Catechin- and caffeine-rich teas for control of body weight in humans1–4

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ABSTRACT
Maintaining the level of daily energy expenditure during weight loss and weight maintenance is as important as maintaining satiety while decreasing energy intake. In this context, different catechin- and caffeine-rich teas (CCRTs), such as green, oolong, and white teas, as well as caffeine have been proposed as tools for maintaining or enhancing energy expenditure and for increasing fat oxidation. Tea polyphenols have been proposed to counteract the decrease in metabolic rate that is usually present during weight loss. Their effects may be of particular importance during weight maintenance after weight loss. Although the thermogenic effect of CCRT has the potential to produce significant effects on these metabolic targets as well as on fat absorption and energy intake, possibly via its impact on the gut microbiota and gene expression, a clinically meaningful outcome also depends on compliance by the subjects. Limitations to this approach require further examination, including moderating factors such as genetic predisposition, habitual caffeine intake, and catechin composition and dose. Nevertheless, CCRTs may be useful agents that could help in preventing a positive energy balance and obesity. Am J Clin Nutr 2013;98(suppl):1682S–93S.

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 (EI)5 and energy expenditure (EE) (2). A negative energy balance is needed to produce weight loss (WL) and can be achieved by either decreasing EI or increasing EE (3, 4). Stimulation of EE (or the prevention of its decline during dieting) by the use of natural foods and ingredients such as tea, which is rich in catechins and caffeine, has attracted interest, especially because tea does not contain any energy itself, yet stimulates EE. Green tea (GT), oolong tea (OT), and white tea (WT) are made from the leaves of the Camellia sinensis L. species of the Theaceae family. GT is a nonoxidized, nonfermented product; and OT is a semioxidized, semi-fermented product (5, 6). WT is made from the youngest buds of the plant that undergo even less processing than GT. All teas contain high quantities of several polyphenolic components, particularly epicatechin, epicatechin gallate, epigallocatechin, and the most abundant and perhaps the most bioactive component, epigallocatechin-3-gallate (EGCG) (7). Tea leaves that have been processed the least contain the most catechins.

Caffeine, which is also present in tea, possesses thermogenic effects and can stimulate fat oxidation (FO) in vitro and in humans, in part via sympathetic activation of the central nervous system (8–11). GT extracts containing caffeine and catechin polyphenols have been reported to have an effect on body weight (BW) (7, 12) and EE (12–14). The observation that GT stimulates EE 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). Nevertheless, there are moderating factors that may limit the beneficial effects of catechin- and caffeine-rich teas (CCRTs), which should be taken into account in examining this benefit. Nonetheless, despite the presence of these factors, tea has been studied extensively and still seems promising with respect to BW regulation. Therefore, results from different types of studies, such as intervention studies and observational studies, are discussed to give a detailed overview of the contemporary evidence on tea as a weight-controlling ingredient.

EFFECTICITY OF CATECHIN-RICH TEAS IN WEIGHT CONTROL
That habitual tea consumption may have positive effects on anthropometric variables was shown by Wu et al (15) in a cross-system (8–11). GT extracts containing caffeine and catechin polyphenols have been reported to have an effect on body weight (BW) (7, 12) and EE (12–14). The observation that GT stimulates EE 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). Nevertheless, there are moderating factors that may limit the beneficial effects of catechin- and caffeine-rich teas (CCRTs), which should be taken into account in examining this benefit. Nonetheless, despite the presence of these factors, tea has been studied extensively and still seems promising with respect to BW regulation. Therefore, results from different types of studies, such as intervention studies and observational studies, are discussed to give a detailed overview of the contemporary evidence on tea as a weight-controlling ingredient.
sectional survey in which 1210 adults were enrolled. Habitual drinkers of tea for >10 y showed a 19.6% reduction in body fat percentage and a 2.1% reduction in waist:hip ratio compared with non–habitual tea drinkers (15). In addition, a prospective cohort study in The Netherlands showed that higher catechin intake was associated with less increase in BMI in women over a 14-y period and vice-versa (16).

CCRTs such as GT, OT, and WT may have the most beneficial effects. CCRTs have been well studied over the long term (12, 17–52), with WL and weight maintenance (WM) (53) as key outcomes. In the short term, the effects of CCRTs on EE and FO, which are important determinants of successful WL and WM, have been studied as well (13, 54–59). Meta-analyses addressing the effects of CCRTs on anthropometric and metabolic variables showed that catechins and caffeine have beneficial effects on weight control (60–62). Based on the collected data from all of the studies conducted to date, CCRTs seem to be promising agents for BW regulation. Whereas GT has been the subject of extensive research, the long-term effects of OT (19, 22, 36, 40, 41) have been investigated more than its acute effects (56, 63). To our knowledge, no studies have been conducted so far that address the effect of WT on EE and BW, despite containing more catechins and caffeine than GT (64–68).

Several placebo-controlled trials have assessed the safety of the long-term use of catechins (29, 51). Yoneda et al (51) assessed the safety in a group of 77 subjects who consumed 588 mg of tea catechins for 1 y, concluding that long-term consumption of catechins is safe because there were no deviations in blood variables and blood pressure. Matsuyama et al (29) examined the safety of 24 wk catechin ingestion (576 mg/d compared with 75 mg/d) in a group of 40 children aged 6–16 y. They also observed no differences in biochemical or hematologic variables, concluding that the long-term use of catechins as a WM tool is safe, even in children.

WL and WM studies

Different study designs have been applied to investigate the effects of CCRTs on BW regulation. Traditionally, WL study designs include subjects receiving a long-term tea treatment in which tea is administered during a defined time period (26). Vieira Senger et al (33) observed a significant WL of 1.2 kg in 24 elderly subjects who consumed GT for 60 d compared with a control group of 21 age-matched subjects who did not lose BW.

The WM design is composed of a term of WL followed by a WM period with tea treatment, which is used to observe whether subjects maintain their recently achieved BW (24, 25, 34). Recently, Cardoso et al (34) conducted a clinical trial in which overweight or obese women, after a 4-wk period with a 1200-kcal/d adaptive diet, received a GT treatment of 8 wk. After the intervention, subjects not only maintained their BW but they lost 5.8 kg and showed a decrease in fat percentage of 4.7% and preservation of lean body mass. The placebo group did not show any significant changes in anthropometric variables.

Whereas there is a substantial body of evidence with regard to the beneficial effects of catechins in combination with caffeine or alone on BW regulation, many studies have obtained null outcomes with tea or tea catechin interventions. Meta-analyses are beginning to place this mixed evidence into context.

Meta-analyses of the effect of tea on metabolic and anthropometric variables

Contradictory outcomes between long-term studies may arise because of differences in study design, differences in subjects’ ethnicity and habitual caffeine intake (HCl), different types of tea or tea mixtures, and different concentrations of catechins. Therefore, the data used in the above-described studies on WL and WM after GT supplementation were combined in a meta-analysis by Hursel et al (60). They showed that catechins significantly decreased BW or maintained BW after a period of WL of ~1.31 kg (95% CI: −2.05, −0.57 kg; \( I^2 = 94\% \)). Moderating factors that might negatively influence the weight-controlling effect of GT show an interaction of ethnicity and HCl as a significant factor, indicating that the high HCl by whites compared with the moderate HCl of Asians may account for the attenuated effect in whites. Nevertheless, the genetic differences between these ethnic groups may still underlie some of the differences in the reported results.

A meta-analysis by Phung et al (61) showed that GT catechins with caffeine decreased BW (~1.38 kg: 95% CI: −1.70, −1.06 kg; \( I^2 = 0\% \)), BMI, and waist circumference compared with caffeine alone. GT catechins with caffeine consumption also decreased BW (~0.44 kg: 95% CI: −0.72, −0.15 kg; \( I^2 = 0\% \)) when compared with a caffeine-free control. Importantly, studies that evaluated GT catechins without concomitant caffeine administration did not show benefit on any of the assessed anthropometric endpoints, suggesting that the synergistic effect between catechins and caffeine is necessary for obtaining positive effects on BW regulation.

Hursel et al (62) also published a meta-analysis in which they showed that CCRT (428.0 kJ/d: 95% CI: 252.7, 603.4 kJ/d; \( \chi^2 = 23.28 \)) and caffeine-only supplementation (429.1 kJ/d: 95% CI: 260.7, 597.5 kJ/d; \( \chi^2 = 23.28 \)) both increased EE by >400 kJ over 24 h, an increase of ~5%. However, 24-h FO was increased only by CCRT, by ~16.0% (12.2 g/d: 95% CI: 1.7, 22.8 g/d; \( \chi^2 = 63.61 \)). Calculations show that CCRT or caffeine-only supplementation stimulates daily EE in a dose-dependent manner by 0.4–0.5 kJ/mg administered.

Due to the amount of heterogeneity between studies, Jurgens et al (69) conducted several meta-analyses in which studies were divided into those either conducted in or outside Japan. Studies conducted outside of Japan had a mean WL of ~0.04 kg (95% CI: −0.5, 0.4 kg; \( I^2 = 18\% \)), whereas Japanese studies had a mean WL of ~1.44 kg (95% CI: −2.38, −0.51 kg; \( I^2 = 96\% \)). However, the Japanese studies were apparently too heterogeneous for analysis. Therefore, it was concluded that GT had only a minor, nonsignificant effect on WL, BMI, and waist circumference and no effect on WM. This conclusion does not seem to correspond with the previous meta-analyses, probably because the authors chose to divide the studies into 2 groups. If heterogeneity is not taken into account, the magnitude of the WL between the studies conducted in Japan and the results of the previous meta-analyses are comparable. The partitioning of studies from Japan and of those performed outside of Japan is remarkable, because the studies conducted outside of Japan are scattered all over the world with different habitual caffeine and catechin consumption as well as different ethnic backgrounds. Also, participants in 4 of the included studies were subjected to an exercise protocol in addition to catechin supplementation,
which might influence the results. Nevertheless, the results did confirm that there might be a possible difference between ethnic groups in their response toward CCRTs. Furthermore, the authors reported that there were hardly any adverse effects after ingestion of catechins during 12 wk.

Thus, many studies support that individuals who consume CCRTs show small improvements in anthropometric variables such as BW, BMI, body fat mass, and waist:hip ratio. HCI and the presence of caffeine appear to be the main determinants of a positive outcome, in addition to genetic predisposition to the effect of catechins and caffeine. The effect of different doses of tea polyphenols warrants further research to help clarify both the efficacy and safety of this intervention.

Effects of CCRTs on blood variables

The putative health benefits of tea originate not only from action on BW and body composition but also from the effect of tea on blood variables that characterize the metabolic syndrome. For instance, serum cholesterol, insulin, glucose, and triglycerides have been studied in healthy and overweight/obese subjects to determine whether CCRTs may favorably affect glucose and lipid metabolism (21, 22, 28, 30, 31, 33, 36, 52). Moreover, in 240 men and women with mild to moderate hypercholesterolemia who received theaflavin-enriched GT extract (375 mg) or placebo for 12 wk, Maron et al (42) reported favorable changes in the test compared with the placebo group in concentrations of total cholesterol (−11.3%), LDL cholesterol (−16.4%), HDL cholesterol (2.3%), and triglycerides (2.6%). In contrast, Chan et al (43) reported no effect on BW, glucose, lipid metabolism, or hormone status in 34 obese Chinese women with polycystic ovary syndrome coinciding with insulin resistance and hyperinsulinemia after supplementation with 687 mg catechins over 3 mo. This conclusion is in accordance with the findings of other studies that assessed an array of blood variables related to the metabolic syndrome (23, 29, 51). Blood variables were also measured in WM studies (24, 25, 46, 70). Here, favorable changes in blood variables occurred with initial WL but disappeared when BW was regained, despite the administration of CCRTs. This finding may indicate that the changes may be more attributed to WL itself than the ingestion of tea.

In conclusion, catechins in combination with caffeine may be able to improve biomarkers of the metabolic syndrome such as BW, BMI, body fat mass, total cholesterol, insulin, and glucose. Patient groups with high concentrations of these biomarkers are important populations for assessing a possible benefit of tea intervention.

Effects of CCRTs on anthropometric variables in combination with exercise

The contribution of physical activity in achieving (negative) energy balance is important for increased activity-induced EE, decreased fat mass, and increased fat-free mass resulting in increased resting EE; these actions may induce WL and prevent BW regain after WL (71). It has been shown that short-term catechin consumption over 3 d was able to increase maximal oxygen uptake during a maximal oxygen uptake (VO_{2max}) test compared with placebo (72). Also, CCRTs improved FO after a moderate-intensity 30-min cycling exercise at 60% of maximal oxygen consumption as shown by Venables et al (73). Several studies investigated the long-term effect of either moderate- or high-intensity exercise in normal, overweight, and obese subjects as well as in athletes (17, 18, 34, 47–50). Kataoka et al (48) observed a reduction in body fat after 12 wk consumption of catechins [placebo compared with low (278 mg), medium (570 mg), and high (845 mg) consumption] in combination with moderate-intensity exercise in 192 subjects. Furthermore, changes in anthropometric variables were positively correlated with the dose of catechins. However, Hill et al (18) reported similar reductions in anthropometric variables after 12 wk of either catechins (150 mg EGCG) or placebo in combination with moderate-intensity aerobic exercise in 38 overweight/obese subjects.

Catechins either in combination with caffeine or alone may improve endurance capacity and exercise tolerance. In chronic studies, catechins, in combination with moderate-intensity exercise, may change anthropometric variables to a greater extent than exercise alone. Also, in athletes, it has been shown that fat mass was reduced after a combination of catechins and exercise.

MECHANISMS OF ACTION AND POTENTIAL MODERATING FACTORS

Catechins and caffeine separately and synergistically may affect EE, FO, fat absorption, and EI with a potential impact on WL and WM. The molecular mechanisms of action affecting EE, FO, fat absorption, and EI after supplementation with CCRTs are outlined in Figure 1. An overview of the mechanisms of action of CCRTs and their interplay with moderating factors is shown in Figure 2.

Intestinal absorption of catechins

A better understanding of the absorption and bioavailability of catechins could help explain the mixed results. So far, the available studies that examined catechins and their metabolites in urine and plasma have not provided consistent or conclusive results. After ingestion, catechins are hydrolyzed by enzymes and colonic microflora. During the process of absorption via active transport and passive diffusion, catechin metabolites are produced by phase II enzymes that conjugate the catechins, mostly in the small intestine, enteroocytes, and liver. Conjugation via methylation, glucuronidation, and sulfation decreases the hydrophilicity of catechins and promotes their excretion via bile and urine (74, 75) and improves their absorption via passive diffusion. Conjugated metabolites circulating in the blood can be bound to albumin. After uptake into the circulation, catechins are either incorporated in tissues or returned to the intestines. In the intestines, catechins can be excreted in the feces or further metabolized and reabsorbed via enterohepatic recycling (76–78).

EE and FO

The absorption rate of catechins may affect thermogenesis. Beneficial effects of CCRTs on EE and FO have been reported in acute and chronic studies (13, 35, 54–58, 62). The methylation of catechins by catechol-O-methyltransferase (COMT), which proceeds more avidly than that of catecholamines, and the inhibition of phosphodiesterase by caffeine appear to be the principal mechanisms behind the stimulating properties of GT. The inhibition of both enzymes activates a signal cascade that
stimulates the sympathetic nervous system and increases EE and FO (14, 79). This has been thoroughly described in a previous review by the authors (80). The role of EE and FO in catechin-induced WL was shown by Auvichayapat et al (30), who showed that urine vanillylmandelic acid, a catecholamine metabolite, was modified after 12 wk of supplementation, indicating activation of the sympathetic nervous system. Furthermore, EE and FO may also increase via an effect of catechins on the gene expression of proteins that play a role in thermogenesis and β-oxidation. However, in an acute study, Lonac et al (81) did not find any effect of EGCG supplementation on resting EE and diet-induced thermogenesis; this result could implicate the importance of including caffeine in study designs to take advantage of its potential for synergy with catechins.

**Dietary fat absorption**

The mixed results on the effect of catechins on EE and FO may partly reflect diminished dietary fat absorption during WL, as examined in animal models. Catechins may inhibit pancreatic and gastric lipases and thus attenuate fat emulsification (82–89). In humans, Hsu et al (90) measured an increase in the excretion of lipids in the feces of 12 healthy subjects after a 10-d treatment with a catechin-rich beverage during a high-fat diet compared with a control beverage. Therefore, catechins may affect fat metabolism by increasing the oxidation of dietary and stored fat but also by decreasing the absorption of dietary fat.

**Gene expression**

Tea catechins block nuclear transcription factor κB (NF-κB) activation by inhibiting the phosphorylation of IκB (inhibitor of κB) (91). This action prevents NF-κB from inhibiting the peroxisome proliferator–activated receptors (PPARs) that are important transcription factors for lipid metabolism (92). Thus, mRNA expression of lipid-metabolizing enzymes such as acyl-CoA oxidase and medium-chain acyl-CoA dehydrogenase (MCAD) is upregulated. The upregulation of acyl-CoA oxidase, a peroxisomal β-oxidation enzyme, and MCAD, a mitochondrial β-oxidation enzyme, in the liver (92) suggests β-oxidation activation followed by an increase in FO. Catechins may also have a direct effect on the gene expression of different uncoupling proteins (UCPs) that influence EE with the production of heat (83).

After treating obese mice with catechins in addition to a high-fat diet for 8 wk, Lee et al (93) observed a decrease in the mRNA levels of adipogenic genes such as PPAR-γ, CCAAT enhancer binding protein-α (CEBP-α), regulatory element-binding protein-1c (SREBP-1c), lipoprotein lipase (LPL), and fatty acid synthase (FAS) as well as an increase in the mRNA levels of carnitine palmitoyltransferase-1 (CPT-1), UCP2, hormone-sensitive lipase (HSL), and adipose triglyceride lipase (ATGL) compared with the high-fat control group. Lu et al (94) investigated >80 obesity-related genes in rats receiving either a control diet, a high-fat diet, or a high-fat diet plus catechins for 4 mo. Catechins prevented the
negative changes in mRNA levels of 12 genes related to EE and EI induced by the high-fat diet. In mice, Sae-Tan et al (89) observed an upregulation of genes such as nuclear respiratory factor (NRF) 1, MCAD, UCP3, and PPARα, which are all involved in fatty acid oxidation.

The increase in mRNA levels of many genes due to the consumption of tea catechins may lead to improvements in fat metabolism and have a positive effect on BW via increased FO and brown adipose tissue (BAT) development and a decrease in adipocyte differentiation. Similarly, caffeine also appears to have the capacity to induce changes in the gene expression of important transcription factors that are involved in EE. Thus, catechins and caffeine may work synergistically to modulate gene expression and benefit overall energy metabolism.

BAT

The increase in EE induced by CCRT may be caused by an activation of BAT via stimulation of the sympathetic nervous system. Choo (95) showed in rodents that the body fat-reducing effect of catechins as well as the increase in BAT protein content, an indicator of BAT thermogenesis, were absent when the β-adrenoceptor was blocked. The activation of the sympathetic nervous system by CCRT may also alter gene expression of UCPs that are present in the mitochondria of BAT and which are involved in nonshivering thermogenesis. Whereas BAT was assumed to be present only in rodents, van Marken Lichtenbelt et al (96) showed its presence in male subjects with a normal BW, which might imply a role of BAT in catechin-induced EE.

Capsaicin stimulates EE through β-adrenergic activation of BAT (97, 98). However, Vosselman et al (99) did not find an activation of BAT in humans after β-adrenergic stimulation by isoprenaline, despite an increase in EE. Gosselin and Haman (100) reported that ingestion of CCRT increased total EE via nonshivering thermogenesis during cold exposure, possibly through BAT activation. When CCRT was ingested before mild cold exposure, EE increased, whereas shivering intensity decreased.

On a molecular level, Hondares et al (101) reported that PPARα acts as a key component of BAT thermogenesis by regulating lipid catabolism and thermogenic gene expression via induction of PPARγ coactivator (PGC)-1α and PRDM16. This relation may also provide evidence for BAT activation by catechins. CCRTs have been shown to upregulate mRNA levels of PPARα (89) as well as cyclic AMP and protein kinase A via norepinephrine (80), similar to the way in which BAT thermogenesis is stimulated (101). Further investigation of the relation between catechin-induced EE and BAT activity in humans is warranted.

Gut microbiota

Research concerning the gut microbiota (GM) provides growing evidence that the role of the gut flora in energy balance is important (102, 103). GM transplantation from obese mice to germ-free mice increased fat percentage in the germ-free mice compared with after receiving GM from lean mice (104). Apparently, the gut flora regulates energy harvesting from the diet and the energy that is eventually stored (105). In humans, the GM differs between obese individuals and their lean counterparts, with obese individuals having more Firmicutes and less Bacteriodetes (106, 107). The principal bacterial phyla Firmicutes and Bacteriodetes appear to change during WL. It has been suggested that the role of tea catechins in BW regulation may be
attributed to their effect on GM (108). Several in vitro studies have shown that CCRT might have prebiotic effects by decreasing the presence of unfavorable GM (109–111). The GM metabolizes catechins and hydrolyzes them to promote absorption. The cleavage of glycosidic linkages in polyphenols generates glycans that are important for the subsistence of GM. Because Bacteroidetes appear to be more capable of degrading glycans than Firmicutes, they are preferred by polyphenols and less repressed, which may lead to a more favorable composition (108). The increase in EE after CCRT ingestion may partly be attributed to the metabolic capacity of the GM. However, Juntzperr et al (112) showed that GM composition might depend more on the ingested caloric load of a meal than on WL, indicating a sensory function of the bacteria. By decreasing fat absorption, catechins may decrease the caloric load and prevent a change in GM composition. The suggested beneficial alteration of GM composition by catechins may also induce changes in gene expression as noted above. Catechins also affect short-chain fatty acids (SCFAs), which are produced during fermentation of dietary fiber and which are involved in the regulation of gene expression (88, 113, 114). SCFAs might also affect EE, FO, and satiety hormones that are involved in EI regulation (115, 116), providing another possible explanation for the mechanisms of action of CCRTs.

Genetic predisposition

Ethnicity may be a potential moderating factor of the efficacy of CCRTs on energy metabolism partly due to interactions of the different ADORA2A and COMT polymorphisms associated with ethnic origins. We have hypothesized that genetic predisposition plays an important role in whether or not CCRT efficiently increases EE. Great intravariability between subjects concerning EE has been reported (117). With respect to CCRT, different polymorphisms for the COMT enzyme exist along with a wide variability in flavonoid O-methylation by COMT (118). The Val (108/158)Met polymorphism, which replaces valine with methionine, changes COMT activity with an interindividual variability of ~3-fold. Asian populations appear to have a higher frequency of the thermo-stable, high-activity enzyme COMTh allele (Val/Val polymorphism) than do white populations, who have a higher frequency of the thermo-labile, low-activity enzyme COMTl allele (Met/Met polymorphism); half of the white population is homozygous for the COMTl allele (25%) and the COMTh allele (25%). The other 50% of this population is heterozygous (Val/Met polymorphism). This genotype may explain the difference in sensitivity to CCRT, and why some studies in whites found no effect after ingestion of CCRT (119). Also, it may explain the differences between results from rodent models and human studies, because the variety in COMT enzyme activity differs between species, with high activity in rats and low activity in humans (74). In a pilot study, Hursel et al (53) examined in 14 subjects whether different COMT genotypes may lead to different outcomes in EE and FO after acute GT ingestion. Acute GT consumption compared with placebo increased EE and FO and decreased respiratory quotient and carbohydrate oxidation in the COMTh allele carriers, whereas no differences were observed in the COMTl allele carriers.

Furthermore, the role of different COMT genotypes after acute GT ingestion has been investigated in humans in other research areas (120, 121). It was shown that beneficial changes only occurred in subjects with the COMTl allele, indicating that the effect of catechins indeed depends on COMT genotype (121). The same authors also examined the effect of COMT genotype on the absorption and metabolism of catechins and concluded that different polymorphisms seem to have no large impact (122). In contrast, Inoue-Choi et al (123) observed in 660 subjects who drank CCRT daily that COMTl allele carriers excreted less urinary catechin metabolites compared with COMTh allele carriers. The absence of an effect in the study by Miller et al (122) was attributed to the low availability of catechins due to 2 different COMT proteins, cytoplasm soluble protein (S-COMT) and membrane-bound protein (MB-COMT). It appears that S-COMT has more affinity for metabolizing catechins, whereas MB-COMT preferentially metabolizes catecholamines. Nevertheless, it is debatable whether this makes a significant difference because S-COMT is the predominant form in most tissues, responsible for the majority of all COMT enzyme activity, whereas MB-COMT accounts for only a small part of total activity (124). However, COMT is not the sole enzyme involved in the catechin metabolism. A complex set of conjugating enzymes and carrier systems, each influenced by genetic polymorphisms, seems to be involved in the absorption and processing of catechins, as well as in the formation of the various catechin metabolites (76).

Nackley et al (125) suggested that, in addition to the Val(108/158)Met polymorphism, there are additional polymorphisms in the COMT gene that modulate enzyme activity. Four polymorphisms in the COMT gene have been shown to combine into 3 common haplotypes (126), which have been associated with variation in COMT enzyme activity (125). Haplotype may thus account more for variability than an individual polymorphism and therefore play an important role in the effect of CCRT on EE and BW control.

Whereas most habitual caffeine consumers appear to develop a tolerance to its acute effects, Cornelis et al (127) found that Hispanic Americans with an ADORA2A 1083TT genotype, which codes for the A2A receptor at which caffeine antagonizes the actions of adenosine, are more likely to limit their HCI than those with the CC and CT genotypes, because of greater sensitivity to the effect of caffeine on the adenosinergic system. Also, the cytochrome P450 1A1 and 1A2 (CYP1A1-CYP1A2) gene regions, which code for enzymes responsible for the metabolism of caffeine, have been associated with HCI. The enzyme activity of the CYP1A2 gene, and therefore caffeine metabolism, differs between individuals (128). The proposed role for genetic predisposition in the efficacy of CCRT may play a role in fat metabolism as well. Subjects differ in their levels of FO (129–131) and possibly also in fat absorption, especially after consumption of CCRT.

EI

There is controversy on whether CCRT leads to hyperphagia or hypophagia. An increase in EI after EGCG supplementation has been observed in rodents (7), although other rodent studies did not observe this effect (94, 95). In humans, Josic et al (132) and Carter and Drewnowski (133) showed increased feelings of satiety and fullness, the latter showing a decreased EI at the next meal due to CCRT consumption. Other reports from human
Adipocyte differentiation

In their extensive review, Gregoire et al (142) discussed a role for the development of adipocytes in energy balance through their ability to increase in size and form new adipocytes from precursor cells, as well as their function as a secretory organ. Catechins have been reported to suppress adipocyte differentiation, which might have preventive effects on the development of obesity (143). The underlying mechanism is similar to the effect of catechins on, for instance, EE and the activation of BAT. CCRTs seem to exert effects similar to methylisobutylxanthine, an accelerator of preadipocyte differentiation. Both inhibit phosphodiesterase, stimulate adenylyl cyclase, increase cyclic AMP (80, 142), and affect transcription factors such as PPAR-γ and C/EBP-α (142, 143).

Dose and composition of tea catechins

The dose, composition, and processing of CCRTs may contribute to the mixed results obtained in different studies. Differences in dosage have been investigated, but it remains unclear whether increasing dosage leads to a greater effect (60, 62). This issue is confounded by the fact that many studies use the same dose but fail to equalize intakes via a subject-specific dose per kilogram BW. Moreover, some studies use tea extractions, whereas others use beverages prepared with tea leaves. This can markedly affect catechin composition of the treatment, which also depends on features such as geographical location and environmental conditions such as soil and temperature. The difference in catechin composition and method of processing also affects the qualitative and quantitative profiles of the catechins in tea, which influence absorption and metabolism (77). For instance, Lu et al (74, 75) showed that gallated catechines have 60-fold higher activities than nongallated catechins at inhibiting COMT. Other compounds in tea in addition to catechines and caffeine, such as trace elements, may also mediate the effects, because their presence in tea varies and therefore their contribution to the qualitative and quantitative phytochemical profiles varies as well. However, the influence of the elements on human health in the context of tea consumption on metabolism is still largely unknown. However, tea contains chromium, an essential mineral involved in lipid and carbohydrate metabolism, and zinc, which contributes to carbohydrate, protein, and lipid synthesis and degradation (144). These actions could be consistent with the effect of CCRT on energy metabolism.

Food matrix

The matrix of foods or meals accompanying tea consumption may influence its actions on energy metabolism. Protein seems to interfere with CCRT in acute (145–150) and chronic studies (70, 151). No synergistic effect of CCRT supplementation was observed with a high-protein diet during WM after WL. During WM results of the high-protein diet + CCRT group were comparable to the results of the high-protein diet + placebo group and the adequate protein diet + CCRT group (70). Miyajima et al (151) tested catechins (540 mg) in combination with soy protein (10 g/d) for 4 wk and found had no effect on BW and BMI. These results may be due to the inhibitory effect of protein, especially proline-rich caseins, on the effect of GT due to the formation of protein-polyphenol complexes that reduce the
absorption or that produce metabolites without thermogenic actions (152–157). In contrast, there may also be compounds in the food matrix that enhance the bioavailability of catechins. Peters et al (158) showed in rodents that bioavailability and intestinal uptake of catechins was improved when GT was ingested in combination with sucrose and ascorbic acid.

CONCLUSIONS AND FUTURE DIRECTIONS

The research related to CCRTs shows promising effects with respect to BW regulation. Studies and meta-analyses of CCRTs in most cases showed improved anthropometric variables such as BW, BMI, body fat mass, and waist:hip ratio. CCRTs may be able to improve blood variables that are biomarkers for metabolic syndrome, including insulin, glucose, and HDL, LDL, and total cholesterol. Endurance capacity and exercise tolerance improved with consumption of CCRT, which over a long term may positively change anthropometric variables to a greater extent than exercise alone.

Despite the substantial number of reports available on the effect of tea on energy metabolism, a great deal of research remains to be done characterizing its efficacy, specificity, and mechanisms of action. Importantly, further studies on the bioavailability and metabolism of catechins are required. New research methods and advances in technology might shed a new light on this topic. Furthermore, the effect of catechins on EI, dietary fat absorption, GM, and SCFAs should be investigated more thoroughly in humans. The role of BAT in the thermogenic effect of catechins, which appears evident in rodents, should be extended to human studies. Similarly, new efforts to determine the role of genetic predisposition are required to understand individual responsiveness to tea intake and to personalize nutrition advice. Large-scale clinical trials on WL or WM with sufficient numbers of subjects with different COMT and CYP polymorphisms would help to better define this matter. The effect of COMT genotype on tea’s action on innate reward systems and EI could lead to novel observations. Similar studies should also be conducted on the basis of haplotype rather than single polymorphisms.

In addition, new areas of investigation require our attention, such as the relation between tea and sleep. Recently, sleep has been shown to play an important role in BW regulation, with evidence showing that increases in BW during the past decades are related to decreases in total sleeping time during the same period. GT contains the amino acid l-theanine, which increases α-wave activity associated with being in an awake and mentally relaxed state. However, some studies report stimulating effects on δ-waves, associated with deep sleep, and θ-waves, associated with light sleep, thereby perhaps affecting sleep quality (159). Functional polymorphisms of COMT that appear to play a role in the effects of GT also modulate sleep homeostasis due to their dopaminergic signaling (160). Thus, investigations on the relation between tea and sleep are warranted.

Whereas many studies have shown tea to have a beneficial impact on energy metabolism, several factors appear to reduce its efficacy, including HCI, food matrices, catechin dose and composition of the tea, ethnicity, and other genetic predispositions. Thereby, the research related to CCRTs also shows that beneficial effects are not always straightforward, because there are many moderating factors that should be taken into account. These factors may eventually affect bioavailability via their impact on absorption, processing, metabolism, transportation, incorporation, and excretion of catechins and caffeine and thereby ultimately the effect on BW regulation.

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