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The role of brown adipose tissue and the thermogenic adipocytes in glucose metabolism: recent advances and open questions

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Purpose of review

Brown adipose tissue (BAT) and the thermogenic adipocytes in white adipose tissue (WAT) are considered emerging targets against obesity-related metabolic perturbations given their high capacity for thermogenesis and glucose and lipid disposal. This manuscript summarizes and critically evaluates the recent advances on the role of BAT and thermogenic adipocytes in glucose homeostasis in humans.

Recent findings

Recent studies support that BAT has high capacity for glucose disposal not only during cold but during rewarming and thermoneutrality as well. Moreover, BAT is now considered a metabolic sink for the disposal of branched-chain amino acids improving whole-body glucose metabolism in rodents and, potentially, in humans. β 3 adrenergic agonism and glucagon-like peptide 1 increase BAT metabolic activity for glucose and/or induce the browning of WAT. Finally, recent findings support the association of glucose disposal in BAT with subclinical atherosclerosis and the reproducibility of two advanced medical imaging methods for the assessment of BAT using a glucose radiotracer.

Summary

Recent studies provide new insights on the role of human BAT and thermogenic adipocytes in glucose metabolism. However, further research is needed to unequivocally establish the clinical significance of BAT and the thermogenic adipocytes in glucose homeostasis in humans.

Keywords

adipose tissue, human research, metabolic health, thermogenesis

INTRODUCTION

Brown adipose tissue (BAT) is an organ well known for its role in thermoregulation and energy homeostasis. Until recently, the contemporary view was that BAT is present in mammals, including human infants but not adults. About a decade ago, three independent studies unequivocally demonstrated that human adults have significant amounts of functional BAT, assessed by using 2-deoxy-2-[^{18}F]-fluoro-d-glucose (^{18}F -FDG) PET/computed tomography (PET/CT; reviewed in ref. [1]).

Human BAT is primarily located in the supraclavicular, cervical, paravertebral, auxiliary, mediastinal, and anterior abdominal wall fat depots [2]. Brown adipocytes are morphologically and structurally distinct from the more abundant white adipocytes, given their smaller cell size, higher innervation and vascularization, multilocular or pauci-locular cells, and higher number of mitochondria rich in uncoupling protein 1 (UCP1), which hotwires

oxidative phosphorylation resulting in thermogenesis [3]. Alternative biochemical pathways to UCP1-mediated respiration (e.g., creatine cycling, calcium cycling, etc.) are also thought to contribute to thermogenesis [4]. Shortly after the 'rediscovery' of human BAT, evidence surfaced that brown-like adipocytes (also known as 'beige') can emerge within classical white adipose tissue (WAT) depots after cold exposure, adrenergic, or other stimuli (reviewed in ref. [5]). Upon stimulation in response to signals from the nervous system, endocrine factors, metabolites, or nutrients, thermogenic adipocytes accelerate

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KEY POINTS

Recent findings support that:

- $\beta 3$ agonism and GLP1 increase glucose disposal in human BAT and/or induce the browning of WAT.
- Human BAT is a tissue with high metabolic activity even in thermoneutrality or rewarming.
- BAT is metabolic sink for BCAA affecting systemic glucose homeostasis in rodents and potentially in humans.
- ^{18}F FDG-PET/CT and ^{18}F FDG-MRI are two reproducible methods of the assessment of BAT in terms of glucose metabolism.

Further research is needed to clarify the clinical and physiological significance of BAT and the thermogenic adipocytes in the regulation of glucose homeostasis in people.

their metabolic rate and uptake rate of circulating glucose, lipids, and other metabolites for thermogenesis [5]. BAT has also been proposed to be a potential endocrine organ that can secrete signaling peptides, lipokines, and exosomal miRNAs, affecting metabolism in distant tissues and coordinating whole-body metabolic function [6–8].

Considering the high prevalence of the obesity-associated metabolic disorders faced by our modern societies [insulin resistance, type 2 diabetes (T2D), etc.], developing and establishing effective strategies to improve the metabolic health of the population is a public health priority. BAT and thermogenic adipocytes are considered emerging targets against perturbations in glucose homeostasis. However, there is an ongoing scientific debate about the clinical significance of BAT and thermogenic adipocytes in the regulation of glucose metabolism in humans. This manuscript aims to summarize and critically evaluate the recent developments (2018 onwards) in this domain, with emphasis on clinical and translational studies in humans.

MAJOR SIGNALING PATHWAYS REGULATING GLUCOSE METABOLISM IN BROWN/THERMOGENIC ADIPOCYTES

Figure 1 provides an overview of the various signaling pathways regulating glucose disposal and its metabolic fate in thermogenic adipocytes. Adrenergic and insulin signaling are the two major and established pathways that regulate glucose metabolism in brown/thermogenic adipocytes [9]. BAT is a highly innervated tissue, with high expression of adrenergic receptors (ADRs). Stimulation of sympathetic adrenergic activity leads to the release of

norepinephrine in the postsynaptic peripheral nerve terminals, which binds to the highly expressed β -ADRs in brown adipocytes. Brown adipocytes express $\beta 1$ -ADR, $\beta 2$ -ADs, and $\beta 3$ -ADR, but $\beta 3$ appear to be most abundant (at least in the transcript level) [10]. $\beta 3$ adrenergic stimulation increases the transcription of glucose transporter 1 (GLUT1) in a cAMP-dependent manner and the translocation of newly synthesized GLUT1 to the cell membrane via activation of the mTOR complex 2 [3,9]. Conversely, insulin signaling induces the translocation of GLUT4 to the cell membrane via phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) signaling. Upon its entry to the thermogenic adipocytes, glucose can have different metabolic fates: 5–25% of glucose undergoes glycolysis and subsequent oxidation; glucose in the form of pyruvate can participate in mitochondrial anaplerosis and production of reducing equivalents to maintain fatty acid oxidation; and it can be directed toward de-novo lipogenesis and fatty acid synthesis to activate UCP1 and to fuel thermogenesis [3,7].

BRIEF OVERVIEW OF PREVIOUS LITERATURE (BEFORE 2018) ON THERMOGENIC ADIPOCYTES AND THEIR ROLE IN GLUCOSE METABOLISM

Studies in rodents

Studies in rodents support that BAT and thermogenic adipocytes are important for the regulation of glucose homeostasis (reviewed in ref. [5,9]). Cold exposure profoundly improves glucose tolerance in mice with obesity, while BAT accounts for ~75% of the total glucose clearance [11]. Moreover, transplantation of BAT or thermogenic adipocytes improves glucose tolerance and the insulin-stimulated glucose uptake in BAT, WAT, and heart muscle, suggesting that BAT can influence metabolism in other peripheral tissues [5,9]. In contrast, inhibition of the browning of WAT leads to decreased glucose tolerance and whole-body and tissue-specific insulin resistance in the liver and WAT.

Studies in humans

Considering that the avidity of BAT for ^{18}F -FDG (a glucose radiotracer) led to the rediscovery of human BAT [1], there has been intense scientific interest to determine the clinical and physiological significance of BAT and thermogenic adipocytes in glucose homeostasis in humans. Results from retrospective population studies, analyzing ^{18}F -FDG-PET/CT scans conducted mostly for cancer diagnosis, support that BAT is associated with decreased odds

FIGURE 1. Conceptual model of major signaling pathways regulating glucose metabolism in thermogenic adipocytes. The figure describes the regulation of glucose metabolism and the major signaling pathways in the thermogenic adipocyte as discussed in the text of the manuscript. For more details, please see 'Major Signaling Pathways Regulating Glucose Metabolism in Brown/Thermogenic Adipocytes' sections. Abbreviations: α 1-ADR, α 1-adrenergic receptor; β -ADR, β -adrenergic receptor; β -ox, β -oxidation; AAC, ADP/ATP carrier protein; AKT, Protein kinase B; BCAA, branch chain amino acids; Cr, Creatine; ETC, electron transport chain; FFA, free fatty acids; GLUT1/4, Glucose transporter 1/4; IR, insulin receptor; MCT, monocarboxylate transporter; mTORC2, mTOR Complex 2; NE, norepinephrine; PCr, phosphocreatine; PI3K, phosphoinositide 3-kinases; PKA, protein kinase A; RyR2, ryanodine receptor 2; SERCA2b, sarco/endoplasmic reticulum Ca^{2+} -ATPase2b; SLC25A44, the mitochondrial BCAA transporter; SLC7A5, L-amino acid transporter; TCA, tricarboxylic acid cycle; UCP1, uncoupling protein 1.

of T2D or hyperglycemia reviewed in ref. [5,9,12]). Similarly, results from prospective cross-sectional studies reported that high BAT activity is associated with improved glycemic control in healthy adults, independent of age, sex, and adiposity. Further, results from experimental clinical studies have demonstrated that cold exposure and insulin accelerate glucose disposal in BAT (12-fold and 5-fold, respectively); BAT takes up glucose and fatty acids in response to meal ingestion; cold-induced BAT

activation is linked to increased whole-body glucose disposal both in the fasting state and during hyperinsulinemia; and chronic cold exposure increases glucose disposal in BAT and improves systemic indexes in metabolic health reviewed in ref. [5,9,12]).

Open questions and challenges

The debate on the role of BAT in glucose metabolism stems from the discrepancy between studies that

support the link between BAT and metabolic health and those reporting that the net contribution of BAT in the total glucose disposal is low (~3–8 g/day due to the small amount of average detectable BAT). Several reasons may underlie this discrepancy, including the underestimation of BAT volume using ^{18}F -FDG-PET/CT imaging [2], inability to assess thermogenic adipocytes in WAT using the current imaging methods, possible indirect effects of BAT on other peripheral tissues (as suggested from previous studies in rodents), and differences in study design (intensity and duration of cold exposure, study population, etc.). These are the challenges that the field needs to overcome to unequivocally determine the clinical significance of BAT and thermogenic adipocytes in glucose metabolism.

BRIEF OVERVIEW OF RECENT EVIDENCE (2018 ONWARDS)

Effects of chronic $\beta 3$ adrenergic agonism on BAT, browning of WAT, and whole-body glucose metabolism

$\beta 3$ adrenergic agonism stimulates BAT glucose uptake and the browning of WAT in rodents and humans [5,13[•]]. Two clinical trials have recently reported the chronic effects of $\beta 3$ adrenergic agonism in adipose tissue biology and whole-body glucose metabolism. Specifically, O'Mara *et al.* [14^{••}] conducted a single-arm, 4-week (100 mg/day) mirabegron (double the FDA approved dose) administration trial in 14 healthy women. Mirabegron increased BAT volume and activity for glucose metabolism assessed using ^{18}F -FDG-PET/CT. Metabolic activity for glucose decreased in the lower lumbar subcutaneous WAT, but no changes were observed in the skeletal muscle. Chronic $\beta 3$ adrenergic agonism also improved in whole-body insulin sensitivity, insulin secretion, and glucose effectiveness.

In the second study, Finlin *et al.* [15^{••}] conducted a single-arm, 12-week mirabegron (50 mg/day) administration trial in people with overweight/obesity and prediabetes/metabolic syndrome. Contrary to the results reported by O'Mara *et al.* [14^{••}], the authors did not detect any significant differences in BAT volume or activity, but they reported an increase in UCP1 protein expression and other markers of browning of subcutaneous abdominal WAT. Moreover, they reported increased WAT lipolysis *in vitro*, a reduction in the fibrosis-related gene expression, and an increase in alternatively activated macrophages. $\beta 3$ adrenergic agonism also improved glucose tolerance and β -cell function and insulin-stimulated glucose disposal. Interestingly, the authors reported a decrease in the oligomycin-induced respiration

and no changes in the *in vitro* uncoupled respiration, suggesting that mirabegron may exert its metabolic effects via the UCP1-independent browning of WAT.

In summary, chronic $\beta 3$ adrenergic agonism appears to increase in BAT metabolic activity for glucose in healthy adults and induce the browning of WAT people with overweight/obesity and insulin resistance. The limitations of those studies include the lack of control group and the possibility of indirect $\beta 2$ adrenergic agonism cannot be excluded. Further research is needed to understand the discrepancies in the findings of those two studies and assess whether the increased metabolic activity for glucose in BAT or the browning of WAT may directly or indirectly explain the reported changes in whole-body glucose metabolism.

Branch chained amino acids uptake in BAT and glucose homeostasis

Until recently, BAT was thought to be a metabolic sink for glucose and lipids, but its potential role in amino acid metabolism was poorly understood. Yoneshiro *et al.* first observed that cold exposure for 2 h preferentially decreased plasma branch chained amino acids (BCAA) concentration in lean participants with high BAT activity, suggesting a potential link between BAT and BCAA metabolism [16^{••}]. To investigate the role of BAT in BCAA clearance, the authors studied genetically engineered mice that lacked the capacity to take up BCAA in BAT. According to the results, impaired capacity for BCAA clearance in BAT leads to decreased BAT thermogenesis, higher adiposity and liver mass, and systemic glucose intolerance during a high-fat diet. Additionally, the authors identified the mitochondrial transporter responsible for BCAA in BAT mitochondria (SLC25A44). These results support that BCAA metabolism in BAT is implicated in the regulation of glucose homeostasis, at least in rodents. However, the exact mechanism remains unclear. Further research is needed to explore the role of BAT in BCAA metabolism and the regulation of glucose homeostasis and insulin sensitivity in humans.

Glucose metabolism in brown adipose tissue during thermoneutrality and rewarming

Glucose metabolism in BAT has been almost exclusively studied during or immediately after cold exposure. The understanding of glucose metabolism in human BAT several hours after the cessation of the cold exposure and during thermoneutrality has been limited. To determine whether BAT glucose metabolism remains elevated after the cessation of cold exposure, Leitner *et al.* studied young lean

participants immediately after and 3 hours after cold exposure [17[•]]. The detectable BAT volume by ¹⁸F-FDG-PET/CT was about three-fold lower three hours after the cessation of cold exposure compared to immediately after, suggesting that glucose disposal in BAT remains elevated for several hours after cold exposure. The limitations of this study include the assessment of the supraclavicular and cervical BAT depots only and the absence of BAT assessment during thermoneutrality (which is usually low).

To assess the glucose metabolism in supraclavicular BAT during thermoneutrality (25°C) and cold exposure, Weir *et al.* [18^{••}] studied six young, lean, healthy men. Microdialysis in conjunction with ¹³³xenon washout technique was used to assess glucose utilization in supraclavicular BAT and abdominal WAT. During thermoneutrality, BAT had high glucose uptake and lactate release than WAT, whereas cold exposure further increased glucose uptake in BAT. These data support that lactate release accounts for ~50% of the glucose uptake during thermoneutrality, and not all glucose taken up by human BAT undergoes oxidation. Consistent with previous studies that used ¹⁸F-FDG-PET/CT for the assessment of glucose disposal [12], the magnitude the glucose uptake was ~5 µmol/100 g/min during thermoneutrality and ~17 µmol/100 g/min. These results highlight the capacity of BAT for high glucose uptake even in thermoneutrality.

Brown adipose tissue glucose uptake and subclinical atherosclerosis

Since the re-discovery of human BAT, results from cross-sectional investigations have reported associations between BAT and clinical indexes of cardiometabolic health (summarized in ref. [5]). Raiko *et al.* [19[•]] recently reported the results of 5-year longitudinal study that investigated the link between of BAT with subclinical atherosclerosis. According to the authors, BAT glucose uptake positively correlated with carotid distensibility and inversely correlated with maximum intima-media thickness and mean bulbus intima media thickness. Although the authors also reported multiple correlations between BAT glucose uptake and perfusion and indexes of cardiometabolic health (including triglycerides, high-density lipoprotein cholesterol, indirect indexes of insulin resistance, and HbA1c), the majority of those did not reach statistical significance after correcting for multiple testing. These results suggest that there is a relationship between BAT glucose uptake and subclinical atherosclerosis in humans. However, the lack of BAT assessment during the 5-year follow-up and statistical adjustment of the results minimally for age and adiposity limit the results of this study.

Glucagon-like peptide 1 (GLP1)

In rodents, GLP1 agonism stimulates BAT metabolic activity, increasing glucose and lipid combustion for the thermogenesis [20]. To assess the effect of chronic GLP1 administration in human BAT, Janssen *et al.* [21[•]] performed a 12-week, single-arm trial involving subcutaneous administration of extended-release exenatide (2 mg) in nondiabetic men. GLP1 agonism increased by 28% BAT volume which was assessed using ¹⁸F-FDG-PET/CT after cold exposure. The authors reported no changes in BAT fat fraction assessed using MRI during thermoneutrality. These results support that chronic GLP1 agonism can accelerate glucose metabolism in BAT without affecting its lipid content. The lack of a control group also limits the results of this study.

Imaging techniques for the assessment of brown adipose tissue

¹⁸F-FDG-PET/CT imaging is the most popular method and the current 'gold-standard' (hence its limitations-summarized elsewhere [1]) for assessing human BAT volume and its glucose kinetics [8]. ¹⁸F-FDG-MRI, which involves lower exposure to radiation compared to ¹⁸F-FDG-PET/CT, has been proposed as an alternative imaging method of assessing human BAT. Fraum *et al.* [22^{••}] first reported on the reproducibility of ¹⁸F-FDG-PET/CT and ¹⁸F-FDG-MRI for assessing BAT and performed a direct comparison of these two methods. The authors reported a strong correlation between BAT volume and activity (SUV_{max}) between and within the two methods. Considering that the correlations for BAT volume and activity were higher between the two methods (measurement conducted in the same session) than within the same method (different sessions 2–14 days apart), it is possible that biological or environmental variability between the two visits may explain this finding.

SUMMARY

Existing evidence supports that BAT is a tissue with increased capacity for glucose disposal in the basal state (i.e. fasting and thermoneutrality) and during stimulation (insulin-stimulation, postprandial condition, cold, or adrenergic stimulation). Results from epidemiological and experimental human studies support that higher detectable BAT volume and activity are associated with improved glycemic control, decreased odds of T2D, and improved insulin sensitivity, thus supporting that BAT is a potentially important tissue for regulating glucose metabolism. Results from recent studies support that: i) BAT glucose uptake is associated with long-term cardiovascular health; ii) BAT maintains

a high capacity for glucose disposal during thermoneutrality and rewarming after cold exposure; iii) chronic $\beta 3$ adrenergic agonism increases BAT metabolic activity for glucose in lean people, induces the browning of WAT in people with obesity and insulin resistance, and improves in whole-body glucose homeostasis; iv) GLP1 increases BAT volume and its metabolic activity for glucose; v) BAT is a metabolic sink for the disposal of branched-chain amino acids improving whole-body glucose metabolism; and vi) ^{18}F FDG-PET/CT and ^{18}F FDG-MRI are two reproducible methods of assessing BAT.

CONCLUSION

Although recent findings have further elucidated the relation of BAT and thermogenic adipocytes with glucose metabolism, additional studies are needed to address the open questions in the field in order to better understand the role of BAT in the regulation of glucose metabolism. Technological advances in metabolic imaging that enable a more comprehensive quantification of BAT and assessment of tissue-specific glucose metabolism in the whole-body level are needed to answer critical questions on the role of BAT and thermogenic adipocytes in glycemic control and metabolic health.

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I apologize for not being unable to cite older papers (i.e., before 2018) that contributed to the progress of this field due to restrictions in the number of older publications that can be included to the references list. Instead, we have used recent reviews that summarize the older literature.

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Conflicts of interest

There are no conflicts of interest.

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