Brown Adipose Tissue – a Future Treatment for Obesity?

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ABSTRACT

Obesity is a major public health concern: in the United Kingdom (UK) over two thirds of the population are obese or overweight, the prevalence of obesity is growing exponentially, and current treatment options have limited success – making the need for novel therapies vital. Brown adipose tissue (BAT) has the ability to safely dissipate chemical energy as heat and in 2009 was found to be active in human adults, leading to hope that its therapeutic manipulation could contribute to weight loss. This review discusses methods proposed for BAT activation and potential pitfalls in our current understanding to evaluate if BAT can be used as a future treatment for obesity. To date, β₃-adrenergic receptor (β₃-AR) agonists and cold activation have been shown to be the most promising options to activate BAT. However, cold activation requires a high degree of patient cooperation and β₃-AR agonists appear non-effective long-term. Nonetheless, β₃-AR agonists are likely to be a more realistic treatment than cold activation, making our next challenge to understand and mitigate the mechanisms that inhibit BAT activation in long-term β_3 -AR agonist administration. Our assumptions about BAT activation are predominately from rodent studies and based on measurements from $[^{18}\mathrm{F}]\text{-fluorodeoxyglucose}$ ($^{18}\mathrm{F-FDG})\text{-positron-emission}$ tomography and computed tomography (PET/CT) imaging, both with their respective limitations. BAT has offered huge insight into weight homeostasis, with the potential of offering prospective therapeutics for obesity and beyond. Nevertheless, before we can truly understand the real possibilities of BAT we need to further our current understanding of the physiological controls of BAT, potentially leading to more suitable therapies. The focus for future research should be to improve and standardise the methodology used to measure BAT activation, enabling larger clinical trials and better comparisons.

INTRODUCTION

Obesity is a major public health concern worldwide. Its prevalence has almost tripled in the last 50 years and continues to rise.1 In the UK alone, it is estimated that over 65% of the population are either obese (body mass index (BMI) greater than 30kg/m²) or overweight (BMI between 25-29.9 kg/m²).² Obesity severely reduces quality of life and is a major risk factor for many chronic illnesses including Type 2 Diabetes Mellitus, cardiovascular disease and musculoskeletal disorders.1 A raised BMI costs the NHS over 5 billion pounds every year, creating an unsustainable pressure on the healthcare system.3 As the prevalence of obesity continues to rapidly increase, it has become apparent that current management approaches are often unsuccessful in both preventing and managing obesity. Often patients who lose weight regain it, current anti-obesogenic drugs have unpleasant side effects, and bariatric surgery is not always a suitable solution. Due to these limitations of current treatment strategies and the growing prevalence of obesity, it has become vital to identify novel therapeutic interventions.¹

Weight homeostasis

Maintenance of body weight can be summarised as the balance between energy intake and energy expenditure (refer to Fig. 1). When energy intake from food consumption repeatedly exceeds energy lost through physical activity and metabolic processes, obesity can develop. Therefore, a weight loss therapy must involve decreasing intake of food and/or increasing energy expenditure. However, it is important to note that there is considerable individual variation in people's ability to gain and lose weight. This is thought to be because of differences in the physiological controls that govern this balance. 5

Adipose tissue is a loose fibrous connective tissue composed of adipocytes. There are two major categories of adipose tissue: white adipose tissue (WAT) and brown adipose tissue (BAT). While WAT is utilised to store excess energy, which contributes to weight gain, BAT, on the other hand dissipates energy as heat (thermogenesis) leading to increased energy expenditure and weight loss. High BMI and adiposity correlate to low BAT activity levels, implying that variations in BAT activity could contribute to increased risk of weight accumulation and an obesogenic phenotype. 6

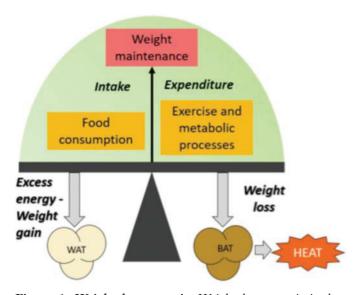


Figure 1: Weight homeostasis. Weight homeostasis is the balance between intake and expenditure. (Figure adapted from Seale P & Lazar MA, 2009.⁴)

Anatomy of adipose tissue

BAT was initially believed only to be present and active in human neonates and hibernating mammals. However, in 2009, metabolically active BAT was demonstrated in adults and this is now an accepted phenomenon. BAT is predominately located in the supraclavicular, paravertebral, axillary, and cervical regions in human adults (see Fig. 2).

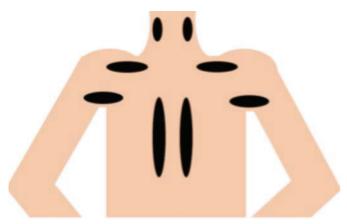


Figure 2: Schematic of the locations of Brown Adipose Tissue. BAT is shown by the black highlighted areas. (Information distilled from Reddy NL et al, 2014.)

Inside a BAT adipocyte there are multiple lipid droplets and numerous mitochondria. In comparison, WAT adipocytes have a single large lipid droplet and fewer mitochondria (see Fig. 3). BAT is highly vascularised due to its high metabolic activity and is richly innervated by the sympathetic nervous system. An intermediate 'beige' adipocyte has also been described and is thought to contribute to BAT mass in human adults. Beige adipocytes are thought to also dissipate energy as heat despite sharing a mixture of features belonging to both white and brown adipocytes.¹

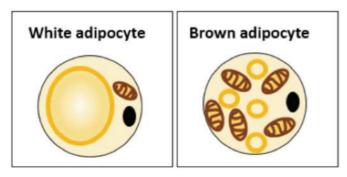


Figure 3: Schematic comparison of white and brown adipocyte. The lighter circles represent lipid droplets and the striped ovals represent mitochondria. The black oval represents the cell nucleus. (Information collated from Reddy NL et al, 2014.¹)

Physiology and activation of BAT

BAT dissipates chemical energy (from food) by uncoupling oxidative phosphorylation from the electron transport chain, thereby inhibiting ATP synthesis and releasing this chemical energy as heat via the uncoupling protein 1 (UCP1), thus and depleting fat stores. BAT has a large quantity of mitochondria (as shown in Fig. 3) that express UCP1 within their inner membrane. BAT is normally activated by cold receptors in the skin that detect reduced external temperatures, by activation of the sympathetic nervous system noradrenaline is released. Noradrenaline activates β_3 adrenergic receptors and stimulates intracellular lipolysis, the released fatty acids activates UCP1, triggering thermogenesis. 9

Currently BAT, although metabolically active in adults, under normal conditions is not activated to its full potential. If BAT activation was increased, more energy could be lost, liberating it from storage and promoting weight loss. The remainder of the review evaluates if BAT is a viable treatment option for obesity by exploring proposed methods of BAT activation and potential pitfalls in current methodological approaches, offering a possible direction for future research.

RESULTS AND DISCUSSION

There are many suggested methods to increase the activity of BAT to augment weight loss. This review evaluates β_3 -adrenergic receptor agonists and cold stimuli in the activation of BAT as they currently appear to be the most promising treatment options. 1,8

Catecholamines and β_3 - adrenergic receptor agonists

BAT is more active in patients with a phaeochromocytoma due to elevated levels of circulating catecholamines (noradrenaline and adrenaline).^{1, 10} Adrenaline and noradrenaline are believed to stimulate UCP1 in BAT, leading to thermogenesis and dissipation of chemical energy, causing weight loss.¹

Despite catecholamines increasing BAT activity, they cannot be used directly, due to lack of receptor specificity (see Fig. 4), leading to multiple side effects. For example, excessive noradrenaline levels cause cardiovascular side effects⁸. Noradrenaline rapidly increases blood pressure by increasing heart rate, stroke volume and vascular resistance by activation of β_1 - and β_1 -receptors.¹¹ This is potentially life-threatening in obese patients, as obesity alone is a major risk factor for hypertension, and can increase the risk of heart failure, stroke and renal failure.¹²

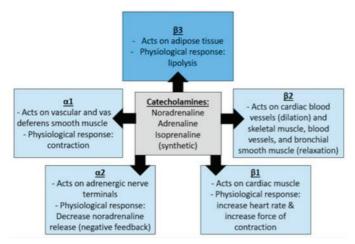


Figure 4: The alpha- and beta- adrenergic receptor subtypes, their location and physiological response to catecholamines. The darker blue box represents the β_3 -AR receptor. (Information collated from Rang HP, 2014. 11)

Consequently, the β_3 - adrenergic receptor (β_3 -AR) is considered a more suitable target due to their specificity towards adipose tissue. Recently, human β_3 -AR agonists have greatly improved in efficacy.¹³ Treatment with β_3 -AR agonist CL 216,243 in humans was shown to have no

significant effect on heart rate or blood pressure and caused no tremors, whilst still potentiating energy metabolism and weight loss. 14

A β_3 -AR agonist was shown to increase resting energy expenditure in otherwise healthy obese men after a single $1000\,mg$ dose. 15 However, when treatment was extended for 28 days with 375 mg of β_3 -AR agonist being administered daily it had no significant effect on energy expenditure or body weight reduction. 16 Explanations for why BAT activity did not respond to chronic administration of β_3 -AR agonists in comparison to a single dose in a human model are explored in Table 1.

Hypothesis	Contradictions/agreements
The dose of β_3 -AR agonist was too low to have a physiological response ¹⁶	The β_3 -AR agonist is considered highly potent, therefore a low dosage is likely to elicit a physiological response ¹⁶
Down regulation of the β_3 -AR ¹⁶	Previous rodent studies showed no β ₃ -AR downregulation with long term administration of β ₃ -AR agonist ¹⁶
Negative feedback mechanisms inhibit lipolysis in response to repeated doses of β ₃ -AR agonists, stopping the activation of UCP1 ¹⁶	In the acute administration group, free fatty acid concentration increased with administration of the β_3 -AR agonist, however this was not seen in the chronic administration group. ^{15, 16}

Table 1: Explanations why energy expenditure increased after a single dose of β_3 -AR agonist (acute administration group) and when the agonist was administered long-term (chronic administration group) there was no change in energy expenditure or body weight. (Information distilled from Baak MA et al, 2002^{15} and Larsen TM et al, $2002^{.16}$)

Prior to use in patients, it needs to be understood if chronic dosing of $\beta_3\text{-}AR$ agonist results in receptor downregulation, activation of compensatory mechanisms, or the study measuring chronic dosing used too low a dose of $\beta_3\text{-}AR$ agonist. To distinguish if the dose of the $\beta_3\text{-}AR$ agonist was too low to activate BAT, the clinical trial (measuring BAT activation in healthy obese men for 28 days) could be repeated, with a higher dosage of $\beta_3\text{-}AR$ agonist. 16

If it is indeed the case that β_3 -AR downregulated in humans, this may suggest that there are different receptor desensitizing mechanisms in humans in comparison to rodents, making the human β_3 -AR more susceptible to downregulation. However, currently there is no literature to support or reject this hypothesis. If the receptor downregulates following repeated β_3 -AR agonist administration in humans these agonists are unlikely to be an effective treatment, as they will have limited long-term effect on weight homeostasis.

It has been a concern that the 'high energy state' formed

by the chronic activation of BAT may lead to the activation of compensatory mechanisms, reducing BAT activation and making long-term BAT activation mediated through any mechanism highly challenging.¹⁷ These mechanisms could include inhibition of lipolysis and/or increased appetite in order to maintain energy homeostasis.^{4, 16} To determine if lipolysis inhibition is affecting treatment efficacy, increased levels of mobilised free-fatty-acids could be released into the patient's bloodstream in order to counteract this inhibition. Potential methods to do this may be endurance exercise or fasting (which may not be practical).¹⁸ There are also concerns that increased BAT activation could stimulate increased patient appetite replacing the calories lost through thermogenesis.¹ In this particular study examining the effect of chronic administration of β_3 -AR agonist, hyperphagia is unlikely to have been a confounding variable as diet was highly controlled and the β_3 -AR agonist had no effect on appetite parameters measured.16

So far, there are limited studies on long-term BAT activation, making it difficult to determine if there is initiation of compensatory mechanisms. It will be imperative to measure blood fatty-acid concentration and/or appetite when these studies are conducted. If lipolysis is inhibited and appetite increased, appropriate exercise regimes and appetite suppressors can be advised alongside treatment in order to override these compensatory mechanisms. However, currently there are no approved appetite suppressors available in the UK.¹

Cold activation

Cold stimuli have been described as the safest and most extensively studied activators of BAT leading to weight loss.¹⁹ Cold stimuli increases sympathetic nervous system signalling to BAT, increasing thermogenesis.^{8, 9} In order to activate BAT through mild cold stimuli, participants need to be exposed repeatedly and frequently to cold conditions.8 This treatment has been described to only be suited for the "very motivated" and may exacerbate the patient's existing comorbidities.²⁰ Despite this, cooling can be mild with temperatures around 18°C for only approximately two hours a day.²¹ This could be a feasible treatment option if the cooling could be conducted in the patient's workplace or home environment, reducing its inference with their everyday lives. It could be argued that cooling is potentially more favourable than some of the current treatment options for obesity, such as Orlistat, which is often associated with diarrhoea, abdominal pain and oily stools.22

In numerous clinical trials, BAT activity was shown to increase in response to chronic cold exposure to different extents. Although there are multiple potential explanations, one important explanation could be due to the different cold exposure protocols used in different studies. If mild cooling is to be a viable treatment option for obesity, reliable cooling protocols would need to be created and matched to the patient's individual characteristics; this is a current area of research.²³ However, in one study BAT activation levels were demonstrated to be independent of age, body weight and fat mass, challenging previous assumptions.²⁴ Thus, in order to truly understand BAT activation, further insight into how it is controlled is

needed, potentially considering other factors such as the gut microbiota.

Potential pitfalls

Most of our understanding about BAT activation and its efficacy as a treatment option has arisen from rodent studies and measurements by positron emission tomography with 2-deoxy-2-[fluorine]-fluoro-D-glucose with computed tomography (¹⁸F-FDG PET/CT). ¹⁸F-FDG PET/CT measures the uptake of glucose showing an area of high metabolic activity.²³ These methods shall be evaluated as they affect the validity of our assumption that activation of BAT can be a treatment for obesity.

Measurement limitations

Despite most studies utilising ¹⁸F-FDG PET/CT, there is no clear methodology to quantify BAT activation due to different threshold values and analysing techniques being used in different studies, making comparisons challenging.²³

A study with improved PET scanning methodology demonstrated BAT activation which had not been previously recognised by conventional PET/CT methods utilised.²⁶ This questions the reliability of previous studies, as perhaps BAT activity was upregulated and it was dismissed as detection methods were not previously sensitive enough.

Methodology to measure BAT activation is not highly specific, for example ¹⁸F-FDG PET/CT levels may increase due to glucose uptake resulting from activation of other tissues with thermogenic potential such as skeletal muscle, potentially leading to misleading data as this energy expenditure may have been falsely attributed to BAT.²⁷ If a more sensitive, specific and standardised way to measure the degree of BAT activation and mass was developed, it would enable more effective comparisons between different studies and more reliable quantification of possible future treatment methods.

Current BAT detection methods have limited sample sizes due to risk of ionizing radiation exposure and expense. Thermal imaging could be a safer, cheaper alternative thus enabling larger sample sizes, and increasing reliability of data. However, there are concerns that, due to the rich vascular supply to BAT, there will be rapid dissipation of heat into the circulation from BAT sites, making BAT heat production challenging to measure. ²⁷

CONCLUSIONS

The belief that activation of BAT will be the cure to the societal issue of habitual overeating and lack of physical activity is over simplified. However, BAT may offer a novel therapeutic target to encourage weight loss and improve metabolic health. Additionally, BAT activation is also associated with improved glucose metabolism and lower blood HbA1c levels.²⁹ This is highly significant as approximately 80% of people with type 2 diabetes are obese or overweight when diagnosed.³⁰ A dual therapy to combat 'diabesity' will be highly relevant.

Based on the assumption that chronic dosing of β_3 -AR agonist does not cause irreversible receptor downregulation and/or irreversible activation of

compensatory mechanisms, the β_3 -AR agonist is likely to be a more effective therapeutic than cold activation. This is because taking a medication would be far less inhibiting and unpleasant for the patient then undertaking frequent cooling.

Progression of BAT activation as a therapeutic solution for obesity is currently being restricted due to limitations in the methodology used to study BAT activation and the lack of standardisation between studies, thus making research results potentially misleading and difficult to quantify and interpret. Research should therefore focus on improving detection methods to study BAT activation and create standardised methodologies, enabling larger clinical trials making data more reliable, with more accurate comparisons between studies as research advances forward. The discovery of human BAT has refuelled interest in the fascinating field of adipose tissue, giving people an appreciation that not all fat is the same. It is imperative that researchers continue their quest to fully understand the activation of BAT and the role that it has on weight homeostasis, as BAT offers unique potential, which should be fully exploited.

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Successful 8th ENT Study Day on 15/03/19 in Lancaster



