Capsinoids and related food ingredients activating brown fat thermogenesis and reducing body fat in humans

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\textbf{Purpose of review} Capsaicin and its nonpungent analog (capsinoids) are known to be food ingredients that increase energy expenditure and decrease body fat. This article reviews the role of brown adipose tissue (BAT) for the thermogenic effect of these compounds in humans and proposes the possibility of some other antiobesity food ingredients.

\textbf{Recent findings} A single oral ingestion of capsinoids increases energy expenditure in human individuals with metabolically active BAT, but not those without it, indicating that capsinoids activate BAT and thereby increase energy expenditure. This finding gave a rational explanation for discrepant results of the effects of capsinoids in the previous studies. Human BAT may be largely composed of inducible ‘beige’ adipocytes more than typical brown adipocytes because its gene expression patterns are similar to beige cells isolated from murine white fat depots. In fact, preadipocytes isolated from supraclavicular fat deposits – where BAT is often detected – are capable of differentiating into brown-like adipocytes in vitro, providing evidence of inducible brown adipogenesis in adult humans.

\textbf{Summary} As human BAT may be inducible, a prolonged ingestion of capsinoids would recruit active BAT and thereby increase energy expenditure and decrease body fat. In addition to capsinoids, there are numerous food ingredients that are expected to activate BAT and so be useful for the prevention of obesity in daily life.

\textbf{Keywords} brown adipose tissue, capsinoids, energy expenditure, food ingredients, transient receptor potential channels

\textbf{INTRODUCTION} The global increase in obesity and associated metabolic disorders such as diabetes mellitus and dyslipidemia underscores the need for effective treatments. As obesity is a result of an imbalance between energy intake and energy expenditure, it can be treated by reducing the former and/or increasing the latter. For the latter, although increased physical activity is usually recommended, research has also been focusing on specific food components and/or natural substances. For example, caffeine and catechins rich in various types of tea have been reported to increase energy expenditure and fat oxidation and, thereby, may be effective for weight loss[1,2].

Another group of food ingredients is capsaicin, a pungent principle of hot pepper, which is also known as a thermogenic to increase energy expenditure and reduce body fat. However, owing to its strong pungency, not all people can ingest it in large quantities. Capsinoids (capsiate, dihydrocapsiate and nordihydrocapsiate) are capsaicin-like compounds found in a nonpungent type of red pepper, ‘CH-19 Sweet’. Although capsinoids are much less pungent than capsaicin, they are equally as potent in increasing energy expenditure and fat oxidation, as well as in reducing body fat in small rodents. Meta-analyses of human studies also confirmed significant effects of capsinoids on...
energy balance [3,4]. Recent investigations revealed the mechanisms for the thermogenic effects of capsinoids, particularly the critical roles of transient receptor potential channels (TRP) and brown adipose tissue (BAT), a site of nonshivering thermogenesis evoked by β-adrenoceptor activation. Here, we review the thermogenic and fat-reducing effects of capsaicin and capsinoids in humans, with special reference to the TRP-BAT axis, and discuss the possibility of some other food ingredients as antiobesity compounds.

**KEY POINTS**

- Brown adipose tissue (BAT) contributes to cold-induced and diet-induced thermogenesis in humans.
- Capsinoids, nonpungent capsaicin analogs, increase energy expenditure through the activation of a subtype of the transient receptor potential channels (TRP) (TRPV1) and BAT in humans.
- There are numerous food ingredients having an agonistic activity to TRPs that are expected to activate BAT and be useful for the prevention of obesity.

**CAPSAICIN AND CAPSINOIDS IN RED PEPPERS**

Red peppers, members of the **Capsicum** genus, contain pungent compounds called capsaicinoids, whose chemical structure is an acid amide of vanillylamine combined with a fatty acid (Fig. 1). Capsaicin is the major pungent component, which

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**FIGURE 1.** Mechanism of cold-induced and capsinoid-induced activation of brown adipose tissue. Acute stimulation of TRP by either cold or food ingredients elicits sympathetic nerve activation, leading to UCP1-dependent thermogenesis in brown adipose tissue and lipid mobilization in white adipose tissue. Chronic stimulation gives rise not only to the hyperplasia of brown adipose tissue but also the induction of UCP1-positive beige cells in white adipose tissue, which also contributes to increased whole-body energy expenditure and decreased body fat content. There are various kinds of food ingredients having an agonistic activity for TRP: capsaicin, capsiate, and 6-paradol are potential agonists for TRPV1, menthol for TRPM8, and isothiocyanate compounds for TRPA1. βAR, β-adrenoceptor; TG, triglyceride; TRP, transient receptor potential channel; UCP1, uncoupling protein 1.
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is responsible for about 70% of the burn of hot red peppers, followed by dihydrocapsaicin and nordihydrocapsaicin. The pungency of capsaicin is mediated through the TRP vanilloid subtype one (TRPV1) on sensory neurons in the oral cavity. TRPV1 is a nonselective calcium channel located on primary afferent neurons throughout the body – including the alimentary tract – and is activated by various kinds of stimuli such as noxious heat, proton, and vanilloids [5]. When capsaicin binds to TRPV1, it produces respective sensations of warmth and burning pain at low and high concentrations.

Capsinoids are nonpungent capsaicin anlogus that include capsiate, dihydrocapsiite, and nordihydrocapsiite, which are found in a newly bred nonpungent type of red pepper, ‘CH-19 Sweet’ [6,7]. Capsiite, the primary capsainoid in CH-19-Sweet, differs from capsaicin in chemical structure only at the center linkage of an ester bond (Fig. 1). Although capsiate and capsaicin bind to the TRPV1 with comparable affinities, capsiate is much less pungent, totaling less than 0.1%. The differences in the perceived pungency may be related to the site of TRPV1 activation. Capsaicin activates TRPV1 on sensory neurons located in the tongue, whereas capsiate is rapidly hydrolyzed as it crosses the oral mucosa, rendering it an ineffectve sensory stimulus. When ingested into the stomach, both capsiate and capsaicin can reach and activate TRPV1 in the gastric mucosa. Although capsiate as well as capsaicin seem to be absorbed in the stomach and small intestine, capsiate is usually undetectable in the portal circulation, probably because of its instability. Thus, the primary action site of orally ingested capsiate may be the gastric mucosa and the intestinal mucosa, albeit to a lesser extent.

**THERMOGENIC EFFECTS OF CAPSAICIN AND CAPSINOIDS**

The thermogenic effect of capsaicin and capsinoids is well documented in small rodents. The intraperitoneal or intragastric administration of capsaicin within hours produces an increased whole-body energy expenditure, activation of the adrenosympathetic nervous system, and a rise in BAT temperature followed by a core temperature rise [8,9]. Most of these responses are greatly attenuated by β-adrenergic blockade or in mice deficient in TRPV1 [10]. Capsiue administration was also reported to upregulate uncoupling protein 1 (UCP1), a key molecule for BAT thermogenesis [11]. Based on these observations, the mechanism for the thermogenic effect of capsaicin and capsinoids is proposed as in Figure 1, in which TRPV1 and BAT are involved as indispensable components.

Following animal studies, there have been reports on the effects of a single ingestion of red pepper and capsaicin/capsinoids in humans, although the results are rather inconsistent. Yoshioka et al. [12] first demonstrated that a meal containing 10 g of red pepper enhanced energy expenditure in 3 h and that the increased energy expenditure was diminished by propranolol, a β-adrenergic blocker. The thermogenic effect of red pepper was evident after a high fat, more than a high carbohydrate, meal. A single ingestion of meals supplemented with capsinoids or capsaicin was also reported to increase energy expenditure and lipid oxidation [13,14]. It is to be noted that the thermogenic effect of capsaicin/capsinoids so far reported is relatively small, being about 5–20% above the basal levels. This suggests that its thermogenic effect, if any, may be detected only under strictly controlled experimental conditions. In fact, contrary to these reports, Smeets and Westerterp-Plantenga [15] found no differing effect on energy expenditure and respiratory quotient after a lunch containing capsaicin in comparison with a control lunch. Galgani et al. [16] also failed to find significant effects of capsinoid supplementation (1–12 mg) on postprandial thermogenesis and substrate oxidation.

Possible explanations for such inconsistent findings may, for example, lie in the interstudy differences in the dose of capsaicin/capsinoids and the sex, age, and body composition (adiposity) of individuals. Another possibility may be related to differences in sensitivity to capsaicin/capsinoids. There may be considerable variance in the customary intake of capsaicin-containing foods among individual participants and the participant populations. It is possible that repeated exposure to capsaicin and related pungent compounds results in weaker responses, a so-called ‘desensitization’. The genetic difference in TRPV1 may also influence the responses to capsaicin/capsinoids. There is a functional single nucleotide polymorphism, TRPV1-Ile585Val. Cantero-Recasens et al. [17] demonstrated a decreased Ca\(^{2+}\) channel activity of TRPV1-Val compared to TRPV1-Ile in response to two typical TRPV1 stimuli, heat and capsaicin, along with its association with a lower risk of active childhood asthma. Snitker et al. [18] also reported a significant difference in the fat-reducing effect between participant groups with TRPV1-Val and TRPV1-Ile.

**CRITICAL ROLE OF BROWN ADIPOSE TISSUE FOR THE THERMOGENIC EFFECT OF CAPSINOIDS**

One of the more likely explanations for the discrepant results so far reported is the different
BAT activities of the individual, which were not taken into consideration in previous studies. BAT is well established in small rodents as the major site of sympathetically activated thermogenesis during cold exposure and probably after spontaneous hyperphagia, thereby controlling whole-body energy expenditure and adiposity [19,20]. BAT has long been believed to be absent or negligible in adult humans, but recent studies using fluorodeoxyglucose (FDG)-PET, in combination with computed tomography (CT), demonstrated the existence of metabolically active BAT in healthy adult humans [21]. During the last several years, we and other groups have shown that the metabolic activity of BAT assessed by FDG uptake is markedly increased in healthy humans by acute cold exposure [22–25]. BAT activity is positively correlated to a cold-induced increase in energy expenditure [26,27]. Moreover, thermic effects of meals have also been shown to be greater in individuals with higher BAT activities [28]. Thus, BAT is involved, at least in part, in cold-induced and diet-induced thermogenesis in humans, thereby contributing significantly to the regulation of whole-body energy expenditure.

The metabolic activity of BAT differs among individuals, largely depending on age. In our Japanese participants, cold-activated BAT was detected in about 55% of individuals in their 20s, but was less than 10% for those in their 50s and 60s [29]. It is also known that obese individuals show lower BAT activity than lean individuals [22,29–31]. Moreover, there is seasonal variation in BAT activity, being much lower in summer than winter [22,32]. Taking these variables into consideration, the effects of capsinoid ingestion on energy expenditure were examined in 18 young male participants aged 20–32 years from January to March [33]. FDG-PET/CT examination after 2 h cold exposure revealed that 10 participants showed high BAT activity (BAT-positive), whereas the remaining eight participants (BAT-negative) showed no detectable activity (Fig. 2) [33]. The adiposity-related parameters including body fat content and resting energy expenditure under usual warm conditions were almost equal in the BAT-positive and BAT-negative groups. After the oral ingestion of capsinoids (9 mg), energy expenditure increased significantly by 15.2 kJ/h in the BAT-positive group but only slightly by 1.7 kJ/h in the BAT-negative group. Placebo ingestion produced no significant energy expenditure change in either group. These results clearly indicate that capsinoid ingestion increases energy expenditure through the activation of BAT. It is to be noted that the thermogenic effect of capsinoids was not statistically significant when the data of the two groups were combined.
Yoshioka et al. [12] reported an increase in fat oxidation after ingestion of capsaicin-rich red pepper. Increased fat oxidation after capsinoid ingestion was also shown by Josse et al. [14]. However, Smeets and Westerterp-Plantenga [15] reported no effect of capsinoids on fat oxidation. Similarly, we failed to find any significant effect of capsinoids on fat oxidation in either BAT-positive or BAT-negative individuals [33**].

In contrast, the long-term effects on lipid metabolism and energy expenditure are largely consistent across the studies. Lejeune et al. [34], on examining the effect of capsaicin ingestion (135 mg/day) during a 3-month weight maintenance period after a very low energy diet intervention in mildly obese individuals, found an increased energy expenditure and fat oxidation in the capsaicin group compared with the placebo group. Daily ingestion of CH-19 sweet pepper or capsinoids for 2–12 weeks has also been reported to increase energy expenditure and fat oxidation [18,35–38]. Body and/or visceral fat also decrease after prolonged capsaicin and capsinoids ingestion, probably as a result of increased fat oxidation and energy expenditure. It is interesting to compare the effects on energy expenditure and body fat content in these studies. For example, the increase in resting energy expenditure was 227 kJ/day [18,37], which would theoretically lead to a reduction of 180 g body fat in a month, being too small to be detected in usual experimental conditions. Moreover, such small changes in energy expenditure may be within a range to be compensated for and masked by other factors such as energy intake and muscular activities in normal daily life. Accordingly, it would be useful to evaluate the possible effects of capsaicin and capsinoids on energy intake, although the reported results seem rather divergent [3,4].

**ACTIVATION AND RECRUITMENT OF BROWN ADIPOSE TISSUE BY CAPSINOID**

It is likely that capsaicin and capsinoids are capable of increasing whole-body energy expenditure and reducing body fat. The stimulatory effect of capsinoids on energy expenditure is largely attributable to the activation of BAT, suggesting that BAT is the site responsible for the antiobesity effect of capsaicin/capsinoids. This implies that capsinoids are effective in people with BAT but not in those without active BAT. It is to be remembered that BAT activity is inversely related to body and visceral fat contents. Moreover, BAT activity decreases with age, being closely associated with the age-related accumulation of body fat [29,30]. Thus, BAT activity is low or undetectable in obese and aged people, suggesting that capsinoids may not be as effective as expected. However, Inoue et al. [36] reported that a 4-week ingestion of capsinoids enhanced energy expenditure and fat oxidation more in individuals with a BMI higher than 25 aged 30–65 years. Significant reducing effects of a 12-week capsinoid treatment on body weight and abdominal fat were also confirmed in middle aged (41–43 years old) and mildly obese individuals with BMI of about 30 [18].

This apparent paradox can be best explained by assuming that BAT is induced or recruited by chronic treatment with capsinoids. In fact, many animal studies have clearly demonstrated that BAT can be recruited after chronic activation of the sympathetic nervous system, for example, by prolonged cold exposure or β3-adrenoreceptor treatment [19]. Increased UCP1 expression in BAT was also shown in rats treated with capsinoids for 2 weeks [11]. A more interesting finding is that chronic sympathetic activation produces not only the hyperplasia of BAT but also a remarkable induction of UCP1-positive brown-like adipocytes in white fat pads, called 'beige or brite' cells, in mice and rats [39]. Recent data have shown that beige cells belong to a cell lineage different from brown adipocytes, which are derived from a myf-5 muscle-like cellular lineage [40]. Wu et al. [41**] identified some genes expressed selectively in mouse beige cells and found their high levels of expression in human supraclavicular fat deposits identified as BAT by FDG-PET/CT. Lee et al. [42**] reported that preadipocytes isolated from human supraclavicular fat were capable of differentiating into UCP1-positive adipocytes in vitro, regardless of FDG-PET status. Moreover, we found that BAT activity in humans is remarkably increased during winter in individuals who showed undetectable activities in summer [22]. All these data suggest that human BAT identified by FDG-PET/CT is largely composed of beige cells and is inducible in response to appropriate sympathetic stimulation. In fact, when individuals with undetectable or low BAT activity were kept in a cold environment for 2 h every day for 6 weeks, their BAT activity was significantly increased (Yoneshiro et al. unpublished observation). Collectively, it seems plausible that prolonged treatment with capsinoids and some sympathomimetic agents induce and/or recruit functionally active BAT, even in individuals apparently losing BAT, thereby increasing whole-body energy expenditure and reducing body fat. In support of this idea, we [43] found a slight but significant increase in cold-induced thermogenesis – an index of BAT activity – in individuals given capsinoids daily for 6 weeks.
In food ingredients, particularly in spicy foods, there are many vanilloids with structures similar to capsaicin [44]. For example, piperine is responsible for the pungency of black and white pepper, and gingerols, shogaol, and 6-paradol are found in ginger. All of these are known to act as agonists for TRPV1 and expected to activate BAT thermogenesis and reduce body fat. One report in support of this study shows sympathetic nerve activation and increased BAT thermogenesis after the intragastric administration of 6-paradol in rats [45].

Among the members of the TRP family, TRPM8 and TRPA1 also deserve attention because these are the most likely receptor candidates sensitive to low temperatures. The mean activation temperatures of TRPA1 and TRPM8 are around 20°C, being comparable with those applied in human studies to activate BAT. Accordingly, chemical activation of these receptors would mimic the effects of cold exposure. Actually, there are various ingredients in food acting as agonists for these TRPs [44], such as menthol, a cooling and flavor compound in mint. There are two animal studies demonstrating an increased energy expenditure and activation of BAT shortly after cutaneous or oral applications of menthol [46,47]. TRPA1 is activated by allyl-isothiocyanates and benzyl-isothiocyanates – pungent elements in mustard and Wasabi (Japanese horseradish) – which were reported to increase thermogenesis in small rodents [48]. In addition to isothiocyanates, TRPA1 is also activated by capsaize [49].

CONCLUSION

Capsaicin and capsinoids have the potential to activate and recruit BAT via activity on the specific receptor, TRPV1, thereby increasing energy expenditure and decreasing body fat modestly but consistently. There are numerous herbal plants and foods containing compounds with the agonistic activity to TRPV1 and other types of TRP, some of which have been used in traditional medicine. It is, thus, highly possible that some of these increase energy expenditure through the activation of the TRP–BAT axis. Further human studies focusing particularly on this axis would be helpful for exploring novel antiobesity regimens easily applicable to daily life.

Acknowledgements

This study was supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (22590227), and a Special Research Grant from Tenshi College. T. Yoneshiro is a Special Research Fellow supported by the Japanese Society for Promotion of Science.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest
** of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 93).

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This study describes the thermogenic effect of capsinoids only in human individuals with metabolically active BAT, but not those without it, indicating the capsinoids-induced activation of BAT. It also gives a rational explanation for the discrepant results on the capsinoids effects in the previous studies.


In this study, the authors isolated beige cells from murine white fat depots and found their unique gene expression pattern to be distinct from either white or brown adipocytes. Moreover, they showed evidence that human brown fat identified by FDG-PET is composed more of beige adipocytes than classic brown adipocytes.


This study describes preadipocytes isolated from supraclavicular fat as being capable of differentiating into brown (UCP1-positive) adipocytes in vitro, regardless of whether the participants are BAT-positive or BAT-negative in FDG-PET/CT, providing the first evidence of inducible brown adipogenesis in adult humans.


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This study describes preadipocytes isolated from supraclavicular fat in adult humans. Endocrinology 2011; 152:3597–3592.


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This article describes how menthol enhances UCP1-dependent thermogenesis and locomotor activity, preventing high fat diet-induced obesity and glucose intolerance in a TRPMβ-dependent manner.
