



Brown adipose tissue and its therapeutic application

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Abstract In addition to white adipose tissue (WAT) that stores energy, human and small mammals also have brown adipose tissue (BAT) that dissipates chemical energy for thermogenesis. BAT contains multilocular lipid droplets and much higher numbers of mitochondria than WAT. The mitochondria in BAT uncouple large amounts of fuel oxidation from ATP for heat generation. Accumulating evidences have demonstrated that increased activity and/or amount of BAT can reverse obesity and improve insulin resistance, which highlights that BAT plays an important role in energy metabolism. In this review, we summarized recent findings that shows advantageous effects of BAT activation in metabolic diseases. In addition, we presented the function and role of brown and beige fat cells and regulatory factors for them. Finally, we discussed the potential application of brown adipocytes-based therapy and pharmacological intervention to increase BAT activity for the treatment of obesity and related diseases including insulin resistance, cardiovascular diseases and type 2 diabetes.

Keywords Brown adipose tissue · Lipid metabolism · Therapeutic application

SPECIAL TOPIC: Lipid Metabolism and Human Metabolic Disorder

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1 Introduction

Obesity is a major risk factor for metabolic syndromes, including insulin resistance, type 2 diabetes mellitus, cardiovascular diseases and some types of cancer [1]. The long-term dysregulation of energy balance leads to the occurrence of obesity. Recent anti-obesity approaches are aimed at reducing energy absorption, however, the outcome is not satisfactory. After active BAT has been ‘re-discovered’ in adult humans [2–6], increasing energy expenditure has brought much attention for the treatment of metabolic syndromes since increasing energy expenditure can be achieved either by muscle with physical activity [7] or brown adipose tissue (BAT) with non-shivering thermogenesis (NST). Compared with white adipose tissue (WAT) which stores energy, BAT dissipates energy as heat. In rodents, BAT can be found in interscapular, cervical, axillary and perirenal regions, however, BAT are mainly found around neck and also in interscapular region of newborns in human [8]. Brown adipocytes consist of multilocular lipid droplets and more mitochondria than WAT. BAT specific protein, uncoupling protein 1 (UCP1) dissipates the proton gradient from oxidative phosphorylation to generate heat [9]. UCP1 positive adipocytes that have thermogenesis capacity are also found in WAT depots after cold exposure, which is called brown in white (brite)/or beige adipocytes [10]. Similar to brown adipocytes, beige adipocytes are packed with multiple small lipid droplets and a large number of mitochondria and they contribute to energy metabolism. Either increase of BAT activity [11, 12] or recruitment of beige adipocytes within white adipose tissue [8, 13, 14] is regarded as an alternative option for the treatment of obesity and its related diseases.

2 Metabolic benefits of activating BAT

2.1 Contribution of active BAT to whole body energy expenditure

In rodents, BAT contributes to up to 60 % of resting energy expenditure (REE) during cold acclimation [9, 15]. It is estimated that BAT mass range from ~30 to 300 g in human which could contribute to 20 % of daily REE [3, 16]. The amount of active BAT in adult humans is rather heterogeneous due to different experimental conditions. For example, acute cold exposure leads to increased energy expenditure of $0.8 \text{ kcal d}^{-1}\text{g}^{-1}$ of BAT [11]. On the other hand, fully activated BAT could account for increasing energy expenditure of $1.5 \text{ kcal d}^{-1}\text{g}^{-1}$ of BAT [5]. Therefore, average $1 \text{ kcal d}^{-1}\text{g}^{-1}$ of BAT is assumed to generate 50 kcal/d and might decrease 2 kg of fat mass yearly, if adult human has average 50 g of BAT. The browning of WAT also improves thermogenic function by burning glucose and fat to produce heat, resulting in a reduction of adiposity [17, 18].

2.2 Role of BAT in lipid metabolism

Accumulating evidences have demonstrated that fatty acids (FAs) are the main fuel for UCP1 mediated BAT thermogenesis [9]. Along with this line, it was recently illustrated that prolonged activation of the β 3-adrenergic receptor (β 3-AR) increases fatty acid β -oxidation and lipolysis in both WAT and BAT [19]. The activation of BAT provokes phosphorylation of adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL), which rapidly induce intracellular lipolysis and eventually lead to FAs release from lipid droplets. In rodent studies, it was demonstrated that cold exposure could decrease plasma triglyceride (TG) level and improve hyperlipidemia [20]. In addition, short-term and/or prolonged cold exposure leads to transient reduction in plasma TG level in humans [21, 22]. Similarly, metformin treatment also decreases plasma TG level by increasing BAT activity [23]. Therefore, triglyceride hydrolysis and re-synthesis are a critical factor for BAT mediated lipid metabolism. It is further supported by the evidence that acute cold exposure for 6 weeks elevates FAs uptake dramatically in BAT, not muscle or WAT [24]. Taken together, the activation of BAT is now considered as an encouraging therapeutic strategy to treat hypertriglyceridemia and obesity [25].

2.3 Role of BAT in glucose metabolism

BAT also possesses massive glucose dissipation ability [9]. Indeed, BAT utilizes large amount of glucose. In lean subjects, the glucose uptake rate of cold stimulated BAT

exceeds that of insulin-stimulated skeletal muscle [26, 27]. Glucose uptake by BAT might be mediated by insulin-dependent and insulin-independent manner [9]. In addition, BAT participates in glucose uptake and further contributes to whole-body glucose metabolism. We and others have demonstrated that BAT transplantation ameliorates glucose intolerance in diet induced and genetic obese *Ob/Ob* mice [28–30]. Moreover, β 3 adrenergic agonist induced BAT activation increases glucose disposal rate and improves insulin sensitivity both in mice [31] and humans [32–34]. Consistent with these findings, cold exposure increases insulin sensitivity in humans with active supraclavicular BAT [35]. Above results highlight that BAT plays predominant role in glucose homeostasis and insulin sensitivity.

3 Activators of BAT

As BAT has an important role in glucose and lipid metabolism, it is urgently demanded to find safe and specific BAT activators to prevent obesity and its related diseases.

3.1 Cold exposure

Cold exposure is a well-known safe way to activate BAT. Physiologically, cold exposure stimulates sympathetic nervous system which increases norepinephrine turnover, thereby increasing thermogenic function of BAT [36–38]. Mechanistically, norepinephrine enhances transcriptional factor mediated UCP1 expression by activating PKA and p38-MAPK signaling pathways [39]. Interestingly, it was reported that PET-CT positive biopsies from supraclavicular area displays more similar gene signatures with beige cells rather than classical brown adipocytes in adult human [13]. More recently, it has been demonstrated that cold exposure activates eosinophils and type 2 cytokines that stimulates M2 macrophages to secrete catecholamines and finally induces WAT browning [40, 41]. Indeed, it has been reported that acute mild cold exposure activates BAT and increases total energy expenditure in human subjects [24].

3.2 Exercise

Exercise increases metabolic activity of BAT and activation of thermogenic programs as well as browning in the visceral fat [42, 43]. Interestingly, just 7 d of aerobic exercise (60 min/d) upregulates mitochondrial UCP1 expression in BAT and reduces body weight in mice [44]. Also, the browning effect was found in subcutaneous WAT after 12 weeks of training in human subjects [45]. In contrast, a case-controlled study demonstrated significant reduction in BAT activity as well as browning of subcutaneous WAT in endurance trained group compared with

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