The Effect of Green Tea Extract on Fat Oxidation at Rest and during Exercise: Evidence of Efficacy and Proposed Mechanisms[1]

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ABSTRACT

Green tea is made from the leaves of the *Camellia sinensis L* plant, which is rich in polyphenol catechins and caffeine. There is increasing interest in the potential role of green tea extract (GTE) in fat metabolism and its influence on health and exercise performance. A number of studies have observed positive effects of GTE on fat metabolism at rest and during exercise, following both shorter and longer term intake. However, overall, the literature is inconclusive. The fact that not all studies observed effects may be related to differences in study designs, GTE bioavailability, and variation of the measurement (fat oxidation). In addition, the precise mechanisms of GTE in the human body that increase fat oxidation are unclear. The often-cited in vitro catechol-O-methyltransferase mechanism is used to explain the changes in substrate metabolism with little in vivo evidence to support it. Also, changes in expression of fat metabolism genes with longer term GTE intake have been implicated at rest and with exercise training, including the upregulation of fat metabolism enzyme gene expression in the skeletal muscle and downregulation of adipogenic genes in the liver. The exact molecular signaling that activates changes to fat metabolism gene expression is unclear but may be driven by PPAR-γ coactivator 1-α and PPARs. However, to date, evidence from human studies to support these adaptations is lacking. Clearly, more studies have to be performed to elucidate the effects of GTE on fat metabolism as well as improve our understanding of the underlying mechanisms. *Adv. Nutr. 4: 129–140, 2013.*

Introduction

In humans, substrate use changes depending on metabolic signals, such as fasting or insulin stimulation, and energy demands. At rest, in a fasted state, fat is the predominant fuel for energy. However, under insulin-stimulated conditions, the predominance shifts to carbohydrate oxidation. In healthy individuals, the ability to respond to signals, which requires a change in metabolism, is rapid and complete. This has been termed as "metabolic flexibility" (1). In obesity and non-insulin–dependent diabetes mellitus, despite high concentrations of circulating fatty acids (FAs), there is often a reduced ability to oxidize these fats during periods of fasting. It has been reported that these individuals cannot respond rapidly to changes in metabolic requirements. For these reasons, obesity and non-insulin–dependent diabetes mellitus are not metabolically flexible (1). More specifically,

an inability to oxidize FAs is related to insulin resistance and weight gain (2). Weight loss and exercise interventions have been shown to improve fat oxidation during fasted, rested conditions and exercise (3). This has been associated with improvements in insulin sensitivity. Thus, interventions to increase fat oxidation may improve metabolic flexibility and provide benefits to obese and insulin-resistant individuals.

Endurance athletes may also benefit from an increased capacity to oxidize fat. Augmenting fat oxidation during exercise has been shown to spare muscle glycogen (4). Endurance exercise training is known to increase fat oxidation rates (4), reducing the utilization of glycogen during exercise and thus delaying the onset of fatigue and enhancing endurance capacity and performance (4). Research over the past 2 decades has focused on strategies and interventions to enhance rates of fat oxidation at rest and during exercise. These include exercise training (4–8), high-fat diets, low-carbohydrate diets (9), and, more recently, the use of specific foods, usually in the form of dietary supplements (10,11).

During a single exercise bout, fat oxidation rates are upregulated (up to 10-fold compared with rest) to meet the

energy demands of the working muscles (4). The contribution of fat and carbohydrate to overall energy expenditure $(EE)^2$ depends on exercise intensity, duration, training status, and diet (4). However, it has been determined that maximal fat oxidation rates occur when exercise is performed at a moderate intensity. This intensity has been referred to as FatMax, and although highly individual, it typically occurs at 45–65% VO_2max (4). The most effective way to increase fat oxidation is through endurance exercise training (4), which is associated with skeletal muscle adaptations in favor of enhancing fat metabolism. The primary adaptation that occurs is associated with an augmentation to mitochondrial density, otherwise known as mitochondrial biogenesis (12). In addition, endurance exercise training induces increased expression of oxidative enzymes and proteins involved in FA transport, uptake, and oxidation, which can overcome some of the limiting factors to oxidizing fat (8). Further, adaptations also occur to enzymes involved in the tricarboxylic acid cycle and respiratory chain (8).

However, exercise training requires effort, is time consuming, compliance is often poor, and the effects are only visible in the longer term. Therefore, ingestion of dietary supplements has become a popular alternative, because it is often claimed they are an easy and fast method to increase fat oxidation at rest and during exercise (10). However, evidence to support the use of a number of these supplements is somewhat lacking [for review, see (10)]. One of the more researched and promising supplements to upregulate fat metabolism at rest and during exercise is green tea. Green tea, produced from the plant *Camellia sinensis* L. species of the Theaceae family, contains naturally occurring flavonoids and caffeine. Tea is manufactured through non-, partial, and full fermentation of the leaves to produce green tea, oolong tea, and black tea, respectively (13). Therefore, green tea preserves a high quantity of the catechin polyphenol concentration (a subgroup of flavonoids). The 4 main types of catechins are: (-)-epigallocatechin-3-gallate (EGCG), (-)-epicatechin-3-gallate, (-)-epigallocatechin (EGC), and (-)-epicatechin (**Fig. 1**). EGCG is the most abundant and thought to be the most pharmacologically active catechin (14). The type of tea, origin of the leaves, brewing technique, and source of green tea can all influence the catechin content (13). However, a standard cup of green tea (250 mL) contains between 100 and 300 mg of total catechins and 50 and 90 mg of caffeine (15) (**Table 1**).

Currently, chronic green tea extract (GTE) ingestion, with and without caffeine, has been shown in some, but not all studies, to promote weight loss (16). It is beyond the scope of this review to discuss the evidence of GTE intake on weight loss [for a full review, see (16,17)]. However, it is thought that the antiobesity effects of GTE intake may be attributed to elevated fat oxidation and total EE. At present, a growing number of studies have investigated the
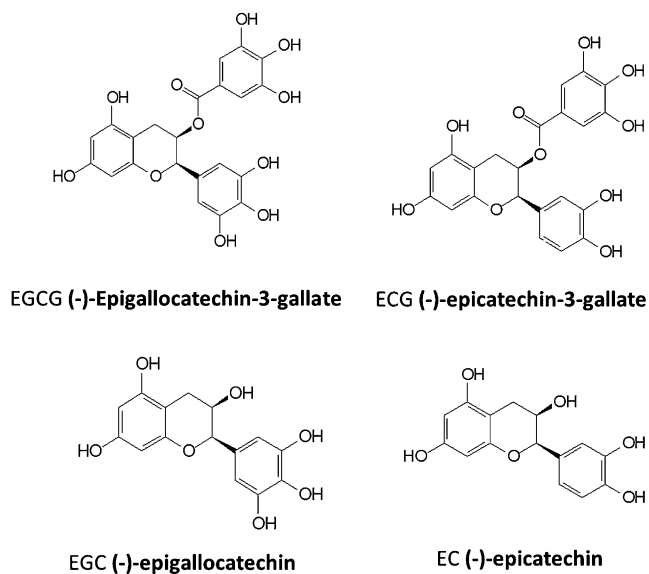

EGCG (-)-Epigallocatechin-3-gallate   ECG (-)-epicatechin-3-gallate

EGC (-)-epigallocatechin   EC (-)-epicatechin

Figure 1 Chemical structure of green tea catechins.

effects of GTE intake on upregulating fat metabolism at rest and during exercise in humans. In addition, animal and in vitro evidence has suggested a number of proposed mechanisms whereby GTE alters fat metabolism. However, no review to date has specifically discussed the efficacy. Therefore, this review will discuss the effects of GTE ingestion solely on fat metabolism.

This review will first evaluate the research that has studied the effects of GTE intake on fat metabolism at rest and during exercise. These sections will be further broken down to discuss whether shorter or longer term ingestion of GTE is more effective (see **Table 2** for definitions of supplementation periods). The second purpose of this review is to discuss and critically evaluate the possible mechanisms that may explain changes in fat metabolism with GTE.

Shorter term green tea intake and its effects on resting fat metabolism

Dulloo et al. (18) were the first to investigate whether GTE could increase fat oxidation at rest. In this double blind, cross-over study, 3 doses of encapsulated GTE (270 mg/d EGCG + 150 mg/d caffeine), caffeine (150 mg/d), and placebo (cellulose) were taken over a 24-h period in a respiratory chamber. The authors observed that compared with placebo and caffeine, consumption of GTE significantly increased 24-h fat oxidation (76.2 ± 10.6, 81.9 ± 8.7, and 103 ± 13 g/24 h, respectively). Interestingly, fat oxidation rates were 20% higher following GTE compared with caffeine. Thus, the authors concluded that the increase in fat oxidation, following GTE intake, was independent of its caffeine content per se. Using a comparable study design, Rumpler et al. (19) showed that a catechin-rich oolong tea taken during a 24-h period (662 mg/d catechins, 270 mg/d caffeine) caused a 12% increase in 24-h fat oxidation rates compared with water. However, the authors showed no difference for a lower dose (331 mg/d catechins, 135 mg/d

Table 1. Catechin and caffeine content in a variety of tea products[1]

Beverage	Serving size/brewing technique	Total catechins	Caffeine
		mg/serving	
Green tea leaves	1 g tea leaves/100 mL of hot water	42–201	25–43
Lipton green tea	Teabag/100 mL of hot water	195–205	32–33
Decaf green tea	Teabag/100 mL of hot water	72–73	<1
GTE supplement	Per capsule	200–210	5–6

[1] Data from (9,11). GTE, green tea extract.

caffeine), suggesting that a higher catechin dose is required to stimulate fat oxidation.

Berube-Parent et al. (20) investigated the dose-response relationship of GTE on 24-h fat oxidation. On 4 separate occasions, subjects ingested caffeine-rich (600 mg/d) GTE capsules differing in doses of EGCG (270, 600, 900, and 1200 mg/d EGCG). All GTE doses significantly increased 24-h EE by 8% (750 kJ) compared with placebo. However, there were no significant differences between the treatment groups. GTE did not increase fat oxidation in any of the GTE groups compared with placebo. Similar results have also been shown following 3 d of GTE (540 mg/d) and caffeine (300 mg/d) intake compared with placebo (21). However, Berube-Parent et al. (20) speculated that due to the lack of dose response, a ceiling effect at 270 mg/d EGCG may be apparent. In addition, the authors also speculated that the relatively high caffeine content (600 mg/d) could mask the effects of GTE on fat oxidation. A dose-dependent response of GTE has been found in animals when caffeine was absent (22). Based on these animal data, caffeine may only work synergistically with catechins to augment fat oxidation in small doses (<600 mg/d). In support of this notion, Thielecke et al. (23) showed an increase in fat oxidation at `rest, in the postprandial and fasted state, when EGCG (300 mg/d) and a small dose of caffeine (200 mg/d) were consumed for 3 d. For this reason, the exact composition of catechins and caffeine may be integral to altering fat oxidation in humans.

To date, the exact composition of GTE catechins required to stimulate fat oxidation is unknown. To elucidate this in vivo, a recent study (24) compared the effects of combined (∼500 mg/13 h total catechins) and individual (EGCG and EGC ∼600 mg/13 h) catechins + caffeine (150 mg/13 h) on resting metabolism for 13 h. Subjects received GTE in small and frequent doses (82–214 mg) throughout this period. The authors found no increase in fat oxidation with any of the treatments compared with placebo. Because GTE catechins are poorly absorbed (25), ingesting small amounts, in bolus throughout the day, may result in low plasma catechin concentrations, which may explain why the authors (24) did not observe a change in fat oxidation. Yet 2 d of moderate intake of EGCG in only some (300 mg/d) (26) but not all cases (405 mg/d) (27) has been shown to increase fat metabolism at rest through a reduction in the respiratory quotient (RQ). Therefore, it currently remains unclear which catechin or catechins is/are required to elicit changes in fat oxidation at rest.

Recently, a meta-analysis was published to address whether acute intake of GTE (with and without caffeine) or caffeine only has the potential to increase fat oxidation at rest (28). In total, 6 articles were used following strict controls. It was found that GTE treatment groups yielded significantly greater mean fat oxidation rates (16% higher) compared with placebo. This effect was not seen in the caffeine-only studies ($P = 0.11$), supporting the assumption that the effects of GTE are independent of the caffeine content per se. In addition, a dose-dependent response was observed with a 0.02-g/24 h increase in fat oxidation for each 1 mg increase of ingested catechins. However, due to the limited number of studies and the large variation in dose, the authors were unable to give a lower and upper dose to elicit maximal changes to fat oxidation.

On balance, research has supported an increase in fat oxidation at rest in response to shorter term GTE intake. However, not all studies showed increases in fat metabolism (or EE). The effects of GTE on fat oxidation at rest may be small and only apparent when tested in larger sample sizes, as demonstrated by the conclusive evidence in the meta-analysis (this is discussed in more detail later in the review). Therefore, the inconsistencies in the studies reported could be related to the small sample sizes implemented, the exact catechin composition, and the amount of caffeine present in the GTE. Hence, further research is required to elucidate the most effective supplementation protocol to enhance fat oxidation during resting conditions.

Longer term green tea intake and its effect on resting fat metabolism

The previous section discussed the shorter term effects of GTE on substrate metabolism. The following section will discuss the effects of longer term GTE intake.

Auvichayapat et al. (29) gave GTE (750 mg/d catechins + 87 mg/d caffeine) or placebo for 12 wk to obese Thai men and women. Resting EE and substrate oxidation were measured at baseline and wk 4, 8, and 12. Compared with baseline, longer term GTE intake significantly lowered fasting RQ at wk 8 and elevated EE at wk 8 and 12. Harada et al. (30) administered

Table 2. Definition of GTE intake durations[1]

Duration	
Shorter term	
Acute	Within 24 h
Short term	1–7 d
Longer term	
Medium term	1–4 wk
Long term	>4 wk
Chronic	>10 wk

[1] GTE, green tea extract.

either a high-catechin (593 mg/d catechin + 22 mg/d caffeine) or a low-catechin drink (78 mg/d catechin + 81 mg/d caffeine) to 12 Asian males during a 12-wk period. Using a stable isotope method (^{13}C-labeled TG meal), $^{13}CO_2$ excretion was significantly higher in the high-catechin group compared with the low-catechin group at wk 12 compared with baseline. This is indicative of increased dietary fat oxidation. In addition, diet-induced thermogenesis in the 8-h post meal increased from baseline to wk 12 (51.4 and 90.3 kcal, respectively) only in the high-catechin group. These studies suggest that longer term GTE has the potential to increase fat oxidation and alter energy metabolism.

Long periods of dietary restriction are associated with a suppression of resting EE (31). Thus, long-term GTE intake may prevent this (32). Diepvens et al. (32) investigated the effect of GTE intake (1125 mg/d catechins + 225 mg/d caffeine) for 83 d during dietary restriction compared with a placebo in overweight Caucasian women. Resting EE and RQ were measured at d 4 and 32. Compared with placebo, there was no significant difference in fasting EE, diet-induced thermogenesis, or RQ in the GTE group. However, participants used in this study were moderate habitual caffeine consumers (300 mg/d), which may have affected the results, as suggested by a recent study by Westerterp-Plantenga et al. (33). The authors showed that intake of encapsulated GTE (270 mg/d EGCG + 150 mg/d caffeine) or placebo for 12 wk following a 4-wk low-energy diet caused a significantly lower fasting RQ only for those who had a low habitual caffeine intake (<300 mg/d) compared with a high habitual intake (<300 mg/d). This was also true for reductions in body weight and body fat.

To date, there are only a few studies that have investigated the effect of longer term GTE ingestion on fat oxidation. Taken together, these studies suggest that longer term intake of GTE may potentially augment fat metabolism but only if habitual caffeine intake is low.

Shorter term green tea intake and its effects on fat metabolism during exercise

During exercise, fat oxidation rates are up to 10-fold higher than at rest due to the energy demand of the working muscles (4). In this section, we shall discuss studies that have investigated the effect of GTE intake on fat metabolism during exercise.

In 2008, Venables et al. (34) were the first to study the effects of acute (24 h) GTE intake on fat oxidation rates during exercise. In this crossover, double blind study, subjects consumed GTE (890 ± 13 mg/d catechins containing 366 ± 5 mg/d EGCG) or placebo before completing a bout of moderate intensity cycling [30 min at 50% maximum power output (W_{max})]. Average fat oxidation rates during exercise were 17% higher in the GTE condition (0.41 ± 0.03 g/min) compared with placebo (0.35 ± 0.03 g/min). More recently, during a 60-min cycle at 60% VO_2max, fat oxidation did not increase following 6 d of EGCG (270 mg/d) compared with caffeine and a placebo (35). Interestingly, more fat was oxidized following caffeine and placebo trials

compared with EGCG (0.13 ± 0.05, 0.16 ± 0.06, and 0.16 ± 0.05 g/min, respectively). However, at such low fat oxidation rates, it makes it difficult to detect differences because of the variation of the measurement. This is discussed in more detail in the following section.

In conclusion, there are only a limited number of studies that have investigated the effect of shorter term GTE intake on fat metabolism during exercise. The results to date remain equivocal. Thus, more research is needed before more firm conclusions can be drawn.

Longer term green tea intake and its effects on fat metabolism during exercise

GTE intake over a more prolonged duration may result in further increases in fat oxidation rates during exercise. A recent study conducted a 2-h cycling exercise test (50% W_{max}) following 3 wk of GTE (159 mg/d catechins) and placebo ingestion in a randomized, crossover study design. Despite longer term GTE intake, the authors did not observe a difference in average respiratory exchange ratio (RER) during the first or second hour of exercise between the groups (1 h: 0.95 ± 0.01 and 0.96 ± 0.01; 2 h: 0.91 ± 0.01 and 0.91 ± 0.01 for placebo and GTE, respectively) (36). However, the subjects ingested a total of only 159 mg/d catechins, of which 68 mg was EGCG. This is a much lower dose than that administered in other studies (34).

More promising results have been found when GTE has been ingested chronically (≥12 wk) alongside an exercise training program. Maki et al. (37) reported that overweight adults had a greater loss in total and s.c. abdominal fat area following a 12-wk training program (180 min/wk) plus daily consumption of a GTE (625 mg/d catechins, 39 mg/d caffeine) compared with a control beverage (39 mg/d caffeine). Unfortunately, fat oxidation was not measured in the study. In animal studies, fat oxidation has been measured following longer term GTE intake in combination with exercise training. Shimotoyodome et al. (38) found that mice, after completing 15 wk of regular exercise in combination with GTE ingestion, had significantly lower RER and increased fat utilization during exercise than the exercise-only group of mice. Furthermore, a 30% increase in running time has also been found in mice fed a 0.5% GTE diet in conjunction with exercise training (39). This increase in endurance capacity was accompanied with increased β oxidation rates and a lower RER compared with the mice that only exercised. Similarly, more recent evidence has demonstrated that the age-related decline in endurance capacity in senescence-accelerated prone mice was prevented when fed a 0.35% GTE diet combined with exercise training. These adaptations to endurance capacity were also paralleled with greater skeletal muscle β oxidation rates following GTE and exercise training (40).

In humans, Ota et al. (41) supplemented 14 healthy male subjects with a placebo or GTE beverage rich in catechins (570 mg/d catechins, of which 218 mg was EGCG) for 2 mo, during which they took part in regular treadmill exercise (5 km/h for 30 min 3 times/wk). The authors found
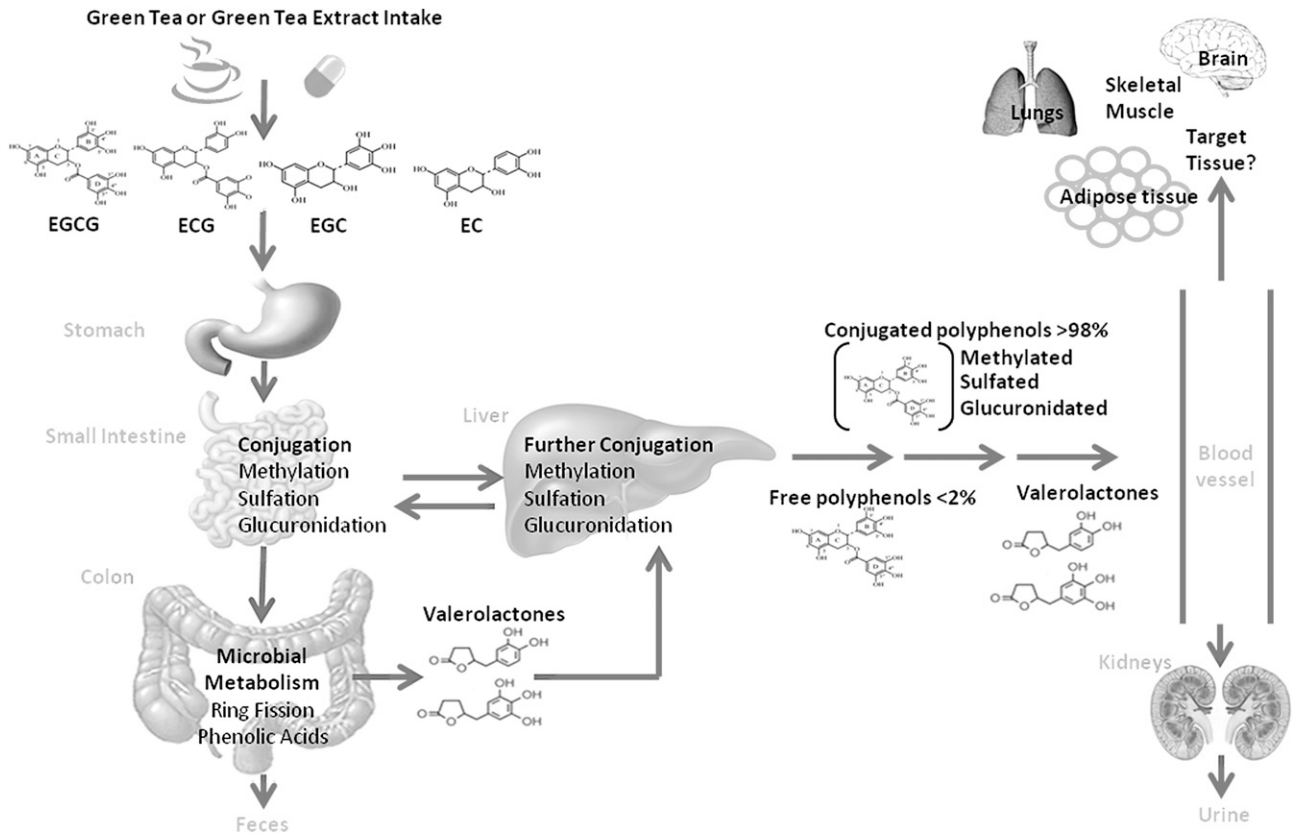
Figure 2 The bioavailability and metabolism of green tea following ingestion in humans. EGCG, (-)-epigallocatechin-3-gallate; ECG, (-)-epicatechin-3-gallate; EGC, (-)-epigallocatechin.

that subjects consuming the GTE test beverage had 24% higher fat oxidation rates during exercise than the placebo group. A similar effect was found when the supplementation and exercise training period was extended to 10 wk (42). In this study, daily consumption of a test beverage containing 573 mg of GTE catechins plus regular exercise (60 min cycle at 60% VO₂max 3 times/wk) significantly lowered RER compared with placebo. These studies provide an early insight into the possibility that longer term GTE intake in combination with exercise training may be efficacious in elevating fat oxidation.

It appears that in a small number of studies, both shorter and longer term GTE intake have the potential to increase fat oxidation. But this has not been consistently shown. However, no study has directly compared shorter and longer term GTE intake on fat oxidation during exercise. For these reasons, the practical relevance and use of GTE remains ambiguous. The exact mechanisms may differ dependent on the duration of intake. This shall be discussed later in this review.

Factors influencing the effect of GTE on fat metabolism

Establishing the influence of GTE on fat metabolism may be dependent on a number of factors, including the bioavailability of catechins, the sensitivity of measuring fat oxidation, and the effects of GTE in different populations. These factors will be discussed in the following section.

Bioavailability and bioactivity of catechins

In humans, the bioavailability of GTE following ingestion determines the bioactivity (43) (**Fig. 2**). The majority (98%) of ingested GTE undergoes extensive conjugation in the liver and gut microbiota and appears transiently (60–120 min after ingestion) in the plasma (25). Conjugated catechins are chemically different from the free catechins (found within GTE beverages) (25). Therefore, the free and conjugated catechins are likely to have different physiological and biological effects in the human body (44). Little is known about the bioavailability of the free catechins that are found at low concentrations in plasma following GTE intake (<2%) (25). Catechins are also able to pass into the colon, where they are catabolized to ring fission products and phenolic acids (45) known as valerolactones. These catabolites of GTE are known to take longer to peak in the plasma (8–15 h) and their biological effects in vivo are unknown (45).

Research investigating the potential mechanisms of GTE on fat oxidation has been done mainly in vitro using supraphysiological concentrations of free catechins [100–500 μmol/L compared with 0.1–10 μmol/L in plasma (25)]. Therefore, due to the differences in the form and dose of catechins used in vitro, the mechanisms of GTE that are
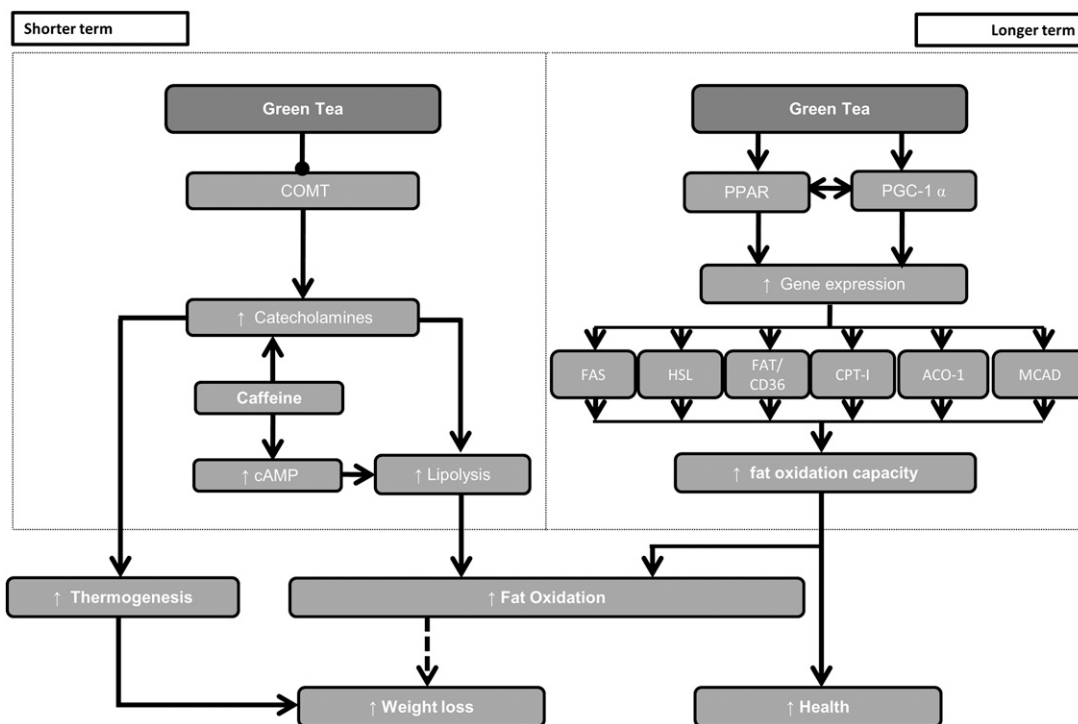
Figure 3 Overview of the shorter term and longer term mechanisms of green tea.

reported in the following section below may be different in vivo. In addition, catechins are known to accumulate in various tissues (46), yet the specific interaction that GTE may have on these tissues are unknown. It is also unknown how plasma catechin concentrations reflect tissue uptake and accumulation. Therefore, we can only speculate on how ingestion of GTE may have the potential to upregulate fat metabolism. It is imperative that to elucidate the potential mechanisms of GTE on the human metabolism, future in vitro studies should use only physiological catechin compounds and doses. This will ensure that similar environments are created in vitro as what might occur in vivo.

Reproducibility and sensitivity of measuring fat oxidation

To establish the magnitude of effect of GTE on fat oxidation, the GTE effect (signal) has to be big enough to be detected over and above the variation (noise). The better the signal: noise ratio, the more likely changes in fat oxidation can be detected. The noise in measuring fat oxidation includes variation within a person during a trial, day to day, and within a piece of equipment.

It appears that fat oxidation within a trial is small under rested conditions (47,48). Data from our laboratory has shown that during exercise, fat oxidation varies 4–12% CV within a trial, with less variation observed during longer bouts of exercise (>1 h: 3–6% CV). On the other hand, day-to-day variation in fat oxidation appears to be greater than the within-trial variation at rest (25% CV) (49) and during exercise (9.6% CV) (50). The greater variation in fat oxidation day to day can be partly explained by a number

of factors, including diet (51), muscle glycogen content (52), training status (53), physical activity level (54), gender (54), and body composition (55). However, although these factors may explain some of the variance, it appears that ∼60–75% of the variance remains unexplained (54). Further, within- and day-to-day variation in a piece of equipment measuring RER has been shown to be small (0.6–1.4% CV) (56). Consequently, the variance in fat oxidation is predominantly explained by human variation rather than the actual measurement itself.

Based on these points, detecting a change in fat oxidation may prove difficult when considering that the variance may be greater than the possible effect of the GTE. Therefore, to maximize the chance of detecting a possible effect, a highly reliable and sensitive measure of fat oxidation, while controlling for factors that may explain the variance in fat oxidation, at rest and during exercise is essential.

Population differences

It could be suggested that the lack of consistent findings is explained by differences in study populations. Hursel et al. (16) concluded in a recent meta-analysis that ethnicity may influence the effect of GTE on weight loss. On average, studies that used Asian populations found greater weight loss (1.51 kg) than studies that used Caucasian individuals (0.82 kg). This may explain why some studies did not find that GTE intake stimulated fat oxidation, because the majority of studies used Caucasian individuals (20,21,24,27,36). The potential factors that might explain this difference among ethnic groups is described in more detail later in this review.

The mechanisms behind the potential effects of green tea on substrate utilization

Several mechanisms have been proposed by which GTE could influence substrate utilization (**Fig. 3**). The majority of evidence originates from in vitro studies, which may have limited application in vivo. Such studies do not consider the bioavailability of catechins in humans, reflected in the dose and form of catechins used in vitro. The mechanisms that explain the potential shorter term and longer term effects of GTE ingestion may be distinctly different. Thus, both will be discussed in the following section.

Mechanisms behind the shorter-term effects of green tea intake on fat metabolism

For some time now it has been proposed that shorter term intake of GTE, more specifically EGCG as well as caffeine, may target the sympathetic nervous system (SNS; ~1–2 h after ingestion). Here we will critically review the evidence.

GTE and catechol-*O*-methyltransferase inhibition

Catechol-*O*-methyltransferase (COMT) is known as an intracellular enzyme and is ubiquitous throughout all mammalian tissues, including skeletal muscle and adipose tissue (58). COMT is a constitutively active enzyme that degrades catechol compounds, such as many of the neurotransmitters, by transferring a methyl group (58). EGCG has been reported to directly inhibit COMT (59). Herein, it is thought that circulatory catecholamine concentrations will be greater, in turn increasing the SNS (60), thus stimulating lipolysis via adrenergic receptors and potentially increasing fat oxidation (4). As a result, the COMT mechanism has been extensively referenced in the literature despite a lack of evidence in humans.

The most cited study to support EGCG inhibitory effects of COMT are reported in an early in vitro study by Borchardt (59). Based on this early work, others (61) have reported that COMT is directly inhibited by certain catechins. Interestingly, no specific tea catechin was identified by Borchardt (59). Therefore, it is difficult to conclude, based on this study alone, whether GTE catechins are capable of inhibiting COMT. More recently, it was suggested that specific tea catechins are substrates and inhibitors of the *O*-methylation of COMT in human, mice, and rat liver (62–65). It has been shown that those catechins that possess a galloyl-type D ring [EGCG and (-)-epicatechin-3-gallate] (Fig. 1) are 100–1000 times more potent at inhibiting COMT in vitro (62). Furthermore, it seems that COMT activity is highly variable within a population, which may explain the large individual responses to GTE. This may also explain the aforementioned ethnic differences in the response to GTE (16), because a higher expression and activity of COMT is apparent in Asian populations (66,67). What is currently unclear is the specific site of inhibition or where the accumulation of catecholamines may occur in vivo.

To date, there is only one study to show an increase in 24-h noradrenalin urinary excretion following shorter term GTE intake at rest in humans (18), with other studies showing no effect (20,21,24). Interestingly, data from our laboratory has recently shown no change in plasma catecholamines at rest or during moderate intensity exercise following 7 d of GTE intake in humans (68). However, the metabolic effects of GTE on catecholamines are difficult to tease out, because both catechins and caffeine were ingested in the aforementioned studies. However, it has been shown that following shorter term GTE intake, greater plasma FA and glycerol concentrations were observed during exercise, suggesting an increase in lipolysis, which was paralleled with a 17% increase in fat oxidation (34). This provides indirect evidence that GTE may have caused an increase in fat oxidation via the inhibition of COMT. However, no measures of plasma catecholamines were reported. Yet it would appear that in vivo, the low circulatory concentrations of catechins are unlikely to inhibit COMT, especially in the conjugated form. In support, the potency of catechins' ability to inhibit COMT is lost once they are glucuronidated (62). Therefore, the inhibitory effects of catechins in vivo may be lost once conjugated (methylated, glucuronidated, and sulfated) which limits the application of the COMT mechanism in vivo.

In conclusion, there is little or no evidence that the COMT mechanism is responsible for changes in fat oxidation in humans despite the well-referenced in vitro evidence. Even if the COMT enzyme was important in the degradation of catecholamines, the link to increasing fat oxidation is an assumption that is often made. In addition, the exact site of action and dose of catechins (free and conjugated) that are required to alter COMT activity in humans still need further investigation.

Caffeine and fat metabolism

Caffeine in vitro has been shown to ubiquitously affect tissues by indirectly controlling levels of intracellular cAMP, calcium, and catecholamine release (69). This is specifically through antagonism of $\alpha 1$ receptors found in various tissues in the human body (70). Caffeine has been proposed to inhibit phosphodiesterase (PDE) activity (69), which is responsible for degrading cAMP, a secondary messenger in the sympathetic pathway. The increase of cAMP is thought to promote lipolysis by activating the phosphorylation of hormone-sensitive lipase (71), which in turn is thought to increase lipolysis and fat oxidation (4). Once again, there is a wealth of in vitro evidence to support the potential mechanisms of caffeine using supraphysiological concentrations (100–6000 μmol/L in vitro compared with 20–40 μmol/L in humans) (72). This clearly limits the application of these results to humans. However, there are limited human investigations to support the in vitro-based mechanisms of caffeine (73), with no evidence supporting an increase in fat oxidation despite increases in circulating catecholamines (74).

Thus, based on the numerous mechanisms of caffeine, there is very little evidence to support the efficacy of caffeine increasing fat oxidation specifically through PDE or the SNS. For a more detailed review on the metabolic effects of caffeine alone, please see the review by Graham et al. (73).

Synergistic effects of GTE and caffeine

It is often hypothesized that the intake of both GTE and caffeine may result in synergistic effects by targeting the SNS through COMT and PDE. Dulloo et al. (61) investigated the thermogenic effects of GTE and caffeine in vitro on brown adipose tissue. In isolation, GTE stimulated BAT thermogenesis greater than caffeine. Therefore, the authors argued that the combination of both of these ingredients would augment thermogenesis further. In theory, the argument for synergistic effects of GTE and caffeine is sound. However, there is no direct in vivo evidence to support it. A number of human studies at rest have shown that GTE and caffeine ingestion has no effect on markers of lipolysis [through changes in plasma FAs and glycerol (32,75,76)] or the SNS [represented by no apparent differences in plasma catecholamines (20,21,24)].

However, the metabolic significance of increasing catecholamines at rest and during exercise following shorter term GTE intake (catechins and caffeine) is unclear. Previous evidence has shown that increasing circulating adrenaline concentrations, through infusions, has not led to an increase in fat oxidation despite an increase in lipolysis (77). In support of this, recent data from our laboratory have shown that following 7 d of GTE intake (1200 mg/d catechins and 240 mg/d caffeine), FAs and glycerol were significantly increased during moderate intensity exercise compared with placebo. However, the observed increase in FAs did not result in a change in fat oxidation (78). As already mentioned, these changes were independent of any change in catecholamines at rest or during exercise following GTE intake (68). In addition, increases in fat oxidation have been shown following an intralipid-heparin infusion (51) (plasma FA $\sim$1.0 nmol/L). Therefore, the lack of consistent effects of GTE on increasing fat oxidation may be due to the small increase in FAs [$\sim$0.2 nmol/L (34)]. For these reasons, the effect of GTE and caffeine increasing catecholamine concentrations through the COMT, PDE, and SNS mechanisms provides little evidence to suggest an increase in fat oxidation.

In summary, the metabolic effect of GTE and caffeine in vivo is unlikely to be explained by alterations in COMT and PDE due to the lack of change in catecholamines and markers of lipolysis. In addition, the increase in FAs and glycerol, indicative of GTE causing an increase in lipolysis, is likely too small to induce changes to fat oxidation. To identify the mechanisms of shorter term GTE, future in vitro research should focus on the specific target tissues as well as physiological doses and compounds (free and conjugated catechins).

Mechanisms behind the effects of longer term green tea intake

The mechanisms behind the effects of longer term GTE may be different than those that explain the shorter term effects of GTE. The reported increase in fat oxidation following longer term GTE ingestion may be explained by alterations to fat metabolism-specific gene expression, which will be discussed below. At present, only animal and in vitro evidence is available to support the potential mechanisms following longer term GTE intake.

Mechanisms behind the effects of longer term green tea intake at rest

A number of animal studies have shown that longer term intake of GTE results in a decrease in adipogenic genes such as PPARγ, Ccaat-enhancer binding protein-α (C/EBP-α), sterol regulatory element binding protein-1c (SREBP-1c), activated protein 2 (aP2), lipoprotein lipase, and FA synthase (79). In addition, others have illustrated that longer term GTE intake increases mRNA expression for lipolytic and β oxidation enzymes in the liver and adipose tissue, such as carnitine palmitoyl transporter I (CPTI), hormone-sensitive lipas, and adipose triglyceride lipase (80,81). However, this is not supported by all (82). Recently, 16 wk of EGCG was found to elevate mRNA expression of fat metabolism enzymes (MCAD, NRF-1, UCP3, and PPARα) in mouse skeletal muscle (83). Alternatively, these alterations to lipolytic and β oxidation enzymes are not always apparent in skeletal muscle (80,81). More recently, Sae-tan et al. (83) was the first to show that 16 wk of 0.32% dietary EGCG was able to alter mRNA expression specific to skeletal muscle fat metabolism enzymes in mice, including MCAD, NRF-1, UCP3, and PPARα. This demonstrates that longer term GTE intake may have direct effects on increasing gene expression specific to fat metabolism enzymes not only in the liver and adipose tissue but also in the skeletal muscle.

It seems that the alterations to fat metabolism genes may occur in a variety of tissues following longer term GTE intake. What is less clear is the time course of GTE intake required to induce these metabolic alterations at a tissue level. Recently, Friedrich et al. (84) observed in mice that EGCG (1.0%) consumed for 4 d resulted in lower liver TG and glycogen concentrations in the postprandial state. These metabolic changes were also accompanied by a downregulation of lipogenic gene mRNA expression for acetyl CoA carboxylase (ACC), fatty acid synthase, and stearoyl-CoA in the liver. In a second experiment, the authors showed that 7 d of EGCG (0.25–0.5%) resulted in increased lipid oxidation. However, the authors did not assess changes in liver, skeletal muscle, or adipose tissue gene expression following GTE intake. Taken together, these results suggest that GTE ingestion, even as short as 4–7 d, may increase lipid oxidation due to decreased lipogenic gene expression.

The precise molecular signaling mechanism by which longer term GTE intake activates fat metabolism gene expression is currently unclear. It is understood these adaptations to fat metabolism may be mediated by PPARγ coactivator 1-α (PGC1α) (12), which coactivates PPARs, both of which are responsible for regulating fat metabolism adaptations (12). However, Murase et al. (85) concluded that increases in fat oxidation following longer term GTE intake were not attributable to changes in PGC1α. Further, GTE catechins have been shown in some (86,87) but not all cases (88) to activate PPARs in vitro. Lee et al. (87) showed that GTE increased the activation of PPARα using

a transient transfection assay. It was reported that EGCG and EGC were shown to be most effective. The in vitro evidence is also supported by animal data. GTE supplementation of 4–12 wk has been shown to lead to greater PPARα and PPARγ expression in the liver, adipose tissue, and skeletal muscle (89–91). However, Chen et al. (80) reported no change in liver PPAR expression following 6 mo of EGCG intake in rats.

At present, longer term GTE may induce changes to fat metabolism enzymes that over time would increase the capacity to oxidize fat. However, at this stage, it is too early to conclude whether these adaptations to fat metabolism are due to GTE-induced changes to signaling molecules, such as PGC1α and PPARs. Future human investigations are warranted.

Mechanisms behind the effects of longer term green tea intake and exercise training

As mentioned, exercise training increases fat oxidation in both healthy and obese populations (3). This is due to skeletal muscle adaptations specific to the expression of fat metabolism enzymes and transport proteins following exercise training (4,8,12). These specific adaptations are responsible for improving exercise performance. Few studies have investigated the exact signaling molecules that may explain the adaptations that occur following exercise training with or without longer term GTE intake in human and animal studies. As mentioned above, GTE in vitro and in animal models has been suggested to alter PGC1α and PPAR signaling molecules, which may be responsible for inducing the adaptations to fat metabolism. For these signaling molecules to be activated, it has been suggested that exercise is required (92). It would therefore seem that for GTE to activate the adaptations to fat metabolism enzymes and proteins, exercise may be required.

In support of this, a number of laboratories in Japan have demonstrated that longer term GTE intake in mice, subjected to endurance exercise training, may improve endurance capacity. The performance enhancements were accompanied by increases in fat metabolism-specific enzyme gene expression compared with exercise-only mice (85,88). Murase et al. (85) observed that 12 wk of GTE (0.1–0.5%) increased mRNA expression for sarcolemmal fatty acid transporter and MCAD above that of exercise alone. These adaptations were accompanied by augmented β oxidation as well as exercise performance, assessed by time to exhaustion test. Similar results have been demonstrated by others that an increase in fat oxidation was explained by skeletal muscle adaptations (38,85). In addition these studies, others also showed that the highest GTE concentration caused a significant increase in plasma FA concentrations at the end of exhaustive exercise (39,85,88,93). It could be suggested that the combination of exercise training and GTE intake resulted in greater lipolysis, which in addition to the muscle adaptations explains the increase in β oxidation.

However, what the above studies lack is a direct comparison with a control group consisting of GTE intake only at rest rather than just an exercise-only group. Currently, it is unknown whether longer term GTE is able to induce additive effects to exercise training above and beyond the effects observed from longer term GTE at rest. Furthermore, it is also unknown whether the skeletal muscle adaptations following longer term GTE at rest are different from exercise training only. Previous reviews have discussed the potential use of polyphenolic ingredients as exercise mimetics and drew similar conclusions (94). Future investigation should aim to examine the differences in metabolic and skeletal muscle adaptations following chronic GTE supplementation with or without exercise training.

At present, the underlying mechanisms to explain the improvements in fat oxidation following longer term GTE intake are incompletely understood. Although based on animal evidence only, it seems that GTE, when ingested on a regular basis, may cause alterations to fat metabolism enzyme gene expression in the liver, adipose tissue, and skeletal muscle. It is also important to note that based on allometric scaling, the equivalent GTE doses (3–32 cups/d or ~450–4800 mL/d) given to mice may prove difficult to administer to humans (95).

Conclusion

In conclusion, GTE has been shown in some studies to increase fat oxidation at rest and during exercise. However, these results have not been consistent. Overall, there are more studies that demonstrate positive effects on resting fat metabolism when GTE is ingested, both shorter term and longer term. There is less supporting evidence for the use of GTE during exercise. The interaction between GTE and exercise training is interesting and animal studies are generally supportive of additive or interactive effects of GTE on an exercise training program. However, human intervention trials are warranted.

The inconsistent results may be related to bioavailability as well as the variation in the measurement of fat oxidation. It is well understood that catechins once ingested undergo extensive methylation, glucuronidation, and sulfation in the human intestine. However, the exact role of the catechin metabolites and catabolites in enhancing fat oxidation is unknown. Future in vitro investigations should use only physiologically relevant doses and catechin compounds (conjugated) to specifically identify realistic in vivo effects of GTE. Human studies should aim to investigate the specific effect and mechanisms of the various conjugated catechins in human tissues, including liver, adipose tissue, and skeletal muscle. The day-to-day variation in fat oxidation both at rest and during exercise is similar to the effects often observed and therefore it is not surprising that not all studies have observed positive effects, even if such effects existed. We suggest that a large number of studies have been underpowered and/or factors affecting fat metabolism have been insufficiently controlled.

Finally, the current review focused on the possible mechanisms to explain the effects of GTE on fat oxidation at rest and during exercise. The COMT mechanism is the most

cited to explain the possible changes in fat oxidation. However, this mechanism is purely based on in vitro evidence. The link between the COMT mechanism and the increase of fat oxidation is an assumption that is often made. The mechanism behind the potential effects of chronic GTE supplementation may involve changes in expression of specific fat metabolism genes. However, without supporting evidence from human studies, this mechanism remains rather speculative as well. Clearly, future studies are needed to elucidate the effects of GTE on fat metabolism and its underlying mechanisms.

Acknowledgments

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