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Review

Green tea catechins, caffeine and body-weight regulation

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ABSTRACT

The global prevalence of obesity has increased considerably in the last decade. Tools for obesity management including caffeine, and green tea have been proposed as strategies for weight loss and weight maintenance. These ingredients may increase energy expenditure and have been proposed to counteract the decrease in metabolic rate that is present during weight loss. Positive effects on body-weight management have been shown using green tea mixtures. Green tea, by containing both tea catechins and caffeine, may act through inhibition of catechol O-methyl-transferase, and inhibition of phosphodiesterase. Here the mechanisms may also operate synergistically. A green tea–caffeine mixture improves weight maintenance, through thermogenesis, fat oxidation, and sparing fat free mass. The sympathetic nervous system is involved in the regulation of lipolysis, and the sympathetic innervation of white adipose tissue may play an important role in the regulation of total body fat in general.

Taken together, these functional ingredients have the potential to produce significant effects on metabolic targets such as thermogenesis, and fat oxidation. An ethnic or genetic effect, and habitual caffeine or green tea catechin intake may act as confounders; this remains to be revealed.

Contents

1. Introduction

Overweight and obesity represent a rapidly growing threat to the health of populations in an increasing number of countries [1].

The ultimate cause of obesity is an imbalance between energy intake and energy expenditure (EE) [2]. A negative energy balance is needed to produce weight loss and can be achieved by either decreasing intake or increasing expenditure [3,4]. Amongst others, stimulation of EE (or the prevention of its decline during dieting) by the use of natural herbal nutrients such as green tea and caffeine has attracted interest. Green tea (GT) is consumed primarily in China, Japan and a few countries in North Africa and the Middle East [5,6]. Tea is made from the leaves of *Camellia sinensis* L. species of the Theaceae family, GT being the non-oxidised, non-fermented product. As a consequence of this, it contains high quantities of several polyphenolic components such as epicatechin, epicatechin gallate, epigallocatechin and, the most abundant and probably the most pharmacologically active, epigallocatechin gallate [7].

From caffeine, that is also present in GT, it has been reported that it has thermogenic effects and can stimulate fat oxidation in vitro, in part via sympathetic activation of the central nervous system [8]. In humans, caffeine has been shown to stimulate thermogenesis and fat

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oxidation [9–11]. GT extracts, containing caffeine and catechin-polyphenols, have been reported to have an effect on body weight [7,12] and EE [12,13]. The observation that GT stimulates thermogenesis cannot be completely attributed to its caffeine content because the thermogenic effect of GT extract containing caffeine and catechin-polyphenols, is greater than that of an equivalent amount of caffeine [13].

2. Efficacy of green tea and caffeine; evidence from short-term experiments

2.1. Green tea

In a short-term human study epigallocatechin gallate plus caffeine (EGCG/caffeine), (90/50 mg), caffeine (50 mg) or placebo capsules were consumed three times daily on three different occasions [13]. Relative to the placebo and to the caffeine alone, treatment with the green tea extract resulted in a significant increase in 24 h EE (4% = 328 kJ) and fat oxidation, suggesting that green tea has thermogenic properties beyond that explained by its caffeine content per se [14]. Rudelle et al. [15] conducted a similar study in which three servings of a 250 ml thermogenic beverage per day (during 3 days), containing 94 mg EGCG and 100 mg caffeine, were consumed. 24 h EE was significantly increased with 4.6% = 445.2 kJ after the thermogenic beverage [15]. Komatsu et al. observed an increase in EE over 2 h with 4% (= 49.5 kJ) after a beverage containing 161 mg caffeine and 156 mg EGCG [16]. These observations were confirmed by determining 24 h energy expenditure using respiratory chambers and giving the subject different dosages of green tea [17]. These 24 h studies in 10–24 male and female Caucasian and Asian subjects, with a BMI of 21–35 kg m^{-2} and age of 18–60 years, and regular caffeine intake of 100–300 mg/day, showed an elevation of 24 h energy expenditure of 4–8% and increased fat oxidation of 3.5–9.9%, due to consumption of a green tea/caffeine mixture containing 270–1200 mg of green tea and 100–161 mg of caffeine. However, a recent 13.5 h study in 15 male Caucasian subjects, BMI 22.4 kg m^{-2}, age 24 years, regular caffeine intake <250 mg/day, only showed an insignificant increase of 2.3% in EE and fat oxidation, after intake of 645 mg green tea with 150 mg caffeine [18]. It may well be that the duration of the study was too short, and that the effect is building up over 24 h.

2.2. Caffeine

While consuming the same breakfast, normal-weight subjects presented a greater thermic effect over 3 h, when it was accompanied with a caffeinated coffee (8 mg/kg body weight) in comparison to a decaffeinated coffee [19]. Moreover, energy expenditure was increased by 16% over a 2-h period with caffeinated (100 mg) compared to decaffeinated coffee [20]. In accordance with this effect, an increase in basal metabolic rate by 3–4% was seen after consumption of a single oral dose of 100 mg caffeine in 9 lean and 9 post-obese subjects [20]. A linear, dose-dependent stimulation of thermogenesis, that lasted longer than 3 h after administration of 100, 200 or 400 mg oral caffeine, was observed in subjects with a habitual caffeine intake of less than 200 mg/day [10]. In 20 female subjects (10 lean and 10 obese), an increase in thermogenesis was seen with 4 mg/kg caffeine 5 times a day but this increase was smaller in the obese (4.9 ± 2.0%) than in the lean subjects (7.6 ± 1.3%). The thermogenic effect of caffeine was prolonged even over night, which may suggest a possible long-term effect of caffeine [11].

3. Efficacy of green tea and caffeine; evidence from long-term experiments

3.1. Green tea

When investigating the effect of a green tea extract (375 mg catechins from which 270 mg EGCG and 150 mg caffeine per day, divided over 4 capsules) on body weight with 70 overweight Caucasian subjects, body weight was decreased by 4.6% and waist circumference by 4.5% after three months, which is substantial since the study had an open uncontrolled design [12]. In accordance with this observation, the long-term (12 weeks) administration of tea catechins in a dose of 400–700 mg/day to Asian subjects reduced body fat and body fat parameters [21–26]. Harada et al. [27] demonstrated that after a 12-week administration of a 350 ml tea beverage a day (592.2 mg) energy expenditure and dietary fat oxidation were increased. Furthermore, a recent study in Asian subjects observed that the daily consumption of 340 ml tea containing 576 mg catechins for 24 weeks reduced body fat ratio and waist circumference compared to the control group, who had a daily consumption of 340 ml tea with 75 mg catechins [28]. In 104 Caucasian overweight/moderately obese subjects, after a very-low-energy diet (2.1 MJ/d) of 4 weeks, it was shown that during a weight maintenance period of 13 weeks in which subjects received placebo or green tea (caffeine/catechins: 104/573 mg per day)[29], body weight regain and the rate of regain were not significantly different between the green tea and placebo group. Significantly stronger body weight maintenance after weight loss was shown by post hoc analysis, i.e. 16% body weight regain in the habitually low caffeine consumers vs. 39% in the habitually high caffeine consumers relative to habitual caffeine consumption [29]. From a follow-up study it was concluded that habitual high caffeine intake was associated with a significant greater weight loss (6.7 vs. 5.1 kg) and relatively higher thermogenesis and fat oxidation, while green tea was associated with greater weight maintenance in habitual low caffeine consumers, supported by relatively greater thermogenesis and fat oxidation [30]. Thus the effect of green tea may partly depend on habitual caffeine intake [30].

In a different study with 46 Caucasian females following a low-energy-diet combined with green tea (caffeine/catechins 225/1125 mg per day) or placebo supplementation during 12 weeks, with caffeine intake being standardized at 300 mg/day, resting energy expenditure as a function of fat free mass and fat mass did not decrease significantly over time when green tea was ingested independently of habitual caffeine intake [31]. On the other hand, the decrease in resting energy expenditure was significant in the placebo group [30]. However, this did not imply a significant difference in body weight loss between the green tea and placebo group [31]. Here moderate use of caffeine may have made the green tea supplement ineffective [30].

Studying Asian obese people in a long-term weight loss experiment, the group consuming the green tea mixture (100 mg EGCG and 87 mg caffeine per day) lost significantly more weight within 12 weeks compared to the placebo group (2.7 vs. 2.0 kg) that ate the similar standardized meals during the entire study. REE was significantly increased after 12 weeks of green tea supplementation, which led to the body weight reduction [32]. At the same time a study from Hsu et al. was conducted in 78 Asian obese women who were divided into either a placebo or green tea group (491 mg catechins, 302 mg EGCG); however after 3 months of administration no significant difference was seen between both groups from which the green tea group only lost 0.15 kg [33]. Recently, Wang et al., showed a larger weight loss and decrease in body fat in 139 green tea catechin mixture consuming Asian overweight subjects vs 43 placebo consumers, over 13 weeks [34]. A meta-analysis by Hursel et al., [35] on the effects of green tea mixtures on weight loss and weight maintenance thereafter, including most of the studies mentioned above, shows that effects of consumption of green tea mixture is significantly attributed to weight loss and prevents weight regain, with an average of 1.3 kg. Heterogeneity was caused by caffeine intake and ethnicity; these factors may affect the outcomes of the different studies [35]. On the basis of that analysis it was concluded that a green tea catechin and caffeine mixture is a promising agent for body-weight regulation [35]. Details of the studies included are: duration (12–24 weeks), sample size (25–182 subjects), BMI 18.5–35 kg m^{-2},

male and female subjects of 18–69 years old, green tea/caffeine ingestion 270–1207 mg/day/75–237 mg/day [35].

3.2. Caffeine

Although caffeine seems to increase thermogenesis in the short-term, greater weight loss was not achieved when consuming caffeine in comparison to a placebo in obese subjects in the long-term [36,37]. The observation that a habitually high (N300 mg/day) caffeine intake group receiving a green tea–caffeine combination did not show greater body weight maintenance after body weight loss than a habitually high caffeine group receiving placebo leads to the suggestion that sensitivity to caffeine may be lost over time [30]. In men (but not in women) caffeine consumption (300 mg) appeared to reduce energy intake (by 22%) [36]. Moreover, a positive relationship between satiety and daily caffeine intake, in men and women, was shown [30]. Lopez-Garcia et al. studied the effect of caffeine on long-term weight change in a prospective study. In their cohort they found that people who increased the caffeine consumption over 12 years gained less weight than those who decreased the caffeine consumption [38]. Thus caffeine may influence both energy expenditure and energy intake.

4. Mechanisms of action

Catechins in green tea inhibit the enzyme catechol O-methyltransferase (COMT) that is present in almost every tissue and degrades catecholic compounds like norepinephrine (NE) [13,30]. COMT decreases the hydrophilicity by methylation, followed by sulfation and glucuronidation to make the excretion in urine and bile possible [39]. NE cannot be degraded through the inhibition of COMT and consequently the sympathetic nerve system (SNS) will be stimulated continuously due to the presence of NE, which attaches to β-adrenoceptors and causes an increase in energy expenditure and fat oxidation [40,41]. The SNS plays an important role in the regulation of energy homeostasis but the above described phenomenon does not always appear equally clear in all ethnic groups. For instance studies with Asian subjects seem to report more positive results than studies with Caucasian subjects. This may be caused by differences in relevant enzyme activity, causing differences in sensitivity for these ingredients. In that respect Hodgson et al. [42] stated that there is a wide variability in flavonoid O-methylation, a major pathway of flavonoid metabolism, by the enzyme COMT. The inter-individual variability of the activity of COMT could vary as much as 3-fold. Moreover, there is evidence that there is a difference in COMT enzyme activity between ethnic groups [43]. Asian populations have a higher frequency of the thermostable, high activity enzyme, $COMT^H$ allele (*Val*/*Val* polymorphism) than the Caucasian populations. The Caucasian populations have a higher frequency of the thermolabile, low activity enzyme, $COMT^L$ allele (*Met*/*Met* polymorphism) [43]. 50% of Caucasians are homozygous for the $COMT^L$ allele (25%) and $COMT^H$ allele (25%). The other 50% is heterozygous (*Val*/*Met* polymorphism) [43]. This may explain the difference in sensitivity to interventions with green tea caffeine mixtures, and why, in some studies with Caucasian subjects, no effect was seen after ingestion of green tea. Another explanation may be the higher intake of dairy proteins in the Caucasians. It has been suggested that absorption is reduced after the formation of a protein–polyphenol complex in the upper part of the digestive tract that is resistant to gastric hydrolysis [44].

As caffeine is also present in green tea, its effect will also take place after green tea consumption. Caffeine affects the thermogenesis by inhibiting the enzyme phosphodiesterase. This enzyme degrades intracellular cyclic amino mono phosphate (cAMP) [45]. Phosphodiesterase usually hydrolyses cAMP to AMP, but after consumption of caffeine, cAMP concentration rises and SNS activity will be increased and inactive hormone-sensitive lipase (HSL) will be activated, which promotes lipolysis [46]. The SNS activity and lipoysis are dependent on cAMP, because cAMP activates the protein kinase A [46]. Besides the inhibition of phosphodiesterase, caffeine also affects the thermogenesis through the stimulation of substrate cycles like the Cori-cycle and the FFA-triglycreride cycle [40,41]. Caffeine is a methylxanthine, which has a thermogenic impact. In the Cori-cycle lactate moves from the muscles to the liver where it will be converted into pyruvate. The pyruvate will be converted to glucose by the enzyme lactate dehydrogenase and circulate back to the muscles via the blood [40,41]. Acheson et al. showed that FFA turnover and lipid oxidation are increased after the consumption of caffeine but that it requires a large increase in FFA turnover to have a small increase in lipid oxidation. Nonoxidative lipid turnover, the hydrolysis and reesterification of triacylglycerol, is greater than the increase in oxidative lipid disposal [46]. They also found that caffeine antagonises the inhibitory effects of adenosine on lipolysis via adenylyl cyclase. Nonadrenergic thermogenic mechanisms can also be involved, as caffeine antagonises the ryanodine receptor, the calcium ion release channel of sarcoplasmatic reticulum in skeletal muscle that for instance increases glycolysis and ATP turnover after stimulation [46].

Catechins and caffeine inhibit two enzymes, which interrupt the pathway of norepinephrine-activated thermogenesis [47]. As SNS activity is determined by the concentration of NE, more NE means a higher activity and increased energy expenditure. SNS activity regulates the resting metabolic rate, which is the largest component of the daily energy expenditure. NE makes it possible to increase the usage of ATP through ion pumping and substrate cycling [41]. The rate of mitochondrial oxidation is also involved in the increased thermogenesis due to the poor coupling of ATP synthesis, which leads to heat production. Catechins also have a direct effect on the gene expression of different uncoupling proteins (UCPs) that influence the thermogenesis with the production of heat [48]. Gene expression of the UCPs also increases when cAMP activates the protein kinase A, after the inhibition of phophodiesterase by caffeine [49]. The protein kinase A stimulates HSL, which increases the concentration of free fatty acids by the conversion of triglycerides. UCP activity will be enhanced through this [49].

The increase in energy expenditure is accompanied by a change in substrate oxidation as Dulloo et al. showed an increase in fat oxidation after the supplementation of green tea [13]. Another mechanism is triggered by the tea catechins that block the nuclear factor-κ B (NFκB) activation by inhibiting the phosphorylation of IκB [50]. NFκB is an oxidative stress sensitive transcription factor that regulates the expression of several genes, which are important in cellular responses like inflammation and growth [51]. NFκB is no longer able to inhibit the peroxisome proliferator activated receptors (PPARs) that are important transcription factors for lipid metabolism [51]. The mRNA expression of lipid-metabolizing enzymes such as acyl-CoA oxidase (ACO) and medium chain acyl-CoA dehydrogenase (MCAD) is up-regulated. ACO is a peroxisomal β-oxidation enzyme and MCAD is a mitochondrial β-oxidation enzyme in the liver [51]. The up-regulation of these lipid-metabolizing enzymes indicates that β-oxidation activation after the supplementation of tea catechins is enhanced followed by an increase in fat oxidation.

5. Obesity and sympathetic nervous system activity

Evidence for body-weight management using caffeine and green tea has been shown in several studies as well as by meta-analysis [30,35]. Caffeine stimulates thermogenesis by inhibiting the phosphodiesterase-induced degradation of cAMP, and catechins in green tea through inhibition of catechol O-methyl-transferase (COMT), an enzyme that degrades norepinephrine (NE). Moreover, tea catechins have anti-angiogenic effects which may prevent

development of overweight and obesity. The sympathetic nervous system (SNS) has been considered as an essential component of the autonomic nervous system playing an important role in maintaining energy homeostasis by hormonal and neural control. The SNS has been described as a complex regulatory system, involving direct effects of sympathetic nerves which supply most body tissues and, indirect effects of the catecholamines, epinephrine and to a lesser extent NE, which are released into the blood from the adrenal medulla. It is important to realize that the SNS does not produce uniform activation of all body tissues which have a sympathetic nerve supply, but rather that in any particular situation there is selective activation of specific tissues or systems, with either no effect or even inhibition of other areas. It should be appreciated, therefore, that renal or brown fat or muscle changes in electrophysiological activity of efferent nerves innervating these tissues is specific to that tissue, as well as the NE turnover [40,41]. Sympathetic activity to effector organs of metabolism is considered as being a key factor for maintenance of body weight. Effects imply thermogenic effects of increased sympathetic activity, as well as regulation of fat metabolism.

Examples of thermogenic effects are sympathomimetic induced changes in energy balance through increases in EE. It has been shown that SNS activity (determined by NE concentrations) modulates resting EE (resting metabolic rate measured after an overnight fast), the largest component of daily EE. Since NE has the ability to increase the use of ATP, for example, through ion pumping and substrate cycling, or to increase the rate of mitochondrial oxidation with poor coupling of ATP synthesis leading to increased heat production, it is speculated that the SNS is involved in thermogenesis [41]. Indeed, human studies have demonstrated that thermogenesis, measured by whole body calorimetry, increased significantly during the infusion of NE or epinephrin. The thermogenic response to catecholamines has been shown to be mediated by a combination of β1-, β2- and β3-receptors. The activity of the SNS has been assessed in several ways, including plasma catecholamine levels, catecholamine turnover, urinary catecholamine excretion and muscle sympathetic nerve activity.

With respect to sensitivity of SNS to positive energy balances, in non-human animals SNS activation appears to be a key element of the counter-regulatory response to excessive food intake in heart and brown adipose tissue, thus SNS activation is an important aspect of the response to overfeeding [41]. SNS activation increases thermogenesis and wastes excess energy as heat, and thereby compensates for surplus energy intake. The result is the prevention of body weight gain. Also human obesity is accompanied by activation of the SNS rather than its suppression. In human obesity, the whole body NE spillover rate, which is an indication of overall sympathetic activity, is typically normal. Renal NE spillover, indicative of renal sympathetic activity is approximately doubled, while cardiac sympathetic activity is reduced [41].

Only during negative energy balance SNS activity seems to be negatively affected. In obesity-prone subjects low resting muscle sympathetic nerve activity, (an indicator of reduced SNS activity) was related to a reduced EE which is responsible for weight gain and obesity. Furthermore, a negative energy balance was associated with a reduction of sympathetic activity at the muscular level which reduces resting EE and thus prolongs survival. In addition, a negative energy balance was associated with an increased lipolysis in response to catecholamines in adipose tissue [41].

6. Safety of caffeine and green tea administration

Caffeine appears to be a safe thermogenic agent for weight control. In adults, the short-term lethal dose for caffeine is estimated at 5–10 g per day (either intravenously or orally), which is equivalent to 75 cups of coffee, 125 cups of tea, or 200 cola beverages [52]. Long-term ingestion of caffeine has been suggested to have some minor adverse effects on human health. Astrup et al. [10] observed only small and insignificant changes in blood pressure and pulse rate after 100 and 200 mg caffeine. In contrast, 400 mg caffeine significantly increased systolic and diastolic blood pressure by an average value of 6.3 mm Hg. Furthermore, after 400 mg caffeine, significantly more subjects reported side effects such as palpitation, anxiety, headache, restlessness, dizziness compared with placebo [10]. Robertson et al. [53,54] administrated 250 mg oral caffeine to nine subjects who were not used to coffee. Systolic blood pressure increased 10 mm Hg 1 h after caffeine consumption. Heart rate showed a decrease after the first hour followed by an increase above baseline after 2 h [53,54]. However, in a subsequent study that examined the chronic effects of caffeine ingestion (150 mg/day for 7 days), tolerance to these effects was developed after 1–4 days [53,54]. Thus no long-term effects of caffeine on blood pressure, heart rate, or plasma rennin activity were demonstrated. Furthermore, in the short term, Bracco et al. [11] did not find a significantly altered heart rate during the day after 4 mg caffeine per kg body weight was consumed 5 times daily. So far, the use of caffeine seems to be relatively safe.

Green tea has been widely consumed in China and Japan for many centuries and is regarded as safe. A possible side effect of green tea consumption is a minor increase in blood pressure as seen by Berube-Parent et al. [17]. They observed a nonsignificant increase (7 mm Hg) in 24 h systolic blood pressure accompanied by a significant increase (5 mm Hg) in 24-h diastolic blood pressure. No increase in heart rate was seen [17]. This small short-term increase in blood pressure induced by green tea might be neglected since systolic blood pressure, diastolic blood pressure, and heart rate were not affected by green tea in other short-term [13] or long-term research [12,21–35].

Taken together, tools for obesity management are caffeine and green tea since they increase energy expenditure and counteract the decrease in metabolic rate during weight loss. Green tea containing tea catechins and caffeine inhibits catechol O-methyl-transferase and phosphodiesterase; these mechanisms may operate synergistically. A green tea–caffeine mixture improves weight maintenance through thermogenesis, fat oxidation, and sparing fat free mass. Caffeine and green tea mixture can until now be considered as relatively safe. Thermogenic ingredients may be considered as functional agents that could help in preventing a positive energy balance and obesity. In order to gain a stronger consensus on the effects of green tea catechin and caffeine mixtures, a multidisciplinary study on bio-availability and bio-activity is required that unravels the effects of interference with other nutrients on absorption, effects of the genetic background, related enzyme activities, and possible habituation due to level of regular consumption.

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