Review

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Brown fat fuel utilization and thermogenesis

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Brown adipose tissue (BAT) dissipates energy as heat to maintain optimal thermogenesis and to contribute to energy expenditure in rodents and possibly humans. The energetic processes executed by BAT require a readily-available fuel supply, which includes glucose and fatty acids (FAs). FAs become available by cellular uptake, *de novo* lipogenesis, and multilocular lipid droplets in brown adipocytes. BAT also possesses a great capacity for glucose uptake and metabolism, and an ability to regulate insulin sensitivity. These properties make BAT an appealing target for the treatment of obesity, diabetes, and other metabolic disorders. Recent research has provided a better understanding of the processes of fuel utilization carried out by brown adipocytes, which is the focus of the current review.

Significance of brown fat

The main function of BAT is to dissipate energy in the form of heat, a property driven by the presence of the mitochondrial protein UCP1 (uncoupling protein 1) that uncouples mitochondrial respiration. BAT is also densely innervated by the sympathetic nervous system (SNS) and is highly vascularized [1]. The thermogenic capacity of BAT may be important for heat production in newborns, essential for rodents and hibernating mammals, and possibly helps burn excess dietary energy consumption.

Imaging studies in humans have revealed that adults possess BAT depots around the neck, clavicle, and spinal cord [2–8] that are metabolically active and able to take up and utilize glucose and FAs [9,10]. This observation has sparked interest in the possibility that human BAT manipulation might represent a target for obesity management. However, the amount of BAT and its level of activity vary greatly among people, with higher levels observed in younger, leaner people, or by season and cold-exposure [2–10]. Nevertheless, uptake and oxidation of glucose and FAs for heat production make BAT an attractive target for the treatment of obesity, diabetes, and other metabolic disorders (Figure 1). In fact, two recent studies have demonstrated that cold acclimation in humans, after repeated daily cold-exposure, results in an increase of BAT activity with a surge in energy expenditure [11,12].

In addition to classical BAT, brown adipocytes also can be induced to appear in white adipose tissue (WAT) through a process termed 'browning'. These recruitable brown adipocytes [13] (also known as beige [14] or brite [15] adipocytes) can appear after cold-exposure or after treatment with sympathetic mimetics such as the β3-adrenergic receptor agonist CL 316, 243, as well as other agents (reviewed in [16–18]). The induction of browning may be a novel method for increasing whole-body energy expenditure and combating obesity.

An important goal in the study of BAT biology is to better understand the mechanisms underlying the uptake and utilization of FAs and glucose in energy-expending processes, including the role of fuel-switching (Box 1). Enabling brown adipocytes to increase these rates of catabolism may lead to greater energy expenditure to combat obesity and diabetes. Here we will discuss recent findings related to fuel utilization and to the activation of classical and recruitable brown adipocytes, including uptake and utilization of glucose and FAs, as well as what is known about the regulation of these processes.

Glucose utilization by BAT

The use of positron emission tomography–computed tomography (PET-CT) imaging with the tracer fluorodeoxyglucose (FDG) allows imaging of metabolically active BAT in humans that readily takes up glucose. Experiments in adult humans demonstrated that the rate of cold-activated glucose uptake exceeded that of insulin-stimulated glucose uptake in skeletal muscle. Specifically, glucose uptake after cold-exposure was increased 12-fold in BAT, and was correlated with an increase in whole-body energy expenditure, whereas insulin-stimulated glucose uptake in BAT increased only fivefold [9]. Interestingly, gene expression of the glucose transporter GLUT4 was higher in BAT than white adipose tissue (WAT) [9] in these subjects, and in mice GLUT1 and GLUT4 are more highly expressed after cold-exposure in BAT than in other tissues [19], further underscoring the importance of glucose for BAT function. Previous experiments using cold-exposed mice have also shown that many of the genes upregulated in BAT are involved in glucose uptake and catabolism, [20], and activation of adrenergic signaling by cold-exposure resulted in translocation of the glucose transporters GLUT1 and GLUT4 into the plasma membrane of brown adipocytes [21]. In obese, glucose-intolerant mice, cold-exposure was able to normalize

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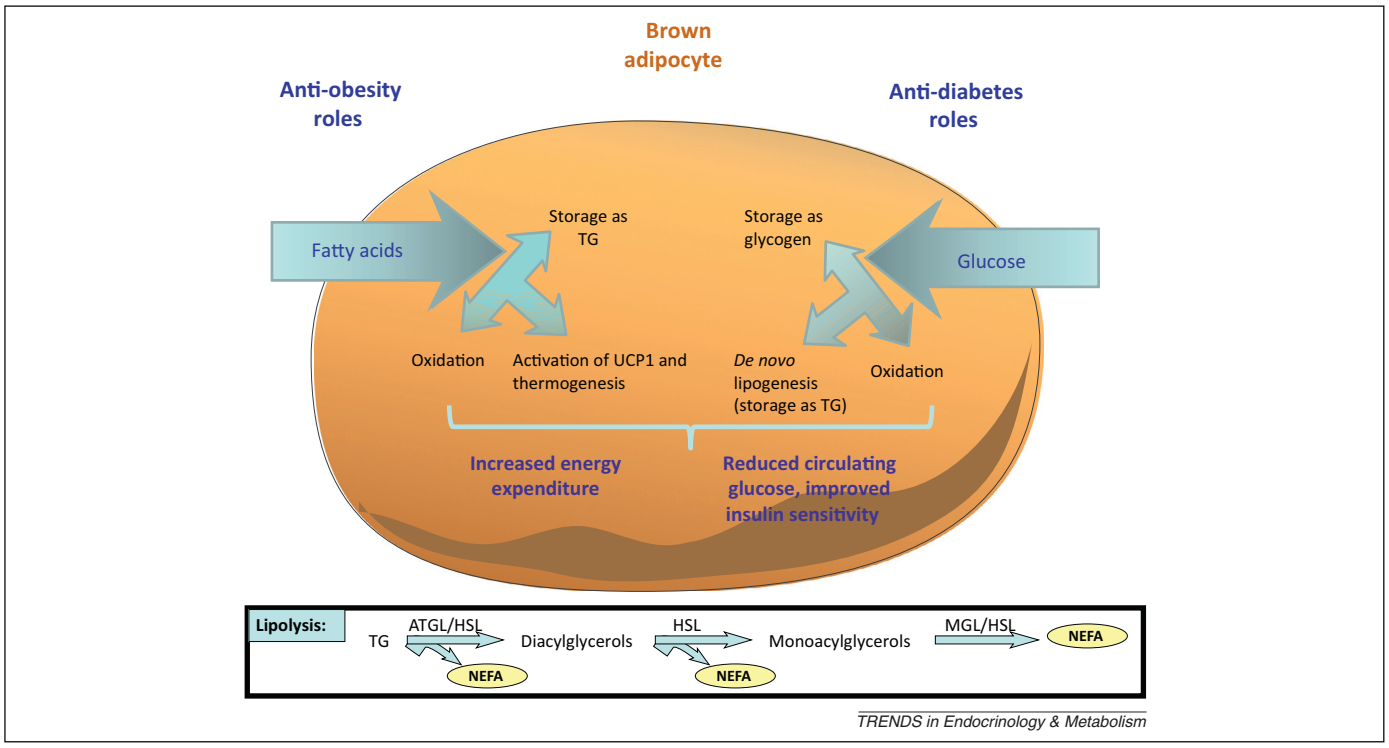

Figure 1. Glucose and FAs in BAT combat diabetes and obesity. BAT holds great promise for combating metabolic diseases such as obesity and diabetes, in part through its ability to take up and oxidize (or store) FAs and glucose. By targeting glucose and FAs as fuels, BAT may be able to mitigate the weight gain caused by high sugar and HFD. FAs may be stored as TGs, oxidized, or utilized to activate thermogenesis via UCP1 (Box 2). Glucose may be oxidized, stored as glycogen, or it may undergo *de novo* lipogenesis to provide TGs for storage. Pathways involved in lipolysis are presented in the lower box. Abbreviations: ATGL, adipose triglyceride lipase; BAT, brown adipose tissue; FAs, fatty acids; HFD, high-fat diet; HSL, hormone-sensitive lipase; MGL, monoglyceride lipase; NEFA, non-esterified fatty acids; TGs; triglyceride; UCP1; uncoupling protein 1.

glucose tolerance and increased both glucose and FA uptake in BAT of lean and obese mice [19,22,23]. This increase in glucose uptake in BAT was greater than in brain, heart, liver, WAT, and muscle combined [19,23]. Collectively, these data indicate that BAT may serve as an important glucose sink able to improve insulin sensitivity and glucose uptake after cold-exposure [24,25].

BAT can also take up glucose in an insulin-independent manner. Using a class of selective partial agonists of the non-canonical hedgehog signaling pathway, Teperino *et al.* demonstrated that these compounds cause robust insulin-independent glucose uptake in BAT and skeletal muscle via activation of the Smo–AMPK axis [26], that involves the G protein-coupled receptor (GPCR or GPR) of the hedgehog pathway Smoothened (Smo) and AMP-activated protein kinase (AMPK), indicating that energy-sensing by AMPK in BAT may regulate fuel utilization. Another hormone that might regulate BAT glucose uptake and thermogenesis is thyroid hormone. Thyroid hormone is converted from the low-activity form thyroxine (T4) to the active form 3,3′,5-triiodothyronine (T3) by the enzymes type 1 and type 2 deiodinase (DIO1 and DIO2). BAT is a site of high expression of DIO2, and DIO2 knock-out (KO) mice have defects in lipolysis, lipogenesis and adaptive thermogenesis, despite increased levels of UCP1 [27,28]. In addition, DIO2 KO mice are insulin-resistant and are susceptible to diet-induced obesity, perhaps a result of defects in BAT energy expenditure [29]. Together, these findings indicate there may be some insulin-independent pathways which can regulate BAT glucose uptake.

BAT mass and glucose disposal

Given the ability of BAT to take up glucose, one hypothesis is that increasing BAT mass in an individual may increase their glucose disposal. A recent rodent study utilizing BAT transplantation from donor mice into the visceral cavity of recipient mice, in an effort to increase BAT mass, demonstrated improved glucose tolerance, increased insulin sensitivity, reduced body weight, and decreased fat mass [30]. Similarly, BAT transplantation from chow-fed donor mice into the visceral cavity of high-fat diet (HFD) recipient mice resulted in complete reversal of HFD-induced insulin resistance [30]. Likewise, in a separate study transplantation of BAT into the interscapular region was able to reverse diet-induced obesity and improve insulin sensitivity [31]. In another study, subcutaneous transplantation of embryonic BAT was also able to restore euglycemia in streptozotocin (STZ)-treated type 1 diabetic mice [32].

It is well established that administration of CL 316, 243, via subcutaneous miniosmotic pumps leads to an increase in BAT mass, and to increased basal and insulin-stimulated whole-body glucose disposal, without affecting body weight in non-obese rats [33], an effect mostly mediated by WAT and BAT, and not by muscle. Collectively, these data suggest that manipulation of BAT mass might be a powerful way of increasing glucose disposal.

FAs as fuel for BAT

FAs fulfill a wide variety of roles in physiology (reviewed in [34,35]), including providing structural support in cell membranes, affecting the activities of particular transcription factors, and activating GPCRs. After a meal, FAs and