

Metabolic effects of spices, teas, and caffeine

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Abstract

Consumption of spiced foods or herbal drinks leads to greater thermogenesis and in some cases to greater satiety. In this regard, capsaicin, black pepper, ginger, mixed spices, green tea, black tea and caffeine are relevant examples. These functional ingredients have the potential to produce significant effects on metabolic targets such as satiety, thermogenesis, and fat oxidation. A significant clinical outcome sometimes may appear straightforwardly but also depends too strongly on full compliance of subjects. Nevertheless, thermogenic ingredients may be considered as functional agents that could help in preventing a positive energy balance and obesity.

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1. Introduction

Certain spices and herbs are used to give flavor to foods and drinks without adding calories. On the contrary, consumption of spiced foods or herbal drinks often leads to greater thermogenesis and in some cases to greater satiety. Therefore, it is suggested that these ingredients can realistically be considered as functional agents that could help in preventing a positive energy balance and obesity. Examples of these spices that will be discussed in this review are capsaicin, black pepper, ginger, and spice mixes; examples of the herbs used in drinks are green tea, black tea and caffeine.

2. General concept of ingredient induced thermogenesis

The Sympathetic Nervous System (SNS) is involved in the regulation of both sides of the energy balance equation and is an important regulator of energy expenditure. Possible SNS in-

volvement in thermogenesis is suggested by the ability of norepinephrine (NE) to control biochemical mechanisms that lead either to an increased use of Adenosine Tri Phosphate (ATP) (for example, through ion pumping and substrate cycling) or to an increased rate of mitochondrial oxidation with poor coupling of ATP synthesis leading to increased heat production [1,2]. Studies demonstrate that, during the infusion of NE or epinephrine, thermogenesis increased significantly [3,4].

Based on catecholamine levels, there is evidence for reduced SNS activity and adrenal medullary secretion in some individuals who are already obese, when compared with lean subjects [5].

SNS activation increases thermogenesis to expend excess energy as heat, which compensates for at least a fraction of the surplus energy intake and therefore helps in preventing body weight gain. In obesity-prone subjects, SNS activity was diminished, which may contribute to the diminished EE leading to weight gain and obesity [6]. Also a negative energy balance is accompanied by a reduction of sympathetic activity at muscular level that reduces REE, thus prolonging survival, and increases lipolysis in response to catecholamines in adipose tissue [7–9]. Moreover, in obese children a decreased responsiveness to

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catecholamines was observed [10]. Thus a decreased responsiveness to sympathetic stimuli may be equally important as decreased SNS activity for the development of obesity [11].

Furthermore, a reciprocal relation between SNS activity and food intake has been described in several different experimental animals, and the same is also true for human beings [12].

Since it is known that an increase in SNS activity achieved by treatment with sympathomimetic compounds possibly reduces food intake and increases EE, there is considerable interest in natural nutrients/drugs with potential thermogenic properties which interfere with the sympatho-adrenal system [13,14].

The stimulatory effect of pungent principles in spices on oxygen consumption is likely due to the involvement of a Transient Receptor Potential Vanilloid receptor 1 (TRPV1) - linked thermogenic mechanism [15]. The regulation of TRPV1 is complex. Multiple mechanisms act together to keep TRPV1 in a closed or inactive state in rest; heat, protons and vanilloids can activate the receptor [16]. However, TRPV1 agonists can have different responses through differences in activation and desensitization kinetics and different subtypes of vanilloid receptors may exist [17]. In addition, the thermogenic effect of pungent principles seems to be the result of influences on mitochondrial functions, including the inhibition of oxidative phosphorylation, the accumulation and retention of calcium ions, and the stimulation of ATPase activity [18].

3. Thermogenic effects of consumption of capsaicin, black pepper, ginger, mixed spices, black tea, green tea, and caffeine

3.1. Capsaicin

Capsium species, or hot peppers, are used worldwide as food and spices. Capsaicin is the major pungent principle in red hot pepper. Capsaicin has been reported to increase thermogenesis by enhancing catecholamine secretion from the adrenal medulla in rats, mainly through activation of the central nervous system [19–22]. Increase in thermogenesis induced by capsaicin is probably based on β -adrenergic stimulation [23]. Both animal and human studies showed that the increase in thermogenesis is abolished after administration of β -adrenergic blockers such as propranolol [20,21]. Furthermore, the presence of a functional capsaicin-like vanilloid receptor in the vasculature of the rat hindlimb that mediates oxygen uptake, and thus thermogenesis, was observed [24]. This vanilloid receptor, i.e. the Transient Receptor Potential Vanilloid receptor 1 (TRPV1), is expressed in sensory neurons, the brain and various non-neuronal tissues, and is also involved in the pain pathway [16,25].

3.2. Black pepper

Black pepper is obtained from unripe berries of the vine *Piper nigrum*, whereas white pepper is extracted from ripe berries [16]. Black pepper is a widely consumed spice as it is used for the seasoning of food, and is increasingly used to stimulate metabolism, the absorption of nutrients, and the

efficacy of drugs [16]. The irritating principle in black pepper is piperine, which is almost purely irritative and does not have substantial sweet, sour, salty or bitter tastes or olfactory properties [26]. Lawless and Stevens [26] investigated the perceived intensities of four tastants representing the four classical taste qualities after oral rinsing with piperine. Results showed significant decreases in taste intensity for all substances, which suggest that oral chemical irritation by piperine inhibits the perception of basic tastes, particularly of bitterness and sourness [27].

Piperine, like other pungent compounds present in 'hot spices' such as capsaicin from red pepper, binds to TRPV1 [16]. This receptor is likely the key mediator of the effects of piperine on metabolism. Regarding nutrient intake and processing, piperine has been shown to enhance the bioavailability of several nutrients and drugs [27–30], to have an antisecretory effect on the mice intestine [31], and to inhibit gastric emptying and gastro-intestinal transit in rats and mice [29].

Furthermore, piperine influences energy expenditure or thermogenesis through different mechanisms. Piperine infusion in anesthetized rats resulted in an increase in catecholamine, especially epinephrine secretion from the adrenal medulla. Pretreatment with cholinergic blockers reduced the piperine-induced epinephrine secretion, indicating that piperine activates the adrenal sympathetic nerves and thus stimulates thermogenesis through the sympathetic nervous system [32]. This effect may have important implications for human body weight regulation, as sympathetic activity is negatively correlated with body fat [33]. Another mechanism is the effect of piperine on bioenergetic functions of mitochondria, i.e. piperine inhibits oxidative phosphorylation and calcium accumulation (the latter requiring energy from substrate oxidation or the hydrolysis of ATP), but stimulates ATPase activity of freshly isolated rat liver mitochondria [18]. The possibility that piperine may uncouple the mitochondria could not be excluded because the respiratory stimulation which follows uncoupling could be masked by the inhibitory effect of piperine on the respiratory chain [18]. In addition, piperine resulted in an increased oxygen uptake and vasoconstriction in a concentration-dependent manner when infused into the perfused rat hindlimb, which is consistent with the involvement of TRPV1 in these effects. These effects were not directly mediated via adrenoceptors or indirectly via the release of catecholamines [15].

3.3. Ginger

Ginger, the rhizome of the perennial plant *Zingiber officinale* Roscoe, is used as a flavoring agent for food, mostly in a powdered and candied form. In addition, ginger is widely used as a herbal medicine for a number of conditions including those affecting the digestive tract, headaches and motion sickness [34,35]. The characteristic pungent taste of ginger is attributed to the gingerols (6-gingerol, 8-gingerol and zingerone). Other compounds of ginger include volatile oil, aryl alkenes, shogaols, diarylheptanoids and starch [35]. Individual differences in response to repeated zingerone stimuli are marked, leading to sensitization in some subjects and little effects in

others [36]. Analogous to structurally related capsaicin, 6- and 8-gingerols are relatively potent agonists of TRPV1, which may contribute to the medicinal properties of ginger [34]. Zingerone, a product of gingerol degradation, is a only a weak TRPV1 agonist, due to the absence of the side chain [17,36]. Ginger showed an inhibitory effect on excitatory transmission in the isolated rat ileum, which possibly involves activation of TRPV1 by the gingerol constituents. As zingerone alone failed to induce this effect, it is likely due to 6- and 8-gingerols, but these constituents were not tested separately [36]. In addition, the pungent principles of ginger, gingerols and shogaols have thermogenic properties. Perfusion of the rat hindlimb with extracts of fresh and dry ginger resulted in an increased oxygen consumption, partly associated with vasoconstriction, which was particularly caused by 6-gingerol [17,24]. Though zingerone has been shown to increase catecholamine secretion from the adrenal medulla [17], the effects on oxygen consumption were neither directly mediated via adrenergic receptors nor via secondary catecholamine release [37]. In contrast, the thermogenic activity of ginger was not shown in humans. Ginger added to a meal did not increase the postprandial metabolic rate of subjects as compared to the meal alone [38]. Hence, the gustatory sweating effect of ginger in humans is not necessarily associated with an increased metabolic rate [38].

3.4. Mixed spices

In addition to single spices, several mixed spices are widely used for their beneficial effects on general health. Combinations of black pepper, coriander, turmeric, red chili, cumin and ginger or onion, commonly used in Indian households, appeared to have favorable effects on digestion by stimulating digestive enzyme activities, bile flow and bile acid secretion in rats [39]. Though the stimulatory effect on digestive enzymes was less than expected from the individual spice components, the stimulation of bile flow and bile acid secretion seemed to be additive [39]. A comparable spice mix increased protein utilization at different levels of protein intake in rats, possibly through the suppression of microbial activity in the gut [40]. The aqueous extract of the polyherbal preparation OB-200G, containing *Commiphora mukul*, *Garcinia cambogia*, *Gymnema sylvestre*, *Piper longum* and *Z. officinale*, influenced food intake in mice at a dose of 0.5 g/kg. Though food intake per se was not affected, drug-induced hyperphagia was antagonized by OB-200G [41]. The tested drugs were all serotonin modulators, suggesting that serotonergic mechanisms play a role in the inhibiting effect of OB-200G on food intake [41]. However, it remains to be established which of the spices in OB-200G have serotonergic effects.

3.5. Black tea

Black tea originates from the dried leaves of the plant *Camellia sinensis* (Theaceae) [42]. The dried leaves are infused with boiling water and are generally filtered after a few minutes before consumption of the tea. Black tea contains many

different compounds including polyphenols such as theaflavins and the red-brown thearubigins that are products of the oxidation of flavan-3-ols during fermentation and are different from the polyphenols found in green tea, theanine, catechins, and caffeine. The key taste compounds of black Darjeeling tea are several astringent/mouth-drying flavanol-3-glycosides, the bitter-tasting and astringent epigallocatechin-3-gallate, the puckering astringent catechin, and the bitter-tasting caffeine [42]. In diet-induced obese rats, a Keemun black tea extract reduced food intake, body weight and plasma triglyceride levels via oral administration. In addition, the black tea extract inhibited fatty acid synthase, though this effect was reduced when the extract was prepared with boiling water [43].

3.6. Green tea

Like black tea, green tea is made from the leaves of *C. sinensis* [42]. Green tea is the non-oxidized/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 [44]. The catechins in green tea may stimulate thermogenesis and fat oxidation through inhibition of catechol *O*-methyl-transferase, an enzyme that degrades norepinephrine (NE) [45]. Green tea extract appeared to increase sympathetic nervous system (SNS) activity acutely, and increases EE and fat oxidation in humans in the short-term [46]. A green tea extract also contains caffeine, which has been shown to stimulate thermogenesis. The fact that a green tea extract stimulates thermogenesis cannot be completely attributed to its caffeine content because the thermogenic effect of green tea is greater than an equivalent amount of caffeine [46]. Thus green tea may act at different steps of NE modulatory pathways and in this way exert a thermogenic and possibly an anti-obesity effect [44,46,47].

3.7. Caffeine

Caffeine belongs to a class of compounds called methylxanthines. Other methylxanthines include theobromine, paraxanthine and theophylline. Caffeine is present in coffee, tea, cocoa, chocolate and some cola drinks.

The relative importance of the mechanisms by which caffeine exerts its various effects is not fully clarified. A possible mechanism by which caffeine may stimulate thermogenesis involves inhibiting the phosphodiesterase-induced degradation of intracellular cyclic AMP (cAMP) and antagonizing adenosine receptors that have a negative effect on increased NE release. Thus, the net result of caffeine is an increased concentration of cAMP, and, in this way, the amount of NE available for stimulation of the adrenoceptor is increased and sustained [46,47]. However, other research did not observe a smaller thermogenic effect after treatment with β -blockers [48]. This suggests that the metabolic response to caffeine may result from an effect on adipocyte phosphodiesterase and lipolysis, independently of catecholamines [49,50]. Furthermore, it has

been reported that the thermogenic impact of methylxanthines may be due to stimulation of substrate cycles. Substrate cycles, including the Cori cycle and the FFA-triglyceride cycle, and increased intracellular cAMP concentrations and vascular smooth muscle tone may contribute to explain the thermogenic action of caffeine [51–53].

4. Clinical applications of capsaicin, green tea and caffeine for body weight regulation

4.1. Capsaicin

Clinical research on capsaicin showed for instance that consumption of a breakfast with capsaicin caused an increase in diet-induced energy expenditure (23%) immediately after the meal ingestion in Japanese males [19]. This increase was caused by β -adrenergic stimulation since β -adrenergic blockade abolished this increase [16,19]. In 13 Japanese female subjects addition of red pepper to the experimental meals increased post-prandial energy expenditure and lipid oxidation as well [54]. Red pepper ingested in a standardized meal test was found to reduce hunger level and prospective food consumption before a subsequent ad libitum meal. When offering an isocaloric appetizer, containing a sauce with or without red pepper, a significant decrease in energy intake was observed after the red pepper sauce [55]. In addition, there was a significant negative association between energy intake and the change in low frequency/high frequency heart interval ratio. This association is concordant with data obtained in animals indicating that capsaicin can increase the sympatho-adrenal system [55].

With respect to capsaicin-induced satiety, the relative oral and gastro-intestinal contribution and effects on food intake or macronutrient selection were assessed [56]. Thirty minutes before each meal 0.9 g red pepper (0.25% capsaicin; 80 000 Scoville Thermal Units) or placebo was offered in either tomato juice or in 2 capsules, swallowed with tomato juice. Average daily energy intake over 2 days was reduced after capsaicin capsules by 10%, and after capsaicin in tomato juice by 16%, while satiety was still elevated. Thus in the short-term both oral and gastro-intestinal exposure to capsaicin increased satiety and reduced energy and fat intake. However, the stronger reduction with oral exposure indicates that also the sensory effect of capsaicin plays a role [56].

Furthermore, in 8 Caucasian male subjects, using a respiratory chamber design, red pepper and caffeine consumption was observed to significantly reduce the cumulative ad libitum energy intake and increase energy expenditure [57].

Investigation of possible improved weight maintenance after 6.6% weight loss in 91 moderately overweight subjects treated with capsaicin revealed a relatively more sustained fat oxidation, in contrast to animal studies [58]. However, this did not imply better weight maintenance, probably due to lack of full compliance by subjects. Subjects reported to have ingested only half the prescribed dosage. Therefore, there was some effect, yet this was not strong enough to provide weight maintenance after weight loss. The long-term use of capsaicin may be limited by its strong pungency. A possible solution for

this may be using CH-19 Sweet. CH-19 Sweet is the fruit of a non-pungent cultivar of pepper. In a human study, CH-19 Sweet increased oxygen consumption and body temperature. These effects may be caused by capsiate, which has a structure similar to capsaicin but no pungency [59].

4.2. 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. Relative to the placebo and to the caffeine alone, treatment with the green tea extract resulted in a significant increase in 24 h energy expenditure (4%=328 kJ) and fat oxidation, suggesting that green tea has thermogenic properties beyond that explained by its caffeine content per se [45]. This observation was confirmed by determining 24-h energy expenditure using respiratory chambers and giving the subject different dosages of green tea [60]. No significant difference was seen between the different doses of EGCG [60]. Comparing both studies, the increase in 24 h EE was doubled in the latter, probably due to the difference in the amount of caffeine (200 vs. 50 mg three times daily) since the amount of EGCG was the same (90 mg three times daily) [60]. When investigating the effect of a green tea extract (375 mg catechins from which 270 mg EGCG per day) on body weight with 70 overweight 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 [61]. In accordance with this observation, Japanese studies showed that the long-term (12 weeks) administration of tea catechins in a dose of 400–600 mg/day reduced body fat and body fat parameters [62–64]. Furthermore, a recent Japanese study observed that the daily consumption of 340 ml tea containing 690 mg catechins for 12 weeks reduced body weight compared to the placebo group, who had a daily consumption of 340 ml tea with 22 mg catechins [65].

In the Netherlands, 104 overweight/moderately obese subjects were followed after a very-low-energy diet (2.1 MJ/d) of 4 weeks, during a weight maintenance period of 13 weeks in which subjects received placebo or green tea (caffeine/catechins: 104/573 mg per day) [66]. 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 [66]. 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 [67]. Thus the effect of green tea may partly depend on habitual caffeine intake. In 46 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 independent of habitual caffeine intake. On the other hand, the decrease in resting energy expenditure was significant in the placebo group [68]. However, this did not imply a significant difference in body weight loss between the green tea and placebo group [68]. Moderate use of caffeine is likely to make the green tea supplement ineffective [57,67].

4.3. Caffeine

While consuming the same breakfast, normal-weight subjects presented a greater thermic effect when it was accompanied with a caffeinated coffee in comparison to a decaffeinated coffee [69]. Moreover, energy expenditure was increased by 16% over a 2-h period with caffeinated compared to decaffeinated coffee [70]. 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 [71]. A linear, dose-dependent stimulation of thermogenesis 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 [51]. 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 ($4.9 \pm 2.0\%$) than in the lean subjects ($7.6 \pm 1.3\%$). The thermogenic effect of caffeine was prolonged even over night, which may suggest a possible long-term effect of caffeine [48]. However, greater weight loss was not achieved when consuming caffeine in comparison to a placebo in obese subjects in the long-term [72,73]. The observation that an habitually high (>300 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 [67].

Increased SNS activity has been shown to lead to a decrease in energy intake [11,12]. In men (but not in women) caffeine consumption (300 mg) appeared to reduce energy intake (by 22%) [72]. Moreover, a positive relationship between satiety and daily caffeine intake, in men and women, was shown [67]. Thus caffeine may influence both energy expenditure and energy intake.

5. Side effects

The study of anti-obesity drugs generally reveals undesirable side effects, which are partly explained by the fact that such supplements are influencing numerous targets, which can integrate a signal at a cellular level. Even if ingredients used in the supplementation of food to make it more functional are generally more natural than drugs, they nevertheless promote some effects, which are also not typical of an optimal clinical outcome. For instance, the impact of caffeine–catechin mixtures on energy metabolism was examined, with the intent to increase energy expenditure

with a more natural agent compared to pharmacologically designed compounds [60]. As expected, the caffeine–catechin mixtures induce increases in daily energy expenditure varying between about 600 to 800 kJ/day depending on the dosage. These results were also accompanied by cardio-stimulating effects comparable to those induced by sibutramine. Indeed, 24-h systolic and diastolic blood pressures were increased on average by 6 and 4 mmHg, respectively [60]. This clearly shows that even a natural ingredient is not exempt from concomitant stimulating or inhibitory effects, which are not fitting with an ideal clinical success. This also raises the relevance to combine functional ingredients with other treatment modalities such as physical activity. Such a combination was successfully used when testing the effects of sibutramine and diet on body weight loss in a first treatment phase with the addition of physical activity in a second treatment phase. The results of this intervention showed that the inclusion of exercise in the treatment accentuated weight loss compared to other studies completely abolished the cardio-stimulatory impact of the drug [74]. It is thus evident that the combination of functional ingredients such as caffeine and catechins would also take advantage of the ability of exercise to stimulate metabolism while promoting bradycardia and a decrease in blood pressure during non-exercise time [75,76].

6. Conclusion

In conclusion, the studies presented in this article provide good examples of the complexity of studying functional ingredients, which have the potential to produce significant effects on metabolic targets such as satiety, thermogenesis, and fat oxidation, when they are studied in a standardized laboratory context. Yet, a significant clinical outcome does not always appear, as it depends strongly on full compliance, which may be too difficult to achieve. Nevertheless thermogenic ingredients may be considered as functional agents that could help in preventing a positive energy balance and obesity.

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