Brown Adipose Tissue as a Therapeutic Target for Obesity: From Mice to Humans
Masayuki Saito*
Hokkaido University, Sapporo, Japan

Brown adipose tissue (BAT) is a site of sympathetically activated non-shivering thermogenesis during cold exposure and after spontaneous hyperphagia, thereby involving in the autonomic regulation of energy balance and body fatness. Recent radionuclide studies have demonstrated the existence of metabolically active BAT in adult humans. Human BAT is activated by acute cold exposure, particularly in winter, and contributes to cold-induced increase in whole-body energy expenditure. The metabolic activity of BAT is lower in older and obese individuals. The inverse relationship between the BAT activity and body fatness suggests that BAT, because of its energy dissipating activity, is protective against body fat accumulation. In fact, either repeated cold exposure or daily ingestion of some food ingredients acting on transient receptor potential channels recruited BAT in association with increased energy expenditure and decreased body fatness. Thus, BAT is a promising target for combating obesity and related metabolic disorders in humans.

Key words: Brown adipose tissue, Cold exposure, Energy expenditure, FDG-PET/CT, Obesity, Transient receptor potential channel

Background

Obesity and related metabolic disorders are worldwide epidemics. As obesity is the state of excessive accumulation of body fat because of prolonged positive energy balance, it can be treated by reducing food intake and/or increasing energy expenditure (EE). For the latter, increasing attention has currently been paid on brown adipose tissue (BAT), a specific site for non-shivering thermogenesis to dissipate energy as heat. This is because of several remarkable advancements in BAT research over the last few years. Particularly, 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. There are now piles of evidence suggesting BAT as a significant regulatory site of whole-body EE and body fatness not only in small rodents but also in humans. Moreover, recent prospective studies in humans confirmed that activation and recruitment of BAT actually increases EE and decreases body fatness. Thus, BAT may be a promising target for combating obesity and related metabolic disorders. This review summarizes the regulatory mechanisms of BAT thermogenesis in mice and humans, and discusses its therapeutic potential for combating obesity.

1. Mechanism and physiological roles of BAT thermogenesis

BAT is a unique adipose tissue, of which function is metabolic thermogenesis to produce energy in the form of heat. Significant amounts of BAT are found in small rodents and hibernators, being essential for the survival in cold environment and for arousal from hibernation. BAT has also been proposed to be involved not only in cold-induced non-shivering thermogenesis but also in diet-induced thermogenesis, and to play a role in the regulation of EE, whole-body energy balance, and body fatness. This is supported by various lines of observation, particularly, that mice with genetically ablated BAT show decreased EE and diet-induced obesity, and that activation and recruitment of BAT by various physiological and pharmacological stimuli give rise to consistent reduction of body fatness. Thus, it is undoubted, at least in small rodents, that impaired thermogenesis by BAT is one of the causes of obesity.
BAT thermogenesis is totally dependent on uncoupling protein 1 (UCP1), which is expressed selectively in mitochondria of brown adipocyte, but not in other types of cell including white adipocyte. UCP1 has the activity to uncouple oxidative phosphorylation from ATP synthesis, thereby dissipating energy as heat. UCP1-dependent BAT thermogenesis is directly regulated by sympathetic nerves distributed abundantly to this tissue: that is, noradrenalin released from the sympathetic nerve endings stimulates the β-adrenoceptor (βAR) signaling cascade, leading hydrolysis of intracellular triglyceride by activating hormone-sensitive and adipose triglyceride lipases (Fig. 1). The released fatty acids activate UCP1 and are oxidized in mitochondria to serve as an energy source of thermogenesis. Fatty acids from blood circulation are also used under some physiological conditions. While the principal substrate for BAT thermogenesis is fatty acids, glucose utilization is also enhanced greatly in parallel with UCP1 activation, probably for sufficient supply of oxaloacetate to enable rapid oxidation of fatty acids and acetyl CoA, and also for rapid recovery of cellular ATP levels by activating anaerobic glycolysis.\textsuperscript{19} Thus, UCP1-dependent glucose utilization is a metabolic index of BAT thermogenesis, and has been applied for assessing human BAT as noted in the latter section.

There are two types of UCP1-positive thermogenic adipocyte.\textsuperscript{2,20} The major BAT depot in small rodents is found in the interscapular region. Adipocytes in this depot originate from Myf5-positive myoblastic cells that also give rise to skeletal muscle cells, and are called “classical brown adipocytes”. UCP1-expressing adipocytes also develop in fat depots usually considered as white adipose tissue (WAT) after prolonged cold exposure or repeated administration of sympathomimetics including β3AR agonists.\textsuperscript{21,22} These adipocytes, named “beige or brite adipocytes”, arise from developmentally distinct lineages from classical brown adipocytes; they originate from a Myf5-negative precursor cells. Recent studies have indicated that beige/brite adipocytes have comparable thermogenic activity to classical brown adipocytes and contribute significantly to the regulation of body fatness.\textsuperscript{23,24}

2. Regulation of brown/beige adipocytes

As briefly summarized above, the sympathetic nerve and βAR system is a central regulator of brown and beige/brite adipocytes. This system is activated by various external stimuli, the most typical of which is cold exposure. The principal role of this system for BAT thermogenesis was confirmed by a finding that mice lacking β-AR as well as those lacking UCP1 are unable to maintain body temperature under a cold environment and die in couples of hour.\textsuperscript{13,25} It is also known that prolonged cold exposure or repeated administration of βAR agonists causes hyperplasia of BAT by increased proliferation of classical brown adipocyte and also induction of beige adipocytes in WAT.\textsuperscript{21,22}

In addition to or in combination with this system, some hormones and factors have been identified as activators/recruiters of BAT (Fig. 2).\textsuperscript{26} A representative is triiodothyronine (T3), which is well known as a potent transcriptional activator of the UCP1 gene.\textsuperscript{27} 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.\textsuperscript{28} There have been reports demonstrating significant roles of heart derived natriuretic peptides (NP), well-known regulators of fluid and hemodynamic homeostasis, in BAT recruit-
ment. NP enhances whole-body EE, probably due to an up-regulation of UCP1 in BAT and induction of WAT browning via the cyclic GMP and p38MAP-kinase signaling cascade.29

Currently, much attention has been paid on the mechanism for induction of beige adipocytes. Qiu et al.30 reported that functional beige adipocytes are induced by noradrenalin released from macrophages that are alternatively activated by eosinophils. Critical roles of eosinophils and type 2 cytokine signaling in macrophages were also shown in the action of meteorin-like, a circulating factor induced in muscle after exercise and in adipose tissue upon cold exposure, which stimulates WAT browning and EE.31 The involvement of alternative activation of macrophages in the induction of thermogenic beige fat is a quite contrast with that of classical activation of macrophages, which is closely associated with metabolic and endocrine disorders of WAT. Fibroblast growth factor 21, a liver-derived endocrine factor, is potential for inducing the thermogenic program in BAT and WAT browning, and also for reducing body fatness.32

3. Human BAT detected by FDG–PET/CT

Most information about BAT mentioned above has come from studies using small rodents such as mice, rats, and hamsters. In larger mammals including humans, anatomical and histological studies have reported that BAT is present only in neonates, but disappears rapidly during postnatal periods.33 However, the existence of metabolically active BAT in adult humans has been demonstrated by the studies using fluoro-deoxyglucose (FDG)-positron emission tomography (PET) combined with computed tomography (CT): that is, PET/CT sometimes detects symmetrical FDG uptake in adipose tissue at the shoulder and thoracic spine regions. Such FDG uptake is substantially increased after cold exposure or administration of βAR agonists34, but reduced by pretreatment with β-adrenergic blockers.35 As β-adrenergically stimulated 2-deoxyglucose uptake into BAT is totally dependent on the activation of UCP119, the observations by PET/CT collectively suggest that the FDG uptake in adipose tissue at the specific regions reflects the metabolic activity of BAT. In fact,

![Fig. 2. Factors acting on brown/beige adipocytes.](http://dx.doi.org/10.7570/kjo.2015.24.1.1)

βAR, β-adrenoceptor; FGF21, fibroblast growth factor 21; Metl, meteorin-like; Mϕ, macrophage; NA, noradrenaline; NP, natriuretic peptide; TRP, transient receptor potential; T4, thyroxine; WAT, white adipose tissue.
Histological examinations revealed the presence of UCP1-positive adipocytes in these regions. Expression analysis of some marker genes has shown that BAT in the shoulder region of adult humans is largely composed of beige adipocytes more than classical brown adipocytes. The activity and prevalence of BAT detected by FDG-PET/CT in adults are influenced by various exogenous and endogenous factors (Fig. 3). The prevalence is less than 10% in most retrospective clinical studies, whereas it is 30-100% in dedicated studies for healthy volunteers. 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 hours, whereas retrospective studies are mostly performed at room temperatures (22-26°C) without cold exposure. Acute cold exposure increases FDG uptake into BAT, giving a high prevalence of BAT detection. Indeed, no BAT signals were detected at 27-28°C even in subjects who showed high BAT activities after cold exposure. Moreover, the prevalence and activity of BAT are also influenced by outdoor temperature and show seasonal variations, being higher in winter than in summer even in the same subjects. This suggests that human BAT is a reversibly convertible tissue: in other words, it is inducible by environmental stimuli such as daily cold exposure. In fact, repeated cold exposure results in an induction of BAT in subjects who have undetectable BAT before the cold exposure.

The prevalence and activity of BAT are substantially modulated with age. Our study for healthy participants aged 20-73 years demonstrated that the prevalence of cold-activated BAT was more than 50% in young subjects of the twenties, decreased with age, and in less than 10% of the fifties and sixties. A strong impact of age on BAT prevalence has also been reported in clinical studies. We found that polymorphism of some genes including UCP1 and β3AR accelerates the age-related decrease in BAT activity. Recently, Bakker et al. reported larger BAT volume in healthy lean Caucasians than age-matched south Asians. These findings indicate a significant impact of genetic factors on human BAT.

4. Activation and recruitment of BAT as an anti-obesity regimen in humans

The presence of cold-activated BAT suggests a contribution of BAT to cold-induced thermogenesis. In fact, it has been confirmed that whole-body EE after cold exposure is greater in subjects with higher BAT activities, showing a positive correlation between the BAT activity and cold-induced thermogenesis. Moreover, retrospective readings of FDG-PET/CT in thousands of patients and dedicated studies in healthy participants have demonstrated that the activity and prevalence of BAT are inversely related to body fatness assessed by mass index (BMI), body fat content, and visceral fat. Collectively, it is conceivable that BAT, because of its energy dissipating activity, is protective against body fat accumulation in humans as it is in small rodents.

This has encouraged the search how to activate or recruit BAT, which is particularly intriguing because people with lower or undetectable BAT activities are more obese and to be treated. As noted previously, cold seems the most physiological and powerful stimulus for BAT activation. In addition to the acute stimulatory effects of cold on BAT, prolonged cold exposure produces not only BAT hyperplasia but also a remarkable induction of beige adipocytes, both of which contribute to increased EE and reduced body fatness. Recent studies have confirmed that this is also true in humans. For example, when subjects with undetectable or low BAT activity were kept in a cold environment at 17°C for 2 hours every day for 6 weeks, their BAT activity was significantly increased. More importantly, the change in BAT activity was positively and negatively correlated with those in cold-induced thermogenesis and body fat content, respectively (Fig. 4).

Although daily cold exposure can recruit human BAT, it would...
seem difficult to increase exposure to cold in daily life. It is now well established that cold stimulus is received by transient receptor potential channels (TRP). Among the members of the TRP family, TRPM8 and TRPA1 are the most likely receptor candidates sensitive to low temperatures. Accordingly, chemical activation of these receptors would mimic the effects of cold exposure (Fig. 2). There are various food ingredients acting as agonists for these TRPs, a representative of which is menthol, a cooling and flavor compound in mint, acting on TRPM8. In fact, Ma et al. demonstrated in mice that dietary menthol enhances BAT thermogenesis and prevents high fat diet-induced obesity in a TRPM8-dependent manner. 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. Animal studies have demonstrated 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 BAT-dependent thermogenic and anti-obesity effects of capsinoids. Thus, capsaicin/capsinoids as well as other food ingredients activating the TRP-BAT axis may be promising as anti-obesity regimens easily applicable in daily life.

**Conclusion and Perspective**

BAT is now recognized as an important regulatory site of EE and body fatness in not only small rodents but also adult humans. Moreover, recent studies have indicated regulatory roles of BAT for insulin-sensitivity, glucose homeostasis, and lipoprotein metabolism, suggesting that BAT may also be involved in the etiology of diabetes mellitus and dyslipidemias, independently of and/or secondly to obesity. Thus, BAT is a promising target for combating obesity and related metabolic diseases in humans, but there are many issues to be settled. For example, while FDG-PET/CT has widely been used to evaluate BAT in humans, it has serious limitations, including the enormous cost of the devices, radiation exposure, and acute cold exposure, which make repeated FDG-PET/CT difficult and impede both basic and clinical studies. Moreover, it is to be noted that this method provides information for the glucose metabolic activity, rather than that of mass or thermogenic activity of BAT. A less-invasive, simple, and accurate method is needed. Another important issue is to clarify the underlying mechanisms of age-related reduction of BAT, which would be one of the causes for excessive accumulation of body fat in middle-aged individuals. These insights would be a prerequisite for developing feasible and efficient regimens to activate and recruit BAT in obese humans.

**Conflicts of Interest**

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