Obesity and thermogenesis related to the consumption of caffeine, ephedrine, capsaicin, and green tea.


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The global prevalence of obesity has increased considerably in the last decade. Tools for obesity management, including caffeine, ephedrine, capsaicin, and green tea have been proposed as strategies for weight loss and weight maintenance, since they may increase energy expenditure and have been proposed to counteract the decrease in metabolic rate that is present during weight loss. A combination of caffeine and ephedrine has shown to be effective in long-term weight management, likely due to different mechanisms that may operate synergistically, e.g., respectively inhibiting the phosphodiesterase-induced degradation of cAMP and enhancing the sympathetic release of catecholamines. However, adverse effects of ephedrine prevent the feasibility of this approach. Capsaicin has been shown to be effective, yet when it is used clinically it requires a strong compliance to a certain dosage, that has not been shown to be feasible yet. Also positive effects on body-weight management have been shown using green tea mixtures. Green tea, by containing both tea catechins and caffeine, may act through inhibition of catechol O-methyl-transferase, and inhibition of phosphodiesterase. Here, the mechanisms may also operate synergistically. In addition, tea catechins have antiangiogenic properties that may prevent development of overweight and obesity. Furthermore, the sympathetic nervous system is involved in the regulation of lipolysis, and the sympathetic innervation of white adipose tissue may play an important role in the regulation of total body fat in general.

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consumption has been shown as well (90, 117). Thus caffeine can influence both EE and energy intake. Although a nonhuman animal model showed that caffeine decreased body fat deposition (23), long-term intervention studies in humans showed no effect of caffeine consumption on body weight (5, 85, 128). A possible explanation for the lack of a long-term effect of caffeine is the development of insensitivity to its effects.

**Ephedrine.** *Ephedra sinica* is a shrub native to China and Mongolia. It contains sympathomimetic compounds referred to as ephedra alkaloids (9). These alkaloids have been used for over 3000 years in Chinese medicine. The thermogenic effect of ephedrine is generally considered to be mediated through its ability to increase the sympathetic nervous system output. Ephedrine stimulates thermogenesis by 

- Increasing oxygen consumption and body heat production
- Increasing the production of VEGF, basic fibroblast growth factor, and interleukin-8 (IL-8)
- Activating transcription factors, such as NF-κB and E26 transformation-specific-1 and activating protein-1
- Blunting the production of metalloproteinases necessary for endothelial cell migration and invasion
- Inhibiting the production of vascular endothelial growth factor (VEGF), basic fibroblast growth factor, and interleukin-8

Ephedrine mediates its thermogenic effects, primarily by enhancing sympathetic neuronal release of norepinephrine (NE) and epinephrine (31, 39). However, in vitro research showed that epinephrine stimulates brown adipocyte respiration directly via beta-adrenoceptors (22). The rapid development of tolerance to the pressor effects, but not to its thermogenic effects, suggests that epinephrine influences the cardiovascular system via activation of alpha-adrenoceptors and not entirely through its effects on thermogenesis. The suggestion, therefore, arises that thermogenesis is mediated not only by classical adrenoceptors (38).

In a nonhuman animal study, treatment with ephedrine caused an increase in EE of about 10%, which resulted in body weight loss and body fat loss (36). Intervention studies in humans showed similar effects (87, 88, 105). Thus ephedrine stimulates EE, and the effect is maintained for up to 6 months after administration (36). The long-term use of ephedrine, however, does not necessarily lead to an increase in weight loss. Authors of the studies with favorable effects also reported studies without these effects (5, 86). The disparate findings may be due to the independent thermogenic actions of ephedrine, which enhance sympathetic neuronal release of NE, to the stimulating effects of the beta-adrenoceptors, or adaptation to epinephrine after some months, unless ephedrine is combined with caffeine (see below).

**Ephedrine and Caffeine.** The thermogenic effect of ephedrine can be markedly potentiated by methylxanthines, such as caffeine. Indeed, nonhuman animal studies showed that the effect after an ephedrine/caffeine mixture was larger than that with ephedrine or caffeine alone (35, 36, 92, 121).

The interaction between ephedrine and caffeine in the effect on EE and weight loss has been confirmed in human studies (5, 7, 14, 59, 72, 113, 114) (see Astrup (4) for a review). In a long-term study (6 mo) of 167 obese subjects, the ephedrine/caffeine mixture group lost significantly more weight than the placebo group (11). Thus, with respect to the longer-term use of caffeine or ephedrine, it is theoretically recommended to combine these agents, based upon several longer-term experiments with a positive outcome and likely due to synergistic mechanisms. However, because of adverse effects (see below), the Food and Drug Administration (FDA) has banned the sale of ephedra-containing dietary supplements.

**Capsaicin.** Capsaicin is the major pungent principle in red hot peppers. In rats, capsaicin has been reported to increase thermogenesis by enhancing catecholamine secretion from the adrenal medulla (65, 127). It has been suggested that specific capsaicin-sensitive neurons are involved in this process (126). In addition, a warming action via adrenergic catecholamine secretion is induced (64). Osaka et al. (84) reported that the critical locus that mediates the capsaicin-induced thermogenesis in the brain stem is in the premotor area of sympathoadrenal preganglionic neurons, that is, the rostral ventrolateral medulla.

Yoshieka et al. (136) observed in humans a larger increase in EE immediately after a meal containing red pepper vs. control. In addition, both nonhuman animal and human studies showed that the increase in thermogenesis is abolished after administration of beta-adrenergic blockers such as propranolol (65), which implies that capsaicin-induced thermogenesis is likely based upon beta-adrenergic stimulation.

The nonhuman animal studies also showed that injection or oral treatment with capsaicin stimulates the sympathetic nervous system activity (14, 126, 137, 134). Thus administration of capsaicin favors an increase in lipid mobilization and a decrease in adipose tissue mass (65, 66).

In studies with humans, red pepper induced a reduction of ad libitum food intake and an increased postprandial EE and lipid oxidation (56, 129, 135-138). Participants in a 2-wk study, in which capsaicin was administered in combination with green tea and chicken essence, showed a reduction in body fat (119). In a long-term study, a relatively more sustained fat oxidation in the capsaicin group was observed compared with the placebo group, consistent with nonhuman animal studies (32). The thermogenic effect of red pepper was assumed to be due to lack of full compliance, that is, ingestion of half the prescribed dosage (23). Thus the longer-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 nonpungent cultivar of pepper. In a human study, CH-19 Sweet increased oxygen consumption and body temperature. These effects are thought to be caused by capsiate, which has a structure similar to capsaicin but no pungency (81, 82).

**Green Tea.** Green tea contains high levels of several polyphenolic compounds, such as epicatechin, epicatechin galate, epigallocatechin, and the most abundant and probably the most pharmacologically active, epigallocatechin galate (EGCG) (62). The catechines in green tea may stimulate thermogenesis and fat oxidation through inhibition of catechol O-methyl-transferase (COMT), an enzyme that degrades NE (15). In humans, Duloto et al. (32) showed that a green tea extract results in an increase in EE and fat oxidation in the short-term (32). Green tea extract also contains caffeine. As described above, caffeine 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 (32). Indeed, studies in humans showed that green tea has thermogenic properties beyond that explained by its caffeine content per se (11, 32). Thus green tea, by containing both caffeine and catechines, may have different stimulatory effects in human subjects than other stimulants, that is, via phosphodiesterease, and via COMT, and in this way exert a thermogenic and possibly an antiobesity effect (32, 40, 62).

Studies in rats and mice showed an EGCG-induced reduction in food intake and/or an increase in EE (24, 62, 140). Studies conducted over 3 mo or more showed that the consumption of tea catechines induces a notable reduction of body weight and body fat mass (22, 53, 78, 79, 120) and increases EE (52).

Green tea has also successfully been used as an agent to limit weight regain after weight loss (67, 128). Here, the suggested mechanism is that green tea ingestion during a low-energy diet offsets the expected reduction in EE. Indeed, resting EE as a function of fat-free mass and fat mass did not decrease significantly over time when green tea was ingested together with a low-energy-diet (27).

A different approach to treatment of overweight and prevention of obesity is represented by the antiangiogenic effects of EGCG. This approach is based on the observation of angiogenesis being an important functional role in prevention of obesity (125). The importance of this role is indicated by the phenomenon that angiogenic factors are elevated in overweight and obese individuals (107). Even an angiogenin inhibitor, TNP-470, has been shown to prevent diet-induced and genetic obesity in mice (18). Findings suggest that adipose tissue growth is dependent on angiogenesis, which is similar to growth and organogenesis in other tissues. Leptin also appears to play a role in this process, as adipogenesis and angiogenesis are tightly correlated during the fat mass growth phase. In vitro studies have shown that leptin, in activation of the endothelial Ob-R, generates a growth signal involving a tyrosine kinase-dependent intracellular pathway and promotes angiogenic processes. It is speculated that this leptin-mediated stimulation of angiogenesis might represent not only a key event in the settlement of obesity but may also contribute to the modulation of growth under physiological and pathophysiological conditions (16).

From this viewpoint, inhibition of angiogenesis may be a different pathway to prevent further development of overweight or obesity. In vivo, dose dependently enhancing catecholamine, lysine, proline, and green tea extract induce angiogenic apoptosis, and to have an inhibitory effect on critical parameters in angiogenesis (98). Mechanisms of antiangiogenic effects may involve inhibition of endothelial cell proliferation in response to stimulation with angiogenic factors (68). This can be exerted by inhibition of vascular endothelial growth factor (VEGF) receptors and suppression of vascular endothelial cadherin and protein kinase B (Akt) phosphorylation (111). Activation of certain transcription factors, such as NF-(kappa)-B and E26 transformation-specific-1 and activating protein-1 is also blunted (69), and the protein-proteosines release of endostatin (46, 83). Thus, EGF and EGF receptor (EGFR) can also inhibit the production of VEGF, basic fibroblast growth factor, and interleukin-8 (IL-8) (102, 103, 118).

**Adverse Effects of Thermogenic Agents**
Caffeine appears to be a safe thermogenic agent for weight control. In adults, the short-term lethal dose for caffeine is estimated at 5–10 g per day (either intravenously or orally), which is equivalent to 75 cups of coffee, 125 cups of tea, or 200 cola beverages (26). Long-term ingestion of caffeine has been suggested to have some minor adverse effects on human health. Astrup et al. (8) observed only small and insignificant changes in blood pressure and pulse rate after 100 and 200 mg caffeine. In contrast, 400 mg caffeine significantly increased systolic and diastolic blood pressure by an average value of 6.3 mmHg. Furthermore, after 400 mg caffeine, significant adverse effects reported were slight headache, dizziness, palpitations, and tachycardia compared with placebo (8). Robertson et al. (96) administered 250 mg oral caffeine to nine subjects who were not used to coffee. Systolic blood pressure increased 10 mmHg 1 h after caffeine consumption. Heart rate showed a decrease after the first hour followed by an increase above baseline after 2 h (96). However, in a subsequent study that examined the chronic effects of caffeine ingestion (150 mg/day for 7 days), tolerance to these effects was developed after 1–4 days (97). Thus no long-term effects of caffeine on blood pressure, heart rate, or other cardiovascular activity were found in this short-term, double-blind experiment (97). Furthermore, a short-term study did not find heart rate changes in patients with obstructive sleep apnea due to the use of caffeine (98). Caffeine appears to be a safe thermogenic agent for weight control. In adults, the short-term lethal dose for caffeine is estimated at 5–10 g per day (either intravenously or orally), which is equivalent to 75 cups of coffee, 125 cups of tea, or 200 cola beverages (26). Long-term ingestion of caffeine has been suggested to have some minor adverse effects on human health. Astrup et al. (8) observed only small and insignificant changes in blood pressure and pulse rate after 100 and 200 mg caffeine. In contrast, 400 mg caffeine significantly increased systolic and diastolic blood pressure by an average value of 6.3 mmHg. Furthermore, after 400 mg caffeine, significant adverse effects reported were slight headache, dizziness, palpitations, and tachycardia compared with placebo (8). Robertson et al. (96) administered 250 mg oral caffeine to nine subjects who were not used to coffee. Systolic blood pressure increased 10 mmHg 1 h after caffeine consumption. Heart rate showed a decrease after the first hour followed by an increase above baseline after 2 h (96). However, in a subsequent study that examined the chronic effects of caffeine ingestion (150 mg/day for 7 days), tolerance to these effects was developed after 1–4 days (97). Thus no long-term effects of caffeine on blood pressure, heart rate, or other cardiovascular activity were found in this short-term, double-blind experiment (97). Furthermore, a short-term study did not find heart rate changes in patients with obstructive sleep apnea due to the use of caffeine (98). Caffeine appears to be a safe thermogenic agent for weight control. In adults, the short-term lethal dose for caffeine is estimated at 5–10 g per day (either intravenously or orally), which is equivalent to 75 cups of coffee, 125 cups of tea, or 200 cola beverages (26). Long-term ingestion of caffeine has been suggested to have some minor adverse effects on human health. Astrup et al. (8) observed only small and insignificant changes in blood pressure and pulse rate after 100 and 200 mg caffeine. In contrast, 400 mg caffeine significantly increased systolic and diastolic blood pressure by an average value of 6.3 mmHg. Furthermore, after 400 mg caffeine, significant adverse effects reported were slight headache, dizziness, palpitations, and tachycardia compared with placebo (8). Robertson et al. (96) administered 250 mg oral caffeine to nine subjects who were not used to coffee. Systolic blood pressure increased 10 mmHg 1 h after caffeine consumption. Heart rate showed a decrease after the first hour followed by an increase above baseline after 2 h (96). However, in a subsequent study that examined the chronic effects of caffeine ingestion (150 mg/day for 7 days), tolerance to these effects was developed after 1–4 days (97). Thus no long-term effects of caffeine on blood pressure, heart rate, or other cardiovascular activity were found in this short-term, double-blind experiment (97). Furthermore, a short-term study did not find heart rate changes in patients with obstructive sleep apnea due to the use of caffeine (98).
compensates for surplus energy intake. The result is the prevention of body weight gain. This hypothesis is also supported by Vaz et al. (124) and Grassi et al. (48), who indicated in humans that, on the basis of sympathetic nerve recording in skeletal muscle and skin areas and isotope dilution-derived measurements of renal and cardiac NE release to plasma, human obesity is accompanied by activation of the SNS rather than its suppression. In human obesity, the whole body NE spillover rate, which is an indication of overall sympathetic activity, is typically normal (89, 99, 124). Renal NE spillover, indicative of renal sympathetic activity is approximately double in obese compared with lean subjects (49). The renal NE spillover in obesity is reduced (29).

This renal sympathetic activation is primarily pathophysiological in obesity-related hypertension. The higher renal and lower cardiac sympathetic nerve activity in overweight people represents a differentiation of central nervous system sympathetic nerves and reduced cardiac sympathetic nerve firing. One of the candidates for activation of renal sympathetic outflow is hyperleptinemia, given that administration of leptin in animal models increases renal sympathetic activity (80). The renal sympathetic outflow is associated with a reduction in sympathetic activity at the muscular level, which reduces resting energy expenditure and thus prolongs survival. In addition, a negative energy balance was associated with a reduction of sympathetic activity at the muscular level, which reduces NE release and prolongs survival. Thus sympathetically mediated EE is a risk factor for body weight gain (49).

In obese humans, the whole body NE spillover rate, which is an indication of overall sympathetic activity, is typically normal (89, 99). Nevertheless, the combination of these effects in a compensatory mechanism is possible, that is, an initially low sympathetic activity, is typically normal (89, 99). Thus when discussing the role of sympathetic activity in the control of fat and body mass, it must be taken into account that the findings of unaltered total body NE spillover and increased MSNA in obesity do not unequivocally exclude the possibility that a selective reduction in sympathetic discharge to fat depots could contribute to an accumulation of fat mass and weight gain in general (29). Physiological and neuroanatomical evidence strongly suggests that the SNS is involved in the regulation of lipolysis. Barness and Bamshad (9) reviewed the SNS innervation of WAT. They suggest that in addition to the stimulation of lipolysis by catecholamines in vitro (130), implying that lipid mobilization may be primarily controlled via blood-borne catecholamines, SNS innervation of WAT takes place directly (9). They provide extensive evidence that supports the role of the SNS innervation of WAT in lipid mobilization (9). The physiological evidence includes electrophysiological recording, denervation studies, and electrical stimulation of the nerves innervating this tissue. The neuroanatomical evidence supports that the role of the SNS innervation of WAT is highlighted by the use of a viral transneuronal tract tracer to show that sympathetic activity is connected to WAT. In conclusion, the authors (9) conclude that the direct innervation of WAT by the SNS could play a role in the regulation of total body fat in general (9, 29). These are the first steps to clarify the discrepancies between in vivo and in vitro findings concerning human lipolysis, that is, that lipolysis and obesity are related. However, the concomitant observations in obese subjects show an increased basal lipolysis, a reduced antilipolytic response to insulin and to beta-adrenergic stimulation (29).

As indicated above, there may be a two-way interaction between leptin and the SNS, perhaps constituting a regulatory feedback loop, with leptin acting within the hypothalamus to cause activation of central sympathetic outflow and stimulation of adrenomedullary release of epinephrine (45) and conversely with the SNS-inhibiting leptin release (115). It is assumed, from the increases in renal nerve activity, as well as alterations in the control of fat and body mass, that the renin-angiotensin system (RAS) may play an important role in the regulation of total body fat in general. However, adverse effects of ephedrine prevent the feasibility of this approach. Capsaicin has shown to promote angiogenesis. Ephedrine and capsaicin mediate their effects by enhancement of sympathetic release of catecholamines (60), and the SNS innervation of WAT may play an important role in the regulation of total body fat in general.


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