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Review

Non-pharmacological and pharmacological strategies of brown adipose tissue recruitment in humans

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ABSTRACT

Humans maintain core temperature through a complex neuroendocrine circuitry, coupling environmental thermal and nutritional cues to heat-producing and dissipating mechanisms. Up to 40% of resting energy expenditure contributes to thermal homeostasis maintenance. Recent re-discovery of thermogenic brown adipose tissue (BAT) has brought the relation between ambient temperature, thermogenesis and systemic energy and substrate metabolism to the forefront. In addition to well-known pituitary −thyroid−adrenal axis, new endocrine signals, such as FGF21 and irisin, orchestrate crosstalk between white adipose tissue (WAT), BAT and muscle, tuning non-shivering and shivering thermogenesis responses. Cold exposure modulates the endocrine milieu, and cold-induced hormones cause bioenergetics transformation sufficient to impact whole body metabolism. This review will appraise the nature of human BAT and the basis of BAT-centred therapeutics, highlighting how the interaction between hormones and adipose tissue impacts metabolic responses. Non-pharmacological and pharmacological strategies of BAT recruitment and/or fat browning for metabolic benefits will be discussed.

Contents

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1. Introduction

Despite global research effort, current strategies targeting obesity and related metabolic disorders have been ineffective in halting their expansion. Identification of significant depots of brown adipose tissue (BAT) in adult humans and its relation to leanness represent exciting developments with potential therapeutic implications. In this review, we offer a critical appraisal on the premise that human BAT is an obesity/diabetes treatment target, as well as challenges and pitfalls of BAT-centred therapeutics.

2. Why is BAT an attractive target of obesity treatment?

Adipose tissue can be broadly classified into two main types: white and brown adipose tissues. White adipose tissue (WAT) is primarily a site of energy storage while BAT dissipates heat to maintain core temperature in defence against cold exposure (Cannon and Nedergaard, 2004). It harbours the unique protein, uncoupling protein 1 (UCP1) in the inner mitochondrial membrane. UCP1 is able to induce proton leak in the respiratory chain and releasing energy as heat. This process utilises fatty acid and glucose as substrates. In animal models, triglyceride and glucose clearance in cold-activated BAT amount to as much as two-thirds of total body substrate clearance (Bartelt et al., 2011), thus attesting its remarkable energy utilising capacity, and its potential to be harnessed for metabolic benefits.

In rodents and infants, the most prominent BAT depot is situated in the interscapular region (known as "classic BAT"). Recently, the spectrum of BAT has been extended, with studies revealing the presence of BAT-like cells within WAT, known as beige or brite (brown-in-white) adipose tissue (BeAT). While both classic BAT and BeAT expresses UCP1, they are distinguished by their unique gene signatures that point to their different developmental origins. However, they share similar bioenergetics profiles. In the basal state, BeAT resembles WAT; but upon cold exposure, BeAT within WAT expresses UCP1 and acquires similar energetic capacity as classic BAT (Wu et al., 2012a, 2012b). Pharmacological, genetic and transplantational models of high BAT and/or BeAT states are associated with resistance against high fat-induced weight gain, glycaemic improvement, hyperlipidaemia reversal and hepatic steatosis resolution (Wu et al., 2013), independent of diet and physical activity. In other words, recruitment of classic BAT or induction of BeAT may both lead to metabolic benefits, and represents a mechanism beyond traditional emphasis on diet and exercise that is highly relevant in an over-nutritious and sedentary contemporary society.

3. Do humans have BAT or BeAT or both?

^{18}F-fluorodeoxyglucose (^{18}FDG)-positron emission tomography (PET)/CT imaging, which was introduced in the early 2000s, revealed adipose tissue of high metabolic activity around the supraclavicular and cervical areas in some patients (Hany et al., 2002). Subsequent PET/CT studies and PET-guided biopsies in healthy adults confirmed the presence of BAT in majority of adults (Cypess et al., 2009; Saito et al., 2009; van Marken Lichtenbelt et al., 2009; Virtanen et al., 2009). More recent studies reveal expression of BeAT-specific genes in FDG-avid supraclavicular fat and classic BAT genes in deeper neck fat in adult humans (Cypess et al., 2013; Jespersen et al., 2013; Sharp et al., 2012; Wu et al., 2012a). This is in contrast to infants whose interscapular fat resembles that in animals and retains classic BAT gene signature (Lidell et al., 2013). These results suggest the presence of mixed classic brown and beige adipocytes in adult human "BAT depots". However, as beige adipocytes are interspersed within WAT depots, whole body BeAT abundance may be greater than what PET/CT is able to capture. These findings set the stage for investigations into BAT/BeAT recruitment strategies in humans.

4. Does BAT abundance matter to metabolism in humans?

Although BAT constitutes only a small fraction of body cell mass (~0.1%) in adults based on PET-CT estimation, its remarkable energy utilisation suggests it could contribute to whole body energy expenditure. Studies have estimated energy equivalent attributable to cold-simulated BAT. Based on nearly 10-fold increase in ^{18}FDG uptake in BAT on cold exposure (Orava et al., 2011; Ouellet et al., 2012; Virtanen et al., 2009), and the assumption that glucose represents 10% of BAT fuel (Ma and Foster, 1986), the extrapolated contribution of BAT metabolism to basal EE could be as high as 20%. If such BAT activation were "continuous", one may further hypothesise that the excess energy expenditure equates to an energy consumption of ~100 kcal/day, representing ~5 kg of fat loss in 1 year (Virtanen et al., 2009). As the contribution of physical activity to total energy expenditure dwindles in modern sedentary societies (Healy et al., 2008), the thermogenic contribution of activated BAT may be important since even minor changes in basal energy expenditure can translate into changes in body weight over the long-term (Astrup et al., 1999; Cunningham, 1982; Esparza et al., 2000; Ravussin and Swinburn, 1993). This is supported by associative studies showing negative correlations between BAT activity with fat mass, BMI and fasting glycaemia (Cypess et al., 2009; Lee et al., 2010; Ouellet et al., 2011; Saito et al., 2009; Yoneshiro et al., 2011). Our group showed that body weight was nearly 4 kg lower in 145 individuals when BAT was active (Lee et al., 2010). We also observed greater *UCP1* mRNA abundance in supraclavicular fat among leaner individuals, with UCP1 accounting for nearly 50% of BMI variance (Lee et al., 2011).

5. Can humans recruit BAT?

5.1. Genes vs. environment

The observation that some adults possess cold-activated BAT, and that these individuals are leaner can be interpreted in two ways. Since BAT is present in infancy, is it possible that certain genetic traits are associated with BAT retention through "to adulthood" and that BAT presence on PET/CT scanning merely represents a genetically determined phenotype. Conversely, human BAT may be "plastic" to some extent, with its abundance and activity determined by physiologic and/or environmental cues. The latter is a fundamental question as it forms the basis of the quest for BAT-harnessing therapeutics.

5.2. Do common genetic variations in humans influence BAT?

Given the importance of UCP1 to BAT function, polymorphism of the *UCP1* gene was the first candidate to be examined. A common