Published in final edited form as:

Mol Aspects Med. 2019 August ; 68: 82–89. doi:10.1016/j.mam.2019.07.003.

Contribution of brown adipose tissue to human energy metabolism

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Abstract

The present “obesogenic” environment has favored excessive energy intake resulting in the current obesity epidemic and its associated diseases. The epidemic has incentivized scientists to develop novel behavioral and pharmacological strategies that enhance energy expenditure to compensate for excessive energy intake. Although physical activity is effective to increase total energy expenditure, it is insufficient to induce negative energy balance and weight loss. With the discovery of brown adipose tissue (BAT) in adult humans, BAT activation soon emerged as a potential strategy for elevating energy expenditure. BAT is the only tissue that expresses uncoupling protein 1, conferring on this tissue high thermogenic capacity due to a low efficiency for mitochondrial ATP generation. Potential manipulation of BAT mass and activity has fueled the interest in altering whole-body energy balance through increased energy expenditure. Remarkable advances have been made in quantifying the amount and activity of BAT in humans. Many studies have concluded that the amount of active BAT appears insufficient to induce meaningful increases in energy expenditure. Thus, the majority of studies report that BAT activation does not influence body weight and metabolic control in humans. Strategies to increase BAT mass and/or to potentiate BAT activity seem necessary.

Keywords

Thermogenesis; Obesity; Cold exposure; Glucose homeostasis; Lipid homeostasis

1. Introduction

Affluent societies have been exposed to an excess of palatable, cheap and energy-dense foods. Evidence suggests that this surplus of food mostly explains the positive energy balance that leads to excess body weight (Swinburn et al., 2011). This idea is supported by the association between the increased energy supply and the rise of average body weight

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worldwide (Vandevijvere et al., 2015). Mathematical modeling shows that the excessive energy supply suffices to explain the rising obesity levels, even without needing to consider lower energy expenditure (Vandevijvere et al., 2015). Indeed, physical activity levels of the population have remained stable in face of the obesity epidemic (Westerterp and Speakman, 2008).

The excessive energy intake has been hypothesized to result from the macronutrient composition of modern energy-dense food. For instance, the proportion of dietary protein has been shown to associate inversely with total energy intake (Gosby et al., 2014). As lipid and carbohydrates dilute proteins in energy-dense food, additional energy intake is required to reach satiation (the “protein leverage” hypothesis) (Simpson and Raubenheimer, 2005). Consumption of high-glycemic carbohydrates has also been hypothesized to increase energy intake by promoting increased hunger (the “carbohydrate-insulin model” hypothesis) (Ludwig and Ebbeling, 2018). Independently of the mechanism, elevated energy intake seems to be the main trigger of the obesity epidemic.

As a result, most lifestyle interventions targeting a reduction in body weight often focus on decreasing energy intake (Fig. 1). The extreme approach is the surgical intervention of the digestive tract (*i.e.* bariatric surgery), which has proven very efficacious especially when coupled with lifestyle interventions (Schauer et al., 2017). Despite these efforts, individuals regularly resume their previous feeding behaviors and therefore fail to successfully control body weight. Another strategy to reduce body weight is to increase energy expenditure through physical activity and/or by using thermogenic compounds (*e.g.* pharmacologic agents, food ingredients) (Fig. 1). Unfortunately, these strategies are often plagued by poor adherence to exercise, compensatory increases in energy intake, and/or increases in sedentary behavior following exercise (Burgess et al., 2017; Melanson et al., 2013). Moreover, most pharmacological agents used to increase energy expenditure are associated with unwanted side effects. Common side effects are of cardio-vascular nature, including tachycardia and increases in blood pressure. In addition, compound-specific side effects include rhabdomyolysis (phendimetrazine), diarrhea (phenmetrazine), addiction (diethylpropion), psychiatric symptoms (ephedra and ephedrine), and even death (2,4-dinitrophenol) (Colman, 2007; Müller et al., 2018; Shekelle et al., 2003).

In the absence of effective therapies to decrease energy intake or increase energy expenditure, brown adipose tissue (BAT) became a novel target in the treatment of human obesity (Fig. 1). The primary role of BAT is to preserve body temperature in mammals with high body surface area-to-volume ratios, including newborn infants (Silva, 2006). Specifically, BAT is characterized by high mitochondrial content and expression of uncoupling protein 1 (UCP1). UCP1 uncouples mitochondrial ATP synthesis from fuel oxidation, resulting in most of the energy dissipated as heat (Nicholls et al., 1978). As a result, targeting the thermogenic capacity of BAT has become another avenue to enhance energy expenditure and potentially improve weight management in humans. Here, we review the evidence about the role of BAT in body weight control and obesity-related metabolic disturbances in adult humans.

2. Estimation of BAT mass

A quantitatively relevant contribution of BAT to whole-body energy expenditure and energy balance depends on the amount of BAT in the body. Consequently, accurate and precise measurement of BAT mass is critical. The gold standard technique for measuring BAT mass combines the identification of adipose tissue through X-ray computed tomography (CT) with the uptake of [^{18}F]fluoro-2-deoxy-2-D-glucose (FDG) by positron emission tomography (PET) (Chen et al., 2016). Using this approach, adipose tissue is specifically labeled as BAT when FDG uptake is greater than the upper range observed for white adipose tissue. Although this definition seems straightforward, thresholds for both radio-density in the CT and standardized uptake value in the PET are somewhat arbitrary. Indeed, the use of different thresholds partly explains the variability in BAT mass values among studies (Blondin et al., 2015c; Martinez-Tellez et al., 2018). Increasing efforts have thus been made to standardize FDG-PET/CT BAT quantification in terms of accuracy and comparability among studies (Chen et al., 2016).

From retrospective analyses of large datasets (> 1500 patients), only ~6% of individuals are reported to have detectable BAT under the standard temperature used at medical institutions, likely around 21–24 °C (Cypess et al., 2009; Gerngroß et al., 2017; Ouellet et al., 2011). Among individuals with detectable BAT, the amount of BAT ranged between 1 and 170 g when the cervical, supraclavicular, and superior mediastinal depots were evaluated (Cypess et al., 2009). Such inter-individual variability was partially accounted for by sex (females > males) and age (young > old). Indeed, the odds [95% confidence interval] of having detectable BAT were 3.07 [1.72–5.48] for women compared to men, and 0.32 [0.15–0.67] for the older (> 64 y-old) compared to the younger (< 50 y-old) subjects (Cypess et al., 2009). It is remarkable that reported BAT mass displayed a highly asymmetric distribution, with 75% of individuals having < 30 g of BAT (Cypess et al., 2009). If representative BAT mass values are to be reported, it is important to express them as percentiles, not as mean values.

Using this approach, Cypess et al. (2009) reported a median BAT mass of 11.6 g for men and 12.3 g for women. Retrospective studies thus suggest most individuals lack detectable levels of BAT, and when detected, BAT mass appears small. However, additional evidence indicates these BAT mass values were underestimated due to methodological issues discussed in the following paragraphs.

First, the small percentage of BAT-positive individuals is likely a consequence of the thermoneutral conditions of the measurement. Indeed, lower outdoor temperatures the day of the measurement are associated with a higher probability of BAT detection (Cypess et al., 2009; Gerngroß et al., 2017; Ouellet et al., 2011). Current evidence suggests that BAT is detected in most, if not all, individuals after cold exposure (Blondin et al., 2015c; Leitner et al., 2017). Thus, the standard protocol for BAT determination now includes acute cold exposure, either to a fixed temperature (usually between 16 and 19 °C) or to a personalized cooling protocol that does not induce shivering (Chen et al., 2016). Secondly, each BAT-containing depot has inactive brown and beige/brite cells that may potentially become active (“*brownable*”) (Leitner et al., 2017). If the active and *brownable* tissues are considered, total

BAT volume was estimated to range between 510 and 2358 ml, i.e. 459–2122 g assuming a density of 0.90 g/ml (Leitner et al., 2017). But activating *brownable* cells may be difficult. Indeed, *brownable* tissue remained inactive even after 5 h of cold exposure at a personalized lowest tolerable non-shivering temperature (~21 °C on average) (Leitner et al., 2017). While long-term cold exposure may be needed to fully activate brown and beige/brite adipocytes, administering longer cold exposure in humans may not be clinically feasible.

Another reason of BAT mass underestimation is because not all BAT depots are often quantified. In humans, BAT is found in cervical, supraclavicular, axillary, perispinal, mediastinal, and suprarenal depots. While the supraclavicular depot accounts for most detectable BAT, the addition of the cervical and axillary depots is thought to represent around two-thirds of active BAT mass (Leitner et al., 2017). Lastly, BAT mass may be underestimated in the presence of insulin resistance and aging. Insulin resistance was found to be positively associated with BAT triglyceride content (Raiko et al., 2015), while BAT triglyceride content was found to be inversely associated with FDG uptake (Baba et al., 2010). Low BAT mass detection in individuals with insulin resistance may thus be partly explained by reduced FDG uptake in BAT (Chondronikola et al., 2014; Orava et al., 2013). Older individuals also have lower cold-induced FDG uptake per volume of BAT compared to younger individuals (Blondin et al., 2015a). Then, BAT mass estimation through FDG uptake may result in underestimation of BAT mass in older individuals. The fact that cold-induced oxidative metabolism in BAT is independent of age (Blondin et al., 2015a) indicates that FDG uptake does not reflect BAT metabolic activity, at least when old vs. young individuals are compared (Blondin et al., 2015a). Indeed, BAT thermogenesis is mainly driven by intracellular triglyceride utilization (Blondin et al., 2017b, 2014), which is not associated with age (Blondin et al., 2015a).

Therefore, a bulk of evidence suggests that all humans have BAT mass, and at higher levels than initially presumed. Efforts to manipulate BAT mass/activity to influence body weight and metabolic control have therefore persisted. Thus, several markers for estimating BAT activity have been used, which are discussed in section 3. However, whether BAT activation influences body weight and metabolic control will depend on how strong the activation is, and on how long the activation is maintained. Sections 4 and 5 present the evidence regarding the effects of BAT activation on body weight and metabolic control.

3. Estimation of BAT activity

Several protocols of acute cold exposure aimed at activating BAT have been used, such as staying at cold room temperatures, wearing suits perfused with cold water, placing feet intermittently into cold water or on ice, and using blankets perfused with cold water (Table 1). In response to these protocols, studies have demonstrated that BAT increases its blood flow (Blondin et al., 2017b; Muzik et al., 2013; Orava et al., 2013; U Din et al., 2018, 2016; Weir et al., 2018), glucose uptake (Cypess et al., 2012; Orava et al., 2013; Virtanen et al., 2009; Weir et al., 2018), non-esterified fatty acids (NEFA) uptake (U Din et al., 2018, 2016), metabolic rate (Blondin et al., 2017b, 2015b; Ouellet et al., 2012), oxygen consumption (Muzik et al., 2013; U Din et al., 2018, 2016) and heat production (Koskensalo et al., 2017). As a result, all these markers have been used to quantify BAT metabolic activity. Whether all

of them are equally effective at accurately measuring BAT metabolic activity is debatable. For instance, cold exposure through wearing a suit perfused with cold water for 90–120 min increased BAT metabolic rate by ~4.4 fold, whereas blood flow only increased by 1.6 fold (Blondin et al., 2017b). Administration of nicotinic acid (which inhibits triglyceride lipolysis) blunted this cold-induced increase in BAT metabolic rate, yet blood flow appeared to be unaffected (Blondin et al., 2017b). Using the same cold exposure protocol, FDG uptake in BAT was observed to be lower in old versus young individuals, while NEFA uptake was similar (Blondin et al., 2015a). Collectively, these data suggest that estimates of BAT activity may sometimes dissociate (Table 1), indicating that different conclusions could be obtained depending on the specific metabolic marker used.

In turn, BAT oxygen consumption measured by $^{15}\text{O}_2$ PET represents an actual thermogenic marker of BAT activity (Muzik et al., 2013; U Din et al., 2018, 2016). Estimation of BAT thermogenic potential and its contribution to whole-body energy expenditure should thus consider oxygen consumption rather than other surrogate markers (Jensen, 2015).

4. Influence of activated BAT on whole-body energy expenditure and body weight

One of the best known mitochondrial uncouplers used in humans is 2,4-dinitrophenol. This compound increased basal metabolic rate up to 50%, which was followed by a weight loss of ~900 g per week (Cutting et al., 1933). However, high doses caused deaths, leading to the banning of 2,4-dinitrophenol commercialization in many countries (Harper et al., 2008). The later identification of UCP1 provided the molecular basis for understanding energy dissipation by BAT (Nicholls et al., 1978). Because UCP1 is only expressed in BAT, and BAT was supposedly only present in newborns, manipulating UCP1 to increase energy expenditure in adults was discouraged. Three decades later, demonstration of the presence of active BAT in adult humans (Cypess et al., 2009; van Marken Lichtenbelt et al., 2009; Virtanen et al., 2009) revitalized the interest for manipulation of energy efficiency to control body weight.

High BAT activity is associated with high resting metabolic rate under thermoneutral conditions in some (Bakker et al., 2014; van Marken Lichtenbelt et al., 2009) but not all studies (Vijgen et al., 2011; Yoneshiro et al., 2011a). In turn, BAT activity is consistently related to resting metabolic rate upon cold stimulation (Chen et al., 2013; van Marken Lichtenbelt et al., 2009; Vijgen et al., 2011; Yoneshiro et al., 2011a). Other studies have reported that high BAT activity is associated with low body mass index (Cypess et al., 2009; Saito et al., 2009; van Marken Lichtenbelt et al., 2009; Vijgen et al., 2011; Yoneshiro et al., 2011b) and low fat mass (Saito et al., 2009; Vijgen et al., 2011; Yoneshiro et al., 2011b). This indirect evidence has stimulated the idea of treating obesity by increasing BAT mass/activity.

The contribution of BAT activation to whole-body energy expenditure has been under debate. Studies measuring BAT oxygen consumption following acute cold exposure have calculated that BAT-induced energy expenditure increases up to 25 kcal/d (Muzik et al., 2013; U Din et al., 2016). Recent calculations considering FDG uptake as a marker of BAT

activity led to a value of 193 kcal/d (Marlatt et al., 2018). BAT-related energy expenditure has also been calculated using BAT mass from radiological 3D mapping (Leitner et al., 2017) combined with BAT oxygen consumption (U Din et al., 2016). From those techniques, BAT-related energy expenditure upon cold exposure was estimated to reach up to 211 kcal/d (Carpentier et al., 2018). An alternative approach led to 80 kcal/d (Tapia et al., 2018) after considering BAT as metabolically active as heart or kidneys (the organs with the highest specific resting metabolic rate in humans [Wang et al., 2010]) and a BAT mass of 200 g (the upper value in most individuals [Ouellet et al., 2012]). Importantly, all these theoretical calculations assume a maximally activated BAT across an entire day, which is unlikely to ever occur.

In conclusion, enhanced thermogenesis due to activated BAT seems small and unlikely to lead to clinically meaningful reductions in body weight, even in the absence of compensatory increases in energy intake. In support of this, no change in body weight has been found after exposure to 19 °C for 10 h/d during 4 weeks (Lee et al., 2014), or after exposure to 17 °C for 2 h/d during 6 weeks (Yoneshiro et al., 2013). Additionally, although BAT is more active upon low outdoor temperatures (Cypess et al., 2009; Gerngroß et al., 2017; Ouellet et al., 2011; Saito et al., 2009), obesity prevalence is not associated with outdoor temperature once poverty, race, and education are considered (Speakman and Heidari-Bakavoli, 2016). Activation of BAT and its resulting increase in energy expenditure thus appears ineffective as a potential strategy for obesity treatment. Therefore, association of high body mass index with low BAT activity may simply result from individuals with greater fat mass having less need for thermogenic tissue (Nahon et al., 2017; Speakman, 2018). Despite this, the role of activating BAT to prevent long-term weight gain (Dutton et al., 2016; Hill, 2006) and help in weight maintenance after weight loss (Marlatt et al., 2018) still deserves further investigation.

5. Influence of activated BAT on metabolic control

Enhancing BAT activity may play a role in the metabolic control of carbohydrate and lipid metabolism. Theoretically, the high metabolic activity of BAT could be useful for increasing the clearance and utilization of circulating glucose and lipid, thus improving metabolic homeostasis. Indirect evidence supports this hypothesis. Low outdoor temperature is associated with high BAT activity (Ouellet et al., 2011; Saito et al., 2009), and is also associated with lower prevalence of glucose intolerance and lower prevalence and incidence of type 2 diabetes, independent of age and obesity (Blauw et al., 2017; Speakman and Heidari-Bakavoli, 2016). Finally, presence of BAT determined lower circulating glucose and HbA1c concentrations after controlling for age, sex and body fat mass (Matsushita et al., 2014).

As a result, several studies have analyzed the effect of cold exposure (to activate BAT) on glucose homeostasis. Acute cold exposure (5–8 h) was reported to increase basal and insulin-stimulated whole-body glucose disposal in individuals with high, but not low, BAT mass and activity (Chondronikola et al., 2014). Similarly, 10 days of daily cold exposure increased insulin-stimulated glucose disposal in individuals with type 2 diabetes (Hanssen et al., 2015). Although these studies did not detect changes in glycemia, the overall findings

suggest cold-induced BAT activation improves glycemic control. These observed beneficial effects, however, seem mostly due to a metabolic effect in skeletal muscle rather than in BAT. Recent calculations show that BAT glucose uptake reaches at most only 5 g per day (Carpentier et al., 2018), representing < 2% of whole-body glucose turnover in humans. Indeed, 10 days of daily cold exposure increased cold-induced glucose uptake by skeletal muscle, thus partly explaining the effect of long-term cold exposure on glucose homeostasis (Hanssen et al., 2016).

Concerning lipid metabolism, acute cold exposure has been shown to increase BAT NEFA uptake and NEFA appearance into circulation (Ouellet et al., 2012; U Din et al., 2018, 2016). Because BAT NEFA uptake increased to a smaller extent than NEFA appearance, this resulted in elevated blood NEFA concentration (Ouellet et al., 2012). A separate study reported a reduction in total blood cholesterol and LDL-cholesterol concentrations among individuals with hypercholesterolemia following chronic cold exposure for 90 days (De Lorenzo et al., 1998). As previously discussed, however, the effects of cold exposure do not necessarily depend on BAT activity. In fact, BAT explains at most 0.5% of plasma NEFA turnover following acute cold exposure (Ouellet et al., 2012).

Catecholamines are physiological humoral factors that activate BAT through β 3-adrenoreceptors. The acute and chronic effects of β 3-adrenoreceptor agonists on glucose and lipid homeostasis have therefore been studied. Acute administration of mirabegron (Myrbetriq® a high-affinity β 3-adrenoreceptor [Takasu et al., 2007] developed for treatment of overactive bladder) (Baskin et al., 2018; Cypess et al., 2015) or TAK-677 (another β 3-adrenoreceptor agonist) (Redman et al., 2007) showed no effect on glycemia. Moreover, blood NEFA concentration was not modified by acute administration of mirabegron, but increased after TAK-677 (Redman et al., 2007). Chronic administration of TAK-677 (29 days [Redman et al., 2007]) or CL316,243 (8 weeks [Weyer et al., 1998]) showed no effect on glycemia, but CL316,243 did increase insulin-mediated glucose disposal. These compounds had divergent effects on blood NEFA concentration, with TAK-677 showing no effect (Redman et al., 2007), whereas increased concentration was noted after CL316,243 administration (Weyer et al., 1998). Thus, treatment with β 3-adrenoreceptor agonists appears insufficient to reduce blood glucose and lipid concentrations, despite the evidence showing enhancement in insulin-mediated glucose disposal (Weyer et al., 1998).

6. Efforts to potentiate BAT thermogenesis

BAT activation induces a rather small increase in energy expenditure that appears insufficient to influence body weight or metabolic control. This may result from an insufficient amount of BAT mass or an ineffective BAT activation. Therefore, efforts are being made to identify acceptable and clinically relevant stimuli to increase BAT mass or to potentiate BAT activity. If effective, these stimuli could boost energy expenditure. Herein, we present the effectiveness of chronic cold exposure and of some pharmacological agents.

6.1. Chronic cold exposure

Known influence of different cooling protocols on BAT activation triggered interest for longer application of these protocols in humans (Table 2). Studies in healthy individuals

reported increases in BAT mass, glucose uptake and metabolic rate after one month of daily cold exposure through either cooling suits (10 °C; 2 h/d) or exposure to a room at 19 °C (10 h/d) (Blondin et al., 2017a, 2014; Lee et al., 2014). Similar findings were observed after 10 days of exposure to 15–16 °C for 6 h/d (van der Lans et al., 2013). These data indicate that chronic cold exposure induces BAT acclimation that may potentiate BAT activation.

However, daily cold exposure for 10–42 days did not change (Blondin et al., 2017a, 2014; van der Lans et al., 2013; Yoneshiro et al., 2013), or even decreased (Hanssen et al., 2016) resting energy expenditure measured under thermoneutral conditions. Besides, some (Hanssen et al., 2015; van der Lans et al., 2013; Yoneshiro et al., 2013), but not all (Blondin et al., 2017a; Hanssen et al., 2016) studies show an increase in cold-induced resting energy expenditure after chronic cold exposure. Chronic cold exposure neither affected 24-h energy expenditure measured in a whole-room calorimeter at 24 °C or 19 °C (Lee et al., 2014) (Table 2). Therefore, although BAT responds to chronic cold exposure, the response does not seem to translate into enhanced whole-body energy expenditure.

The fact that the activation of BAT by cold exposure is mediated by the sympathetic nervous system is indeed noteworthy (Carpentier et al., 2018; Lowell and Spiegelman, 2000). In fact, circulating norepinephrine increases in response to individualized cooling protocols using cooling suits (van der Lans et al., 2013). Furthermore, sympathetic nervous stimulation to BAT relates directly with BAT glucose uptake upon exposure to 16–17 °C for 2 h (Bahler et al., 2016). Additional evidence shows that individuals with catecholamine-secreting tumors have elevated BAT mass and whole-body energy expenditure, along with browning of white adipose tissue (Iyer et al., 2009; Lean et al., 1986; Søndergaard et al., 2015). These findings suggest stimulants of sympathetic activity as potential BAT activators, thus paving the way for the development of pharmacological agents.

6.2. Pharmacological agents

Activation of BAT by use of specific pharmacologic agonists has been explored (Arch, 2011; Cypess et al., 2012; Malik et al., 2012). Unfortunately, heart rate and systolic blood pressure have been reported to increase following the use of such pharmacologic agents, mostly due to non-selective β 3-adrenoreceptors activation (Baskin et al., 2018; Cypess et al., 2015; Redman et al., 2007). Mirabegron (200 mg) has been reported to acutely increase BAT activity in individuals known to display BAT activation upon cold exposure (Cypess et al., 2015). Mirabegron also increased resting metabolic rate by ~200 kcal/d, a phenomenon directly related to BAT activation measured by FDG uptake (Cypess et al., 2015). A subsequent study confirmed the effect of 200 mg mirabegron on BAT activity (measured by FDG uptake) and resting metabolic rate (Baskin et al., 2018). Despite these findings, a 200-mg dose of mirabegron also produced clinically meaningful elevations in heart rate and systolic blood pressure (Baskin et al., 2018; Cypess et al., 2015). A smaller dose of mirabegron (50 mg; approved for treatment of overactive bladder), however, barely increased BAT activity, and did not increase resting metabolic rate (Baskin et al., 2018).

7. Concluding remarks

Detection of BAT in adult humans has provided a potential alternative to stimulate energy expenditure, which might eventually result in some health benefits (Fig. 2). Despite these observations, three major challenges remain. First, the amount of detectable BAT mass appears insufficient to support any major effect on whole-body energy balance. Although the amount of potentially active BAT appears several folds greater than the amount of active BAT, potentially active BAT seems strongly resilient to activation (Leitner et al., 2017). Second, BAT activation, even if activated the entire day, may increase energy expenditure to a level that is unlikely to reduce body weight. Still, further studies are required to determine the effect of longer periods of cold exposure on body weight. Finally, BAT activity likely evolved as a cold-induced mechanism to preserve core temperature, and not to burn off calorie excess. Putative BAT activators (*e.g.* drugs, food ingredients, etc.) thus face the challenge of being effective under conditions other than cold exposure.

Funding

This work was supported by FONDECYT-Chile [#11180361 to RFV; #1170117 to JEG].

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Fig. 1.
Strategies used to control body weight.

Fig. 2.
Contribution of brown adipose tissue to human energy metabolism.

Table 1

Protocols for acute cold-induced activation of brown adipose tissue (BAT) in humans.

Protocol	Control for shivering	Subjects	Whole-body energy expenditure	Marker of BAT activity	Reference
RT 17 °C for 120 min before the scan, and for 180 min during blood flow measurement	Subjective	6M, 21 [2] yr, 23 [2] kg/m ²	↑ 1.1-fold	Glucose uptake ↑ 3.1-fold Blood flow ↑ 1.5-fold	Weir et al. (2018)
RT 15.5 °C for 30 min before and also during the scan, plus airflow	Subjective	Low BAT: 7F/9M, 31 [10] yr, 25 [4] kg/m ² High BAT: 8F/1M, 30 [6] yr, 22 [3] kg/m ²	NS ↑ 1.2-fold	O ₂ consumption, NS Blood flow ↑ 1.2-fold O ₂ consumption ↑ 1.5-fold Blood flow ↑ 1.5-fold	Muzik et al. (2013)
RT 17–19 °C for 120 min before the scan. During the scan, one foot in 5–9 °C water 5 min every 5 min	Not reported	5 subjects 20–50 yr	Not measured	Glucose uptake ↑ 15-fold	Virtanen et al. (2009)
		Lean: 20F/7M, 40 [10] yr, 23 [2] kg/m ² Obese: 25F/11M, 38 [9] yr, 34 [4] kg/m ²	↑ 1.2-fold ↑ 1.2-fold	Glucose uptake ↑ 7.8-fold Blood flow ↑ 2.2-fold Glucose uptake ↑ 3.1-fold Blood flow ↑ 1.1-fold	Orava et al. (2013)
RT 20 °C plus cooling vest at 14 °C for 120 min before the scan	Subjective	6F/4M, 27 [5] yr, 24 [4] kg/m ²	↑ 1.1-fold	Glucose uptake ↑ 4.2-fold	Cypess et al. (2012)
Suit at 18 °C for 90–120 min before and also during the scan	EMG	6M, 23–42 yr, 24–31 kg/m ²	↑ 1.8-fold	Metabolic rate ↑ 1.8-fold	Ouellet et al. (2012)
		12M, 24 [4] yr, 26 [3] kg/m ²	↑ 1.8-fold	Metabolic rate ↑ 2.3-fold	Blondin et al. (2015b)
		8M, 30 (25–35) yr, 25 (22–27) kg/m ²	↑ 1.7-fold	Metabolic rate ↑ 4.4-fold Blood flow ↑ 1.6-fold (<i>P</i> = 0.06)	Blondin et al. (2017b)
Blankets at 6 °C for 120 min before and also during the scan	Subjective	2F/5M, 36 [11] yr, 26 [3] kg/m ²	↑ 1.2-fold	O ₂ consumption ↑ 1.7-fold NEFA uptake ↑ 1.6-fold (<i>P</i> = 0.09)	U Din et al. (2016)
		4F/5M, 36 [9] yr, 26 [3] kg/m ²	↑ 1.2-fold	Blood flow ↑ 1.8-fold O ₂ consumption ↑ 2.3-fold NEFA uptake ↑ 1.8-fold Blood flow ↑ 2.5-fold	U Din et al. (2018)
Blankets at 4–18 °C for 120 min before the scan. During the scan, feet in contact with iced bags	ECG and subjective	4F/6M, 25–45 yr, 21–29 kg/m ²	Not measured	Low BAT group: BAT temperature, NS	Koskensalo et al. (2017)
				High BAT group: BAT temperature ↑ 1.1-fold (<i>P</i> = 0.06)	

Values are means [standard deviation] or means (95% confidence interval). ECG, electrocardiogram; EMG, electromyography; RT, room temperature; NEFA, nonesterified fatty acids; NS, non-significant. M, males; F, females.

Table 2

Protocols for chronic cold-induced activation of brown adipose tissue (BAT) in humans.

Protocol	Subjects	Response in BAT	Whole-body energy expenditure (EE)	Body weight and metabolic control	Reference
RT 17 °C for 2h/d, 6wk	12M, 24 [4] yr, 22 [3] kg/m ²	Cold-induced glucose uptake ↑ 1.6-fold	RMR, NS Cold-induced EE ↑ 1.2-fold	Body weight, NS	Yoneshiro et al. (2013)
RT 19 °C for 10 h/d, 4wk	5M, 21 [2] yr, 22 [1] kg/m ²	Volume ↑ 1.4-fold Cold-induced glucose uptake ↑ 1.5-fold	24-h EE at 24 °C, NS 24-h EE at 19 °C, NS	Body weight, NS Glucose, NEFA and TG, NS	Lee et al. (2014)
RT 14–16 °C for 6 h/d, 10 d	9F/8M, 23 [3] yr, 22 [2] kg/m ²	Volume ↑ 1.4-fold Cold-induced glucose uptake ↑ 1.2-fold	RMR, NS Cold-induced EE ↑ 1.04-fold	Glucose, NEFA and TG, NS	van der Lans et al. (2013)
	8 subjects with type-2 diabetes, 59 [6] yr, 30 [3] kg/m ²	Glucose uptake ↑ 1.6-fold	Cold-induced EE ↑ 1.1-fold	Body weight, NS Glucose, NEFA and TG, NS	Hanssen et al. (2015)
	10M, 36 [13] yr, 33 [4] kg/m ²	Glucose uptake ↑ 1.3-fold	RMR ↓ 16% (<i>P</i> = 0.06) Cold-induced EE, NS	Insulin sensitivity ↑ 1.4-fold Glucose, NEFA and TG, NS	Hanssen et al. (2016)
Suit at 10 °C for 2 h/d, 5 d/wk, 4 wk	6M, 23 [2] yr, 25 [3] kg/m ²	Volume ↑ 1.4-fold	RMR, NS	Glucose ↓ 4%	Blondin et al. (2014)
		Cold-induced glucose uptake ↑ 1.3-fold (<i>P</i> = 0.08)		NEFA and TG, NS	
		Cold-induced metabolic rate ↑ 2.2-fold			
	9M, 23 [3] yr, 24 [3] kg/m ²	Volume ↑ 1.4-fold Cold-induced metabolic rate ↑ 2.8-fold	RMR, NS Cold-induced EE, NS	Body weight, NS Glucose, NEFA and TG, NS	Blondin et al. (2017a)

Values are means [standard deviation]. RMR, resting metabolic rate; RT, room temperature; NEFA, non-esterified fatty acids; TG, triglycerides; NS, non-significant. M, males; F, females.