Human brown adipose tissue: regulation and anti-obesity potential

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Abstract. Brown adipose tissue (BAT) is the site of sympathetically activated adaptive thermogenesis during cold exposure and after hyperphagia, thereby controlling whole-body energy expenditure (EE) and body fat. Radionuclide imaging studies have demonstrated that adult humans have metabolically active BAT composed of mainly beige/brite adipocytes, recently identified brown-like adipocytes. The inverse relationship between the BAT activity and body fatness suggests that BAT is, because of its energy dissipating activity, protective against body fat accumulation in humans as it is in small rodents. In fact, either repeated cold exposure or daily ingestion of some food ingredients acting on transient receptor potential channels recruits BAT in parallel with increased EE and decreased body fat. In addition to the sympathetic nervous system, several endocrine factors are also shown to recruit BAT. Thus, BAT is a promising therapeutic target for combating human obesity and related metabolic disorders.

Key words: Beige/brite adipocyte, Body fat, Brown adipose tissue, Energy expenditure, Obesity

IN MAMMALS, there are two types of adipose tissue, white and brown adipose tissues, which are quite different in the physiological functions. White adipose tissue (WAT) is the site of energy storage, while brown adipose tissue (BAT) is specialized for non-shivering thermogenesis to dissipate energy as heat. In small rodents, BAT has long been recognized as the major site of sympathetically activated adaptive thermogenesis during cold exposure and probably after spontaneous overfeeding. This specific thermogenic organ has currently gathered increasing attention as a therapeutic target for combating human obesity and related metabolic disorders [1-3]. This is because of several remarkable advancements in BAT research over the last few years. First, being against the conventional view that human BAT is functional only in neonates, recent radionuclide imaging studies have revealed the existence of a considerable amount of BAT in adult humans [4-7]. There are now piles of evidence indicating BAT as a significant regulatory site of whole-body energy expenditure (EE) and body fatness in not only small rodents but also humans. Second, studies in rodent models revealed two types of thermogenic adipocytes arising from distinct developmental lineages: “classical” brown adipocytes” and “beige/brite” adipocytes [8, 9]. Several key transcriptional regulators and signaling molecules in the developmental pathways of brown and beige/brite adipocytes have been identified [10]. Third, while the sympathetic nervous system is a central regulator of BAT function, several endocrine/paracrine molecules were also identified as significant activators/recruiters of BAT [11]. Lastly, some studies investigating the effects of BAT transplantation suggest possible roles of BAT in the regulation of glucose and lipid metabolism through some body fat-independent mechanisms [12, 13]. Based on these findings, this review summarizes the regulatory mechanism of BAT thermogenesis and its roles in energy homeostasis and body fatness, particularly focusing on its therapeutic potential in human obesity.
1. Sympathetic activation of BAT thermogenesis and induction of beige adipocytes

BAT thermogenesis is totally dependent on uncoupling protein 1 (UCP1) expressed selectively in mitochondria of brown adipocyte, which has the activity to uncouple oxidative phosphorylation from ATP synthesis, thereby dissipating energy as heat [14]. BAT thermogenesis is directly regulated by sympathetic nerves distributed abundantly to this tissue, which activate hydrolysis of intracellular triglyceride via the \( \beta \)-adrenoceptor (\( \beta \)AR) signaling cascade (Fig. 1). The released fatty acids activate UCP1 and are oxidized in mitochondria to serve as an energy source of thermogenesis. Thus, the principal substrate for BAT thermogenesis is fatty acids from intracellular triglyceride and also from circulating free fatty acids and lipoproteins. Sympathetic activation also elicits an increase in fat mobilization in WAT, and released fatty acids are used in BAT as well as in muscle tissues. Together with fatty acids, glucose is also actively metabolized by BAT, probably not as a direct substrate for thermogenesis but for recovery of cellular ATP levels by activation of anaerobic glycolysis [15].

Prolonged sympathetic stimulation by either repeated administration of \( \beta3 \)AR agonists or cold exposure results in up-regulation of UCP1 and increased cell proliferation. In addition to BAT hyperplasia, chronic sympathetic activation induces UCP1-expressing adipocytes in subcutaneous and intra-abdominal fat depots usually considered as WAT [16-18]. These brown-like adipocytes, named “beige or brite” adipocytes, arise from precursor cells distinct from Myf5-positive myoblastic cells, which are precursors of “classical” brown

![Diagram of sympathetic activation in BAT thermogenesis and beige adipocyte induction](https://example.com/diagram)

**Fig. 1** Sympathetically activated thermogenesis in brown adipose tissue, lipid mobilization from white adipose tissue, and induction of beige adipocyte. Sympathetic nerve activity in adipose tissues is increased in response to cold exposure and oral ingestion of some food ingredients through the activation of transient receptor potential channels (TRP). Noradrenaline binds to \( \beta \)-adrenergic receptors (\( \beta \)AR) and initiates the signaling cascade for triglyceride (TG) hydrolysis. Released fatty acids (FA) activate UCP1 and are oxidized to serve as an energy source of thermogenesis. Chronic sympathetic activation produces not only brown fat hyperplasia but also an induction of beige/brite adipocytes in white fat, thereby increasing whole-body energy expenditure and decreasing body fat. AC, adenylate cyclase; ATGL, adipose triglyceride lipase; PKA, cAMP-dependent protein kinase; HSL, hormone-sensitive lipase; LP, lipoprotein.
adipocytes. Recent studies have indicated that beige/brite adipocytes have comparable thermogenic activity to classical brown adipocytes and contribute significantly to the regulation of body fat content [19, 20].

Most information about BAT has come from animal studies, and that for humans has been limited. The presence of BAT in adult humans was first suggested in clinical observations in patients having malignant tumors [21, 22]; that is, fluorodeoxyglucose (FDG)-posi- 

On the powerful diagnostic tools for malignant tumor, showed substantial and bilateral FDG uptake into adipose tissue in the shoulder of some patients. These were revisited by the findings that FDG uptake in these regions is markedly increased after acute cold exposure [4-6], and that tissue samples isolated from these regions contain numerous adipocytes expressing UCP1 [4-7]. It has also been shown that the adipose uptake of FDG is increased after administration of a sympathomimetic agent but decreased by treatment with a β-adrenergic blocker (23). It is thus undoubted that adult humans have significant amounts of BAT, of which metabolic activity is controlled by the sympathetic nerve-βAR system.

The BAT signals in adult humans are found mostly in supraclavicular and paravertebral regions, while in small rodents the major BAT depot containing classical brown adipocytes is found in the interscapular region. Being consistent with such an anatomical difference, comprehensive expression analysis of marker genes for “classical” and “beige/brite” adipocytes has shown that BAT of adult humans is mainly composed of “beige/brite” more than “classical” brown adipocytes [24, 25]. In fact, Lee et al. [26] reported that preadipocytes isolated from human neck fat were capable of differentiating into beige adipocytes but not classical brown adipocytes in vitro.

2. Regulatory role of BAT in energy expenditure and body fatness in humans

The prevalence of BAT detected by FDG-PET/CT in adult humans is less than 10% in most retrospective clinical studies, whereas it is more than 30% in dedicated studies for healthy volunteers [27]. Such apparent discrepancy is largely due to the different temperatures at the FDG-PET/CT scanning: in dedicated studies it is performed after acute cold exposure at 16-19°C for 1-2 h, whereas retrospective studies are mostly performed at room temperatures (22-26°C) without cold exposure. Actually, no BAT signals were detected at 27-28°C even in subjects who showed high BAT activities after cold exposure (Fig. 2). Thus, cold exposure is a powerful stimulus for activation of BAT in humans, as it is in small rodents. This implies possible role of BAT in cold-induced non-shivering thermogenesis (CIT). To test this, we [28, 29] measured whole-body EE under a thermoneutral condition (27°C) and after acute cold exposure (19°C, 2 hours) in healthy subjects with wide ranges of body composition and BAT activity. EE was positively correlated with fat-free lean body mass both under the thermoneutral condition and after cold exposure, while EE was positively correlated with BAT activity only after cold exposure. Thus, CIT calculated from the difference between EE under the two conditions was positively correlated with BAT activity, but not with lean body mass. Being consistent with our results, there have been reports that CIT seen under conditions inducing no muscle shivering is higher in a subject group with detectable BAT activities than that without them [30-32]. All these results indicate that BAT plays a significant role in CIT and thereby whole-body EE in adult humans.

Outdoor temperature and season also significantly influence the activity and prevalence of BAT, which are higher at colder temperatures and in winter [4, 33]. Thus, BAT can be best detected by FDG-PET/CT only when exposed to acute cold in winter. The seasonal variations of BAT activity in the same subjects suggest that human BAT is inducible by environmental stimuli, probably reflecting the characteristics of beige/brite adipocytes. In fact, as noted in the next section, repeated cold exposure results in an induction of BAT in subjects who have undetectable BAT before the cold exposure [29, 34].

The prevalence and activity of BAT are substantially influenced by body fatness (Fig. 2). Retrospective studies in thousands of patients have revealed that BAT prevalence is lower in patients with higher body mass index (BMI) [3, 7, 27]. Similarly, dedicated studies in healthy participants have demonstrated that the prevalence and activity of cold-activated BAT decrease with increasing adiposity [4, 5]. The apparent inverse relationship between BAT and adiposity, however, is to be carefully evaluated, because the prevalence and activity of BAT are also influenced by aging. Our study in healthy participants aged 20-73 years revealed that the prevalence of cold-activated BAT was more than 50%
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seems the most physiological and powerful stimulus for not only activation of "classical" brown adipocytes but also induction of "beige/brite" adipocytes. We [29] currently examined the effects of chronic cold stimulation on BAT activity in healthy volunteers with low or undetectable activities of BAT. After repeated cold exposure at 17˚C for 2 h every day for 6 weeks, their BAT activity significantly increased. Lans et al. [34] also reported increased BAT activity and volume in human adults placed in cold suits for a few hours a day for 10 days. These findings, being comparable with those in small rodents, indicate that human BAT can be recruited by chronic cold exposure. It was also found that the daily cold exposure increased CIT, of which increment was positively related to those in BAT activity. These results, together with a highly positive correlation between CIT and BAT activity, indicate that recruited BAT actually contributes to CIT. More important is that body fat mass significantly decreased after the chronic cold exposure, whereas body weight and fat-free mass did not change. The change in body fat mass was inversely correlated with those in BAT activity and CIT, suggesting a significant contribution of recruited BAT to body fat reduction.

Although daily cold exposure can recruit human BAT, it would seem difficult to apply this in daily life. It is now well established that cold stimulus is received by transient receptor potential channels (TRP) [40].

**Fig. 2** Schematic radionuclide imaging of human brown adipose tissue. Fluorodeoxyglucose (FDG) uptake into adipose tissue at the supraclavicular and paraspinal regions is detected by positron emission tomography. FDG uptake into BAT, which reflects its thermogenic activity, is influenced by various external and internal factors.

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in young subjects of the twenties, decreased with age, and in less than 10% of the fifties and sixties [35, 36]. A strong impact of age on BAT prevalence has also been reported in clinical studies [7, 37-39]. It is well known that the aging process produces notable changes in body composition: that is, in general, percent body fat increases while lean mass and bone mineral density decreases with aging. Thus, it seems possible that age-related accumulation of body fat is attributable to decreased BAT activity. In fact, adiposity-related parameters such as BMI and visceral fat content increase with age in participants without detectable BAT, while they remain unchanged from the twenties to forties in those with it [35].

3. Activation and recruitment of BAT as anti-obesity regimens

The inverse relationship between the BAT activity and adiposity suggest that BAT is, because of its energy dissipating activity, protective against body fat accumulation in humans as it is in small rodents. This encourages us to search how to activate or recruit BAT, particularly in people with lower or undetectable BAT activities because they are more obese and to be treated. As noted above, human BAT is largely composed of “beige/brite” adipocytes and is inducible in response to appropriate sympathetic stimulation. Cold seems the most physiological and powerful stimulus for not only activation of “classical” brown adipocytes but also induction of “beige/brite” adipocytes. We [29] currently examined the effects of chronic cold stimulation on BAT activity in healthy volunteers with low or undetectable activities of BAT. After repeated cold exposure at 17˚C for 2 h every day for 6 weeks, their BAT activity significantly increased. Lans et al. [34] also reported increased BAT activity and volume in human adults placed in cold suits for a few hours a day for 10 days. These findings, being comparable with those in small rodents, indicate that human BAT can be recruited by chronic cold exposure. It was also found that the daily cold exposure increased CIT, of which increment was positively related to those in BAT activity. These results, together with a highly positive correlation between CIT and BAT activity, indicate that recruited BAT actually contributes to CIT. More important is that body fat mass significantly decreased after the chronic cold exposure, whereas body weight and fat-free mass did not change. The change in body fat mass was inversely correlated with those in BAT activity and CIT, suggesting a significant contribution of recruited BAT to body fat reduction.

Although daily cold exposure can recruit human BAT, it would seem difficult to apply this in daily life. It is now well established that cold stimulus is received by transient receptor potential channels (TRP) [40].
TRP is also activated by various compounds, some of which are found in foods [41]. Among the TRP agonists so far reported, the most extensively studied is capsaicin, a pungent principle of chili pepper, which is a potent agonist for TRPV1. There have been many animal studies demonstrating that capsaicin and its non-pungent analogs (capsinoids) increase BAT thermogenesis through the activation of TRPV1 and the sympathetic nervous system, and decrease body fat. Recent human studies have also confirmed similar thermogenic and anti-obesity effects of capsinoids [42-44]. We confirmed in humans that a single ingestion of capsinoids activated BAT thermogenesis [45, 46], and that a 6-week daily ingestion increased BAT-dependent CIT and reduced body fat even in individuals with low activities of BAT before the ingestion [29]. Thus, capsaicin/capsinoids as well as other food ingredients activating the TRP-BAT axis may be promising as anti-obesity tools easily applicable in daily life [47].

4. Endocrine and paracrine activators/recruiters of BAT

The effects of cold exposure and TRP stimulation on BAT are primarily mediated through the activation of the sympathetic nerve and β-AR system, which is a central regulator of brown and beige/brite adipocytes. A recent study showed that noradrenaline released from activated macrophages was also involved in the regulation of BAT thermogenesis [48]. In addition to or in combination with this system, some hormones and factors have been identified as activators/recruiters of BAT (Fig. 3). A representative is triiodothyronine (T3), which is well known as a potent transcriptional activator of the UCP1 gene [49]. It is to be noted that T3 in BAT is produced from thyroxine by the action of type II deiodinase (D2), which is activated in response to sympathetic stimulation. D2 in BAT is also shown to be activated by bile acids coming from the liver [50]. Thus, the effects of thyroid hormones are to be evalu-
ated in association with these other interacting factors.

Currently, much attention has been paid on irisin, which is a peptide identified as a peroxisome proliferator-activated receptor γ co-activator-1 α (PGC-1α)-dependent myokine [51]. Irisin induces beige/brite adipocytes in WAT and protects animals from diet-induced obesity. Since exercise was reported to increase tissue expression of irisin, this unique peptide seems to be expected as a promising factor responsible for various beneficial effects of exercise including on body fatness. However, as recent data in humans are rather controversial [52], it is obvious that further studies are needed, particularly to elucidate possible pathophysiological roles of irisin in humans.

There have been reports demonstrating significant roles of heart-derived natriuretic peptides (NP), well-known regulators of fluid and hemodynamic homeostasis, in BAT recruitment [53]. NP enhances whole-body EE, probably due to an up-regulation of UCP1 in BAT and induction of beige/brite adipocytes.

Fibroblast growth factor 21 (FGF21), a liver-derived endocrine factor, has gathered increasing attention because it reduces body fatness and improves glucose tolerance when administrated to rodent models of obesity and type 2 diabetes [54]. FGF21 is potential for inducing the thermogenic program in BAT, and also for driving beige/brite adipocyte recruitment in WAT [55]. In addition to the liver, FGF21 is also produced in BAT after cold exposure and adrenergic stimulation [26, 56]. Thus, BAT is not only a target for but also a secreting site of FGF21, indicating an autocrine action of FGF21 on BAT.

In addition to FGF21, various biologically active peptides are known to be secreted from BAT [57]. For example, vascular endothelial growth factor is produced in response to cold stimulation, and acts as a paracrine factor for angiogenesis in association with BAT hyperplasia. Similarly, BAT-derived nerve growth factor may be important for growth of sympathetic nerve during tissue hyperplasia. Interleukin-6 and insulin-like growth factor 1 were also reported to be produced in BAT. It is thus intriguing to speculate that some of these BAT-derived endocrine factors may have an impact on the metabolic and endocrine activities in other tissues.

**Perspectives**

BAT is now re-visited as a regulatory site of EE and body fatness in adult humans. Moreover, recent studies on the effects of BAT transplantation in mice have indicated possible roles of BAT in the regulation of glucose and lipid metabolism through some body fat-independent mechanisms [12, 13]. A significant independent impact of BAT on blood glucose and hemoglobin A1c was also shown in humans [58, 59]. These findings collectively suggest that BAT may also be involved in the etiology of glucose intolerance, independently of and/or secondly to obesity. Thus, BAT is a promising target for combating not only obesity but also some related metabolic diseases.

**Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

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