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Epigallocatechin-3-gallate Increases Maximal Oxygen Uptake in Adult Humans

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Abstract

Epigallocatechin-3-gallate (EGCG), a component of green tea, increases endurance performance in animals and promotes fat oxidation during cycle ergometer exercise in adult humans.

Purpose—We have investigated the hypothesis that short-term consumption of EGCG delays the onset of the ventilatory threshold (T_{VE}) and increases maximal oxygen uptake (VO_{2max}).

Methods—In this randomized, repeated measures, double blind study, 19 healthy adults (11 males, 8 females, age: 26 ± 2 years (mean ± SE)) received 7 placebo or 7 EGCG (135 mg) pills. 48-hours prior to data collection participants began consuming 3 pills per day; the last pill was taken 2-hours before exercise testing. T_{VE} and VO_{2max} were determined from breath-by-breath indirect calorimetry data collected during continuous incremental stationary cycle ergometer exercise (20-35 W/min), from rest until volitional fatigue. Each condition/exercise test was separated by a minimum of 14-days.

Results—Compared with placebo, short-term EGCG consumption increased VO_{2max} (3.123 ± 0.187 *vs.* 3.259 ± 0.196 L·min^{-1}, *P*=0.04). Maximal work rate (301 ± 15 *vs.* 301 ± 16 W, *P*=0.98), maximal respiratory exchange ratio (1.21 ± 0.01 *vs.* 1.22 ± 0.02, *P*=0.27), and maximal heart rate were unaffected (180 ± 3 *vs.* 180 ± 3 beats·min^{-1}, *P*=0.87). In a subset of subjects (n=11) maximal cardiac output (determined via open-circuit acetylene breathing) was also unaffected by EGCG (29.6 ± 2.2 *vs.* 30.2 ± 1.4 L·min^{-1}, *P*=0.70). Contrary to our hypothesis, EGCG decreased VO_2 at T_{VE} (1.57 ± 0.11 *vs.* 1.48 ± 0.10 L·min^{-1}) but this change was not significant (*P*=0.06).

Conclusion—Short-term consumption of EGCG increased VO_{2max} without affecting maximal cardiac output, suggesting that EGCG may increase arterial-venous oxygen difference.

Keywords

Green Tea; Cardiac Output; Arterial-venous oxygen difference; Exercise; Ventilatory Threshold

Introduction

Habitual consumption of green tea has been purported to have many health benefits, including weight loss (10,32), fat loss (32), attenuated adipocyte differentiation (43), increased energy expenditure (13,14), augmented blood glucose regulation (39,42), improved lipid profile (19,27,32), and decreased mortality from cardiovascular related causes (33). Many of the benefits of green tea consumption have been attributed to the effects of one of its most pharmacologically active components, epigallocatechin-3-gallate

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(EGCG). In addition to the aforementioned health benefits, EGCG consumption may also exert a positive influence on exercise capacity and the ability to perform work. Compared with control mice, treadmill-running time-to-fatigue was 30% longer in mice consuming a standard diet supplemented with green tea extract (30). In young adult humans short-term (24-hour) consumption of green tea extract augmented fat oxidation (sparing muscle glycogen) during 30-minutes of moderate intensity cycle ergometer exercise (42).

Endurance performance and substrate utilization during exercise are in part determined by maximal oxygen uptake (VO_{2max}) and the relative intensity of the exercise, commonly described with reference to the ventilatory threshold (T_{VE}). VO_{2max} refers to the greatest rate a person can consume oxygen. It is considered by many as the gold standard measure of aerobic work capacity and a powerful predictor of endurance performance. Further, when combined with traditional risk factors it is a valuable tool for predicting future cardiovascular and all-cause death (23,31). Finally, as a determinant of functional capacity, VO_{2max} is intimately linked with overall life-quality, particularly in older adults and clinical populations (1,2,18,44). With this information as background an understanding of the influence of EGCG on T_{VE} and VO_{2max} is of obvious interest. Accordingly, the purpose of this investigation was to compare T_{VE} and VO_{2max} after short-term consumption of EGCG and placebo. We hypothesized that EGCG would delay the onset of T_{VE} (that is, EGCG would increase the VO_2 at T_{VE}) and increase VO_{2max}.

Methods

Subjects

The experimental protocol conformed to the standards set by the Declaration of Helsinki of 1975, as revised in 1983, and was approved by the Institutional Review Board at Colorado State University. We studied 19 healthy adult males and females (aged 26 ± 2 years (mean ± SE)). Subjects were nonsmokers, did not regularly use any medications or supplement their diet with vitamins and/or antioxidants, and did not habitually consume green tea. The nature, purpose and risks of the study were explained to each subject before written informed consent was obtained.

Experimental Procedures

Following screening and habituation procedures (health questionnaire, height, body mass, body composition and initial assessment of VO_{2max}) subjects were studied on two separate occasions, separated by a minimum of 14 and maximum of 60 days, according to a randomized, repeated measures, double blind design. To minimize the influence of sex hormones female subjects were studied during the early follicular phase of the menstrual cycle. Subjects received 7 placebo or 7 EGCG capsules (135 mg/capsule). EGCG content in a single cup of green tea varies dramatically depending on brand of tea, and method and duration of tea storage (Range: 26-226 mg; mean ± SD: 151 ± 4 mg) (15,21). Based on this information we estimate that approximately 0.9 cups of green tea will provide the same dose of EGCG as a single Teavigo capsule. EGCG was administered as Teavigo, a commercially available, caffeine-free, oral supplement (Healthy Origins, Pittsburgh, PA, USA). Administration of Teavigo promotes fat oxidation in humans (42) and rodents (22), decreases adipose tissue mass in rats (43), and, when combined with exercise training, decreases blood glucose concentration in women with impaired glucose tolerance (16). Placebo capsules consisted of ~135 mg of organic cornmeal contained in a gelatin capsule. 48-hours prior to data collection participants began consuming one capsule with each meal (3 capsules per day). The final capsule was consumed 2-hours before exercise testing.

VO_2 at T_{VE} and VO_{2max} were determined from breath-by-breath indirect calorimetry data collected during continuous incremental stationary cycle ergometer exercise (20-35 W/min), from rest until volitional fatigue. The rate of increase in work was dictated by exercise performance during the initial screening/habituation visit such that the test lasted approximately 10-12 minutes. VO_2 at T_{VE} was determined by visual inspection of breath-by-breath data using established criteria (4,11): an increase in the slope of the line depicting the relation between CO_2 production and VO_2, a systematic increase in the ventilatory equivalent for VO_2 and in end-tidal O_2 pressure with no concomitant rise in the ventilatory equivalent for CO_2 production or a decrease in end-tidal CO_2 pressure. During these analyses investigators were naïve as to the conditions under which the data were collected (e.g. placebo *vs*. EGCG). Disagreements were resolved by discussion. When agreement could not be reached the VO_2 at T_{VE} for a specific trial remained undetermined and was not included in the final statistical analysis (34). VO_{2max} was calculated as the greatest mean breath-by-breath VO_2 over 60 consecutive seconds. To confirm that each subject attained VO_{2max}, at least three of the following four criteria were met: 1) a plateau in VO_2 despite increasing work rate; 2) a respiratory exchange ratio ≥ 1.15; 3) a final heart rate within 10 beats min^{-1} of the age-predicted maximal heart rate ($208 - (0.7 \times Age)$) (38); and, 4) subjective fatigue. Gas exchange variables were collected via indirect calorimetry (Parvo Medics, Sandy, UT, USA) and heart rate via short-range telemetry (Polar Electro, Inc., Lake Success, New York, USA).

To obtain further insight into the potential mechanism by which short-term consumption of EGCG might influence VO_{2max} we determined maximal cardiac output in a subset of subjects (n = 11, 6 males, 5 females). Cardiac output was determined via open-circuit acetylene breathing (Beck Integrated Physiological Testing System, St. Paul, MN, USA) as previously described (5,6,20). Three measurements of cardiac output were made immediately prior to exercise, with the subject seated quietly on the cycle ergometer, and three during maximal exercise. The maximal measurements were made shortly after completion of the VO_{2max} protocol. Following a brief period of recovery (2-3 minutes) subjects exercised at a work rate equivalent to the final work rate attained during the determination of VO_{2max}. When subjects indicated they could not continue to sustain this exercise intensity for a period longer than 30 seconds, the acetylene-breathing manoeuvre was undertaken. This process was repeated for a total of three trials, each separated by a brief period of recovery (< 5 minutes). Cardiac output was recorded as the mean of the closest two trials. Stroke volume was calculated as cardiac output divided by heart rate.

Height and body mass were measured using a physician's stadiometer and balance. Body composition was determined using dual-energy x-ray absorptiometry (Hologic Discovery-W with QDR for Windows, Bedford, MA, USA).

Statistics

This was a randomized, placebo controlled, within subjects, repeated measures design. Differences between the primary outcome variables (VO_{2max}, VO_2 at T_{VE}, maximal cardiac output) collected following short-term consumption of placebo and EGCG were analyzed using one-way analysis of variance (ANOVA) with repeated measures. Sex-specific interactions between placebo/EGCG and VO_{2max} and placebo/EGCG and maximal cardiac output were analyzed using two-way ANOVA with repeated measures. Relations of interest were examined using Pearson Product-Moment Correlation. All analysis was performed using commercially available software (Statistica/Mac 4.1, StatSoft, Tulsa, OK, USA). Three subjects were excluded from the final analysis of T_{VE} data due to the magnitude of discrepancy among investigators. The level of statistical significance was set at $P < 0.05$. Data are expressed as mean ± SE.

Results

Selected subject characteristics are displayed in Table 1. Subjects were healthy, normotensive, of normal weight, and, on average, demonstrated moderate aerobic capacity.

Maximal Oxygen Uptake

Compared with placebo, short-term EGCG consumption increased VO_{2max} (Table 2; mean change = +0.136 ± 0.064 L·min^{-1}; P = 0.04;). This increase occurred in 14 out of 19 subjects. Maximal work rate (P = 0.98), maximal respiratory exchange ratio (P = 0.27), and maximal heart rate were unaffected (P = 0.87). Body mass was not different between trials (71.3 ± 2.6 *vs*. 71.6 ± 2.6 kg; P = 0.64), thus when expressed relative to body mass the increase in VO_{2max} with EGCG was consistent with the increase in absolute VO_{2max} (44.1 ± 2.6 *vs*. 45.8 ± 2.6 mL·kg^{-1}·min^{-1}). Baseline (placebo) VO_{2max} was not related to the magnitude of change in VO_{2max} with EGCG (r^2 = 0.00, P = 0.97) suggesting that the improvement in VO_{2max} with EGCG was unrelated to the degree of fitness. Although not a primary focus of this investigation, absolute VO_{2max} was greater in males compared with females (P = 0.006), however there was no sex-specific interaction between placebo/EGCG and VO_{2max} (Placebo: Male 3.55 ± 0.23 *vs.* Female 2.53 ± 0.15 L min^{-1}; EGCG: Male 3.65 ± 0.24 *vs*. Female 2.72 ± 0.23 L·min^{-1}; P = 0.51).

Cardiac Output

In order to obtain further insight into the potential mechanism by which short-term consumption of EGCG might influence VO_{2max} we determined cardiac output immediately prior to the commencement of exercise and during maximal exercise in a subset of subjects (n=11). Immediately prior to exercise heart rate was lower with EGCG (mean change: -6 ± 3 beats·min^{-1}; $P < 0.05$); stroke volume and cardiac output were unaffected (both $P > 0.08$). Short-term consumption of EGCG did not affect heart rate, stroke volume, or cardiac output during maximal exercise (Table 3; all $P > 0.56$). Maximal heart rate obtained during cardiac output determination did not differ from maximal heart rate during determination of VO_{2max} for either placebo (179 ± 3 *vs.* 180 ± 3 beats·min^{-1}; P = 0.27) or EGCG (177 ± 3 *vs*. 179 ± 3 beats·min^{-1}; P = 0.24), suggesting that although VO_{2max} and maximal cardiac output were not determined simultaneously, they were both determined at the same heart rate, and presumably at the same metabolic rate. Noteworthy, maximal cardiac output and VO_{2max} were strongly related (r^2 = 0.88, $P < 0.001$), however the changes in maximal cardiac output and VO_{2max} with EGCG were unrelated (r^2 = 0.01, P = 0.76).

Ventilatory Threshold

Contrary to our hypothesis the VO_2 at T_{VE} was decreased in 12 out of 16 subjects following short-term consumption of EGCG (Table 2; mean change = -0.10 ± 0.05 L·min^{-1}) however, this decrease was not statistically significant (P = 0.06). Further, the change in T_{VE} with EGCG was not related to the change in VO_{2max} (r = 0.02, P = 0.95) or maximal cardiac output (r = -0.08, P = 0.85). Ventilatory threshold was greater in males compared with females (P = 0.02), however there was no sex-specific interaction between placebo/EGCG and T_{VE} (Placebo: Male 1.77 ± 0.16 *vs.* Female 1.32 ± 0.07 L·min^{-1}; EGCG: Male 1.68 ± 0.13 *vs*. Female 1.21 ± 0.07 L·min^{-1}; P = 0.79).

Discussion

The novel finding of this investigation is that short-term consumption of EGCG increased VO_{2max}. This finding cannot be attributed to augmented maximal cardiac output, thus the possibility exists that EGCG increased arterial-venous oxygen difference.

Several studies have suggested that green tea may possess ergogenic properties; of these studies most have been conducted in animals. Following 10-week supplementation of standard diet with green tea extract mice demonstrate prolonged time to exhaustion during treadmill running (30) and swimming against a controlled current (29). In the latter study the increased endurance capacity was attributed to the EGCG content of the green tea extract as a dose-response relation was established between the magnitude by which swim time to exhaustion was extended and the EGCG content of the supplement. In both of these studies the mice demonstrated increased reliance on fat oxidation during exercise following green tea extract supplementation. This observation is consistent with a recent study in young men in which short-term consumption of green tea extract (~ 360 mg over 24 hours) increased fat oxidation during 30-minutes of moderate intensity (~ 60% VO_{2max}) stationary cycle ergometer exercise (42). Endurance performance and substrate utilization during exercise are in part determined by VO_{2max} and the intensity of exercise relative to T_{VE}. In light of these recent observations in animal and human studies we have investigated the influence of short-term consumption of EGCG on T_{VE} and VO_{2max}.

In order to account for our observation that short-term consumption of EGCG increased VO_{2max} it is first important to consider the determinants of VO_{2max}. VO_{2max} is described by the Fick equation:

$$VO_{2max} = \text{Maximal cardiac output} \times \text{Maximal arterial} - \text{venous oxygen difference} \quad \{1\}$$

Thus, EGCG may increase VO_{2max} by increasing cardiac output, arterial-venous oxygen difference, or both. Cardiac output is determined by the product of heart rate and stroke volume, both of which are under considerable control by the sympathetic nervous system. The primary neurotransmitter of the sympathetic nervous system is norepinephrine. Following its release from sympathetic nerves norepinephrine has several fates: it may bind to target adrenergic receptors, return to the nerve terminal (norepinephrine reuptake) or be metabolized in the intracellular space by various enzymes including catechol-*O*-methyltransferase (COMT). EGCG is known to be a potent inhibitor of COMT (45), thus it is plausible that EGCG increases VO_{2max} via augmented heart rate and/or stroke volume through attenuated degradation of norepinephrine. Alternatively, the inotropic response to sympathetic stimuli is attenuated by oxidative stress as intracoronary administration of the powerful antioxidant ascorbic acid increases the inotropic response to beta-1 adrenergic receptor stimulation (dobutamine) (25,26). EGCG possesses potent antioxidant properties (17,41) thus it is plausible that EGCG may also exert its influence on maximal cardiac output, and hence VO_{2max}, via an antioxidant mechanism. Although intuitively appealing, it is unlikely that either of these potential mechanisms contributed to the increased VO_{2max} because EGCG consumption had no effect on maximal heart rate, stroke volume or cardiac output. This suggests that EGCG may impact VO_{2max} via increased arterial-venous oxygen difference. We are unaware of the existence of any exercise-specific data that address this possibility, however intravenous ascorbic acid administration is known to augment the metabolic response to non-selective beta-adrenergic receptor stimulation (isoproterenol) (7), thus, via its antioxidant properties, EGCG may also exert a similar effect during exercise.

An alternative explanation pertains to uncoupling; EGCG has been reported to increase uncoupling protein-2 gene expression in 3T3-L1 adipocytes in a dose-dependent manner (24). The authors speculated that previous observations of increased energy expenditure and lipid oxidation in adult humans following EGCG consumption (13) may be via the uncoupling of mitochondrial respiration from ATP production. Relevant to this final comment, in the present study the increase in VO_{2max} with EGCG occurred in the absence

of a change in maximal work rate, providing indirect support for an uncoupling explanation. To further examine this potential mechanism we have compared delta efficiency ((change in work rate / change in VO_2) × 100%) over a range of sub-maximal workloads (50W − 80% of maximal work rate). Throughout this workload range EGCG had no influence ($P = 0.18$) on efficiency (25.6 ± 6.1%) when compared with placebo (24.7 ± 8.7%). Further, there were no differences ($P = 0.48$) in VO_2 between the placebo (1.820 ± 0.045 L/min) and EGCG (1.849 ± 0.039 L/min) conditions when compared at a mean sub-maximal work rate of 150W. One limitation to both of these approaches is that VO_2 was not measured during steady state, that is, VO_2 was determined during performance of a continuous incremental ramp protocol. In a previous study (42), VO_2 was quantified during 30 minutes of steady state sub-maximal cycling (50% of maximal work rate), on two separate occasions, after consumption of placebo or green tea extracts; average VO_2 during each trial was not different, although the contribution of fat oxidation to total energy expenditure was 17% greater after green tea extract ingestion.

Contrary to our hypothesis the VO_2 at T_{VE} was decreased following short-term consumption of EGCG, however this decrease was not statistically significant ($P = 0.06$). To explain this observation we have again considered the COMT inhibitory properties of EGCG. During incremental exercise there is an increase in sympathetic activation, as evidenced by increased circulating concentrations of norepinephrine and epinephrine, and increased skeletal muscle sympathetic nerve activity (36,37). The purposes of this increase are many and include control of peripheral blood flow, regulation of ventilation, and substrate management (8,28,35). During incremental exercise increased sympathetic outflow may contribute to the onset of the T_{VE} by accelerating the rate of glycolysis, and decreasing blood flow to non-exercising tissue that may normally contribute to the clearance of blood lactate (e.g. liver). Prolonged influence (attenuated degradation) of norepinephrine via COMT inhibition may have led to the earlier onset of the ventilatory threshold via earlier acceleration of glycolysis and redistribution of blood flow.

Prior to the commencement of exercise, in a subset of subjects, we observed a small (~ 6 beats·min^{-1}) but significant decrease in resting heart rate, together with non-significant ($P > 0.08$) decreases in cardiac output and stroke volume following EGCG consumption (Table 3). The influence of EGCG and/or green tea extract on resting cardiovascular function is unclear as several studies have reported no influence on heart rate or arterial blood pressure (3,9,12) while one study described greater decreases in resting heart rate following 12 weeks of EGCG combined with exercise training versus similar exercise training with placebo (16). One notable difference between all of these studies and the current investigation is that resting heart rate was determined under basal (true resting) conditions, whereas in our investigation it was determined while sitting upright on a cycle ergometer, thus our determination of the impact of EGCG on heart rate may have been influenced by interactions with several extraneous factors such as exercise anticipation and upright posture.

There are several important limitations of our study that are worthy of attention. First, although we were able to document the absence of an influence of EGCG on maximal cardiac output we are unable to state with 100% certainty that EGCG did not affect blood flow to exercising muscle. That is, greater reduction in blood flow to non-exercising tissues may have resulted in increased blood flow to active skeletal muscle. Second, we did not include any direct measurement of oxygen extraction in exercising tissue, thus our notion that the increase in VO_{2max} was due not to increased cardiac output but instead an increase in the arterial-venous oxygen difference is not supported with direct empirical data, although the increase in VO_{2max} with EGCG was not related to the change in maximal cardiac output. Third, we did not include measures of plasma (tissue) EGCG concentration prior to and

following consumption of placebo and EGCG, however previous studies suggest that peak EGCG plasma concentration occurs approximately 2-hours after oral consumption (40), and an oral dose of 135 mg would produce a peak EGCG concentration of ~ 233 $ng \cdot ml^{-1}$ (40). In our study subjects consumed their final 135 mg capsule of EGCG 2-hours before exercise, thus plasma EGCG content may have been maximal at the start of the data collection.

The increase in VO_{2max} following EGCG consumption was ~ 4.4%. In our laboratory, based on differences between VO_{2max} determined during the first (habituation) visit and following consumption of placebo, the coefficient of variation for measurement of VO_{2max} is 3.1%, thus we believe the increase in VO_{2max} with EGCG is both statistically and physiologically significant. Maximal oxygen uptake is an important determinant of overall quality of life (1,2,18,44), and a powerful predictor of maximal work capacity, endurance performance, and longevity (23,31). Accordingly, our observation that EGCG increases VO_{2max} has obvious and important implications.

In summary, short-term consumption of EGCG increased VO_{2max}. This increase occurred without a change in maximal cardiac output suggesting that EGCG may increase arterial-venous oxygen difference.

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Table 1

Selected subject characteristics

Variable	
Sex (M/F)	11 / 8
Age (years)	26 ± 2
Height (m)	1.73 ± 0.17
Body Mass (kg)	71.3 ± 2.5
Body Mass Index ($kg \cdot m^{-2}$)	23.6 ± 0.6
Fat Mass (kg)	13.5 ± 1.3
% Body Fat	19.3 ± 1.7
Fat Free Mass (kg)	57.1 ± 2.4

Data are mean ± SE.

Table 2

Selected cardio-respiratory variables during sub-maximal and maximal stationary cycler ergometer exercise following short-term consumption of placebo and epigallocatechin-3-gallate.

	Placebo	EGCG
VO_{2max} ($L \cdot min^{-1}$)	3.123 ± 0.187	3.259 ± 0.196*
RER_{max}	1.21 ± 0.01	1.22 ± 0.02
WR_{max} (Watts)	301 ± 15	301 ± 16
HR_{max} ($beats \cdot min^{-1}$)	180 ± 3	180 ± 3
VO_2 at T_{VE} ($L \cdot min^{-1}$)†	1.57 ± 0.11	1.48 ± 0.10

VO_{2max}: Maximal oxygen uptake. RER_{max}: Maximal respiratory exchange ratio. WR_{max}: Maximal work rate. HR_{max}: Maximal heart rate. T_{VE}: Ventilatory threshold. Data are mean ± SE. EGCG: Epigallocatechin-3-gallate.

*Denotes difference to placebo ($P < 0.05$).

†Denotes n = 16; n = 19 for all other variables.

Table 3

Cardiac output, heart rate and stroke volume, immediately prior to exercise and during maximal exercise following short-term consumption of placebo and epigallocatechin-3-gallate (n=11).

		Immediately Prior to Exercise	During Maximal Exercise
Cardiac Output	Placebo	7.8 ± 0.6	29.6 ± 2.2
($L \cdot min^{-1}$)	EGCG	6.8 ± 0.4	30.2 ± 1.4
Heart Rate	Placebo	77 ± 3	178 ± 3
($beats \cdot min^{-1}$)	EGCG	70 ± 4*	177 ± 3
Stroke Volume	Placebo	102 ± 9	166 ± 12
(ml)	EGCG	98 ± 7	171 ± 9

Data are mean ± SE. EGCG: Epigallocatechin-3-gallate.

*Denotes difference to placebo prior to exercise ($P < 0.05$)