*: caffeine 0.80 (0.02), placebo 0.87 (0.02); *15–20 min*: caffeine 0.81 (0.02), placebo 0.87 (0.02); *25–30 min*: caffeine 0.81 (0.02), placebo 0.86 (0.02); $P<0.01$). See Fig. 3.

Discussion

Methodological concerns

In this study, a caffeine-induced enhancement of the activity of the ANS was observed at 2.5 h after its ingestion. The half-time of elimination of caffeine from the plasma varies between 2 and 8.5 h in healthy subjects (Smits et al. 1985), so it can be speculated that the effect of caffeine may have been attenuated during our measurements as some of the caffeine might have been eliminated at the time of our experiment. Previously, we measured ECG continuously for 60 min following ingestion of caffeine at rest and found significant enhancement of the activity of the ANS occurring at 20–30 min after the ingestion (Hibino et al. 1997).

It needs to be pointed out that the common belief that caffeine and coffee consumption might have very similar physiological effects is not the case. Graham et al. (1998) have shown that the same dose of caffeine, either ingested in a capsule as in the present study, or in coffee resulted in different plasma adrenaline concentrations, i.e. being significantly higher after taking the caffeine capsules. These findings suggest that one cannot extrapolate the effects of caffeine to coffee; there must be something in coffee that moderates the effects of caffeine.

Effects of caffeine on ANS activity

Many studies have observed changes in plasma adrenaline and noradrenaline concentrations and have shown that caffeine enhances the activity of the sympathetic nervous system (Smits et al. 1985; Van-Soeren and Graham 1998). On the other hand, after using power spectrum analysis of HRV, we reported that caffeine ingestion enhanced the activities of both the sympathetic and the parasympathetic nervous systems at rest (Hibino et al. 1997). The present study showed that this enhancement occurs during exercise as well.

The ANS plays an important role in energy metabolism. A change or reduction in activity of the sympathetic nervous system per se has been widely believed to contribute to the pathogenesis of obesity (Peterson et al. 1988; Bray 1991). We have recently demonstrated that obese young women exhibit a much reduced LO frequency component of HRV responsiveness to capsaicin (Matsumoto et al. 2000), as well as a lower capacity for enhancing energy metabolism (diet-induced thermogenesis) after food ingestion (Matsumoto et al. 2001). We have also shown that subjects having Trp64 polymorphism of the β-3 adrenergic receptor mutation (decreased receptor

affinity for adrenaline and noradrenaline), responsible for the control of lipolysis through ANS activity, manifested a significantly lower LO frequency power than normal subjects (Shihara et al. 1999). More than one-third of the Japanese population is known to have the mutation of the β-3 adrenergic receptor (Shihara et al. 1999) which might, at least in part, explain the recent increase in occurrence of obesity and non-insulin dependent diabetes (NIDDM) patients due to drastic changes in the lifestyle and the adoption of a westernized diet.

Our data showed lower R values during submaximal exercise in the caffeine trial compared to those in the placebo trial, as shown in previous studies (Chad and Quigley 1989; Flinn et al. 1990; Donelly and McNaughton 1992). In addition, our HRV power spectrum data together with the gas exchange data strongly suggest that the caffeine-induced stimulation of lipid metabolism might be mediated by enhanced activity of the sympathetic nervous system.

As reported in previous studies (Smits et al. 1985), our data also showed a pressor effect of caffeine. This undesirable phenomenon is also considered to be the effect of increased activity of the ANS. However, the BP_s responses during the exercise were almost identical in the trials with or without caffeine ingestion. Furthermore, the significantly higher activity in the parasympathetic nervous system observed during the caffeine trial would suggest a potential cardio-protective effect against arrhythmia.

Concerning the activity of the sympathetic nervous system, we have recently indicated that obesity is associated with a relative or absolute reduction in the activity of the thermogenic component of the sympathetic nervous system (Matsumoto et al. 1999, 2000, 2001). Furthermore, we reported that activities of both the sympathetic and the parasympathetic nervous systems are reduced in the aging process (Oida et al. 1999). Exercise recommendations should be offered in the light of sympatho-vagal activity to those individuals who show a depressed activity of the ANS, e.g. individuals with obesity or diabetes. Therefore it should be of great importance to discover a food substance that could enhance the activity of the ANS during exercise.

In conclusion we showed that caffeine ingestion 2 h before exercise enhanced the activity of the ANS and fat oxidation during exercise at low intensity corresponding to 40%–50% of VT of each individual. The protocol used in this study is considered to be a sensitive method for evaluating the effects of various foods and nutrients on the activity of the ANS.

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