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Brown Adipose Tissue (BAT) Activation and Its Potential Utilization as a Treatment Option for Obesity and Diabetes

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Abstract

Within the human body, there are two types of adipose tissue: white adipose tissue (WAT) and brown adipose tissue (BAT). WAT is beneficial for insulation whereas BAT has thermogenic capacity. BAT activation increases energy consumption via heat generation. Increased energy expenditure is associated with improved glucose and lipid metabolism. Therefore, BAT activation research has primarily been aimed at its potential use in the treatment of obesity, diabetes, and other metabolic disorders. In this literature review, BAT's thermogenic mechanisms, techniques of activation, potential therapeutic targets, and future research topics are explored.

Keywords

brown fat, brown adipose tissue, obesity, diabetes

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Within the human body, there are two types of adipose tissue: white adipose tissue (WAT) and brown adipose tissue (BAT). Men and women have been found to differ in WAT levels with men having higher levels of abdominal WAT and women having higher levels of subcutaneous WAT (Cypess et al., 2009) Similarly, BAT has been found to differ between men and women (Cypess et al., 2009). However, this difference has been found to be a higher mass and activity of BAT in women instead of a difference in distribution (Cypess et al., 2009) WAT cells are each composed of one, large lipid droplet surrounded by cytosol and few mitochondria (Betz & Enerbäck, 2018). Conversely, BAT cells are each composed of many, small lipid droplets surrounded by cytosol and large numbers of mitochondria (Betz & Enerbäck, 2018). Further, WAT contain mitochondria like liver mitochondria characterized by metabolism of fatty acids and detoxification (Forner et al., 2009). BAT instead contain mitochondria like muscle mitochondria (Forner et al., 2009). Most importantly, while WAT is beneficial for thermal insulation and protection of internal organs, BAT has thermogenic capacity (Fenzl & Kiefer, 2014). Specifically, BAT contains uncoupling protein 1 (UCP1), which can covert energy stored within BAT as triglycerides into heat (Betz & Enerbäck, 2018).

Until 2009, the major consensus among scientists was that BAT was present in small mammals, including infants, but that it slowly dissipated and became an insignificant level in human adults (Betz & Enerbäck, 2018). These BAT deposits in human infants are primarily located between the scapula and around the kidneys and help infants maintain their body temperature (Jung et al., 2018). However, in 2009, a study of fifty-six individuals aged 23-65 years old conducted by Saito et al. (2009) measured 2-[18F]fluoro-2-deoxyglucose (FDG) uptake

in adipose tissue using positron emission tomography (PET) and X-ray computed tomography (CT). Through this study, it was found that when exposed to cold, some of the individuals had FDG uptake into adipose tissue, which is a potential indicator of BAT presence. This presence was histologically confirmed within these individuals. These findings suggested a role of BAT in body temperature regulation in adult humans and laid the foundation for future research into the role of BAT and possible therapeutic uses for its activation (Saito et al., 2009).

Mechanisms of Thermogenesis in BAT

BAT thermogenesis is stimulated by the sympathetic nervous system primarily in response to cold exposure (Jung et al., 2018). When activated, BAT converts energy from the triglycerides stored within itself directly into heat. This process within BAT has been found to be a major contributor to non-shivering thermogenesis in body temperature regulation (Jung et al., 2018). Non-shivering thermogenesis occurs before shivering thermogenesis and continues after shivering thermogenesis ends (Betz & Enerbäck, 2018). It works by increasing energy expenditure without the induction of shivering (Betz & Enerbäck, 2018). BAT has been found to contribute to 60% of the total energy expenditure in rodents but its role in humans is still being explored (Sanchez-Delgado et al., 2021). There have been many mechanisms suggested for BAT's role in non-shivering thermogenesis (Betz & Enerbäck, 2018).

UCP1's Role in BAT Thermogenesis

UCP1 is unique to BAT cells and is found within the inner mitochondrial membrane of them. Mitochondrial respiration usually requires regeneration of ATP. A proton gradient is built across the inner membrane of the mitochondria by the active movement of electrons, which is coupled to proton transfer into the intermembrane space. Activation of UCP1 allows for the

uncoupling of mitochondrial respiration, which means that heat can be generated without the regeneration of adenosine triphosphate (ATP). The uncoupling of cellular respiration from ATP regeneration via UCP1 allows for maintenance of body temperature at low temperatures. This low-cost mechanism allows for body temperature to be maintained for longer than alternate methods, such as shivering. Although quick heat generation is UCP1's primary role, its activation may also serve as an anti-obesity treatment (Betz & Enerbäck, 2018).

mtGPD's Role in BAT Thermogenesis

BAT contains a higher level of mitochondrial glycerol-3-phosphate dehydrogenase (mtGPD) compared to WAT, which suggests that it may also play a role in the thermogenesis of BAT. mtGPD has a shuttle that allows electrons from NADH in the cytosol to enter the electron transport chain. Within the electron transport chain, these electrons are accepted by FAD instead of the typical NAD+. Because this results in less ATP per electron pair, the mtGPD shuttle is less efficient. This decreased efficiency contributes to thermogenesis via the generation of heat. However, when mtGPD was knocked out within a study, thermogenesis did not become defective. Instead, mtGPD has been found to work synergistically with the UCP1-mediated thermogenesis pathway (Betz & Enerbäck, 2018).

Activation of BAT

BAT activation is primarily used to generate heat via non-shivering thermogenesis which subsequently increases energy consumption (Wu et al., 2014). Specifically, BAT activation causes glucose and fatty acids to be burned at a higher rate than under normal conditions when BAT is inactive (Wu et al., 2014). Therefore, activation of BAT has been identified as a potential treatment for obesity and diabetes mellitus as it could theoretically consume excess fat in obese patients and lower glucose levels in diabetic patients (Wu et al., 2014). However, to successfully

utilize BAT activation as a treatment, ways to reliably activate it must be determined. Some possibilities for the activation of BAT that are being explored are cold exposure, diet, diosmetin, CCL5/CCR5 knockout, leptin activation, and even BAT transplantation (Huang et al., 2012; Betz & Enerbäck, 2018; Osuna-Prieto et al., 2021; Pei et al., 2020; Xie et al., 2021; Chan et al., 2022; Jiang et al., 2020; Payab et al. 2021; Cai et al., 2014).

Cold Exposure Stimulates BAT Activation

Temperature-based activation of BAT is stimulated primarily by a decrease in skin and environmental temperature. From a clinical study exploring the activation of BAT in 1740 patients, Huang et al. (2012) only identified 37 people who showed activated BAT using 18F-fluorodeoxyglucose (18F-FDG) PET/CT scans. Using these results and other published reports, a negative correlation between activated BAT and temperature of the environment of the patient was found. In fact, activated BAT was found to decrease approximately 1% for each 5 ºC increase in outdoor temperature. This study focused wholly on outdoor temperatures, which can be inconsistent and fluctuate (Huang et al., 2012).

Therefore, a better analysis of cold-induced BAT activation would be focused on experimentally controlled temperatures. Participants in a study who had no detectable BAT activation at the beginning of the study, were found to have BAT activation after exposure to 17 ºC for two hours each day for 6 weeks. This increased BAT activation was also associated with an increased oxidative capacity and insulin sensitivity which is a desirable outcome for the potential treatment of obesity and diabetes. However, in a similar study which went one step further and explored the difference of BAT activation in healthy and obese individuals exposed to 15 ºC, found that this activation was much lower in obese individuals. Therefore, cold-induced

BAT activation in the treatment of obesity and diabetes may not be the most efficient method (Betz & Enerbäck, 2018).

Diet-Based Options to Stimulate BAT Activation

Another BAT activation method that is being explored is diet-based. A meta-analysis of plant-based diet components' ability to activate BAT, which included studies on tea extract catechins, resveratrol, capsaicin, cacao flavanols, and quercetin, found that, overall, there is promise in the use of these components in the activation of BAT (Osuna-Prieto et al., 2021). Tea extract catechins promoted BAT activation in 6 of 9 studies, resveratrol in 6 of 8 studies, capsaicin in 4 of 8 studies, cacao flavanols in all 7 studies, and quercetin in 1 of 6 studies (Osuna-Prieto et al., 2021). Despite appearing as the least effective in the meta-analysis, a quercetin experiment in another study (Pei et al., 2020) counters this, exemplifying the need for further study in diet-based BAT activation.

Quercetin in the Stimulation of BAT Activation

In Pei et al. (2020), quercetin was found to both activate BAT as well as promote the browning of white adipose tissue (WAT). In fact, mice who were fed a high-fat diet supplemented with 1% quercetin (HFDQ) had a 6% reduction in weight compared to mice that were just fed a high-fat diet (HFD). Further, the HFDQ-fed mice showed an upregulation of the UCP1 gene in comparison to the HFD-fed mice indicating that both browning of WAT and activation of BAT were upregulated with quercetin supplementation. Pei et al. (2020) suggests, however, that quercetin may directly activate UCP1 and fatty acid oxidation instead of activating BAT because energy expenditure and body temperature remained constant between experimental groups despite the upregulation of UCP1. Therefore, while quercetin may be a possible treatment

for obesity and diabetes, it may not have a mechanism involving BAT activation (Pei et al., 2020).

Diosmetin in the Stimulation of BAT Activation

Xie et al. (2021) explored the potential of diosmetin, a natural flavonoid, to protect against obesity and metabolic disorders in mice via an experiment where mice received 50 mg kg^{-1} diosmetin or a placebo daily. After four weeks of treatment, the mice that received diosmetin already had significantly lower body weight than control mice. After the full 8 weeks of treatment, diosmetin-treated mice were found to have an average bodyweight 18% lower than the mice given placebos. Further, diosmetin-treated mice exhibited an increased sensitivity to insulin, supporting its ability to be a protective factor for diabetes. Most notably, diosmetin-treated mice showed higher levels of UCP1 in BAT, indicating enhancement of BAT activation and solidifying diosmetin as a viable option for further studies regarding activation of BAT in humans for the treatment of obesity and diabetes (Xie et al., 2021).

CCL5/CCR5 Knockout Stimulates BAT Activation

Another approach to activating BAT that has been explored is the knockout of chemokine ligand 5 (CCL5) and its receptor CCR5, which are known to be abundant in WAT and linked to inflammation and insulin resistance. Chan et al. (2022) found a strong positive correlation between the presence of CCL5 and CCR5, weight of WAT in mice given a high fat diet (HFD), and the size of lipid droplets, indicating that knockout mice had protection against obesity due to the lack of CCL5 and CCR5. From this, the experimenters suggested that CCL5/CCR5 signaling may regulate energy use in adipose tissue. Knockout mice and wildtype mice were also exposed to cold to examine any differences in cold tolerances given the lipid droplet size disparity between the two groups. Each group was split in half, with half of each group staying at room

temperature and the other half being exposed to 4 ºC temperature for 11 days. Cold exposure resulted in significantly higher body weight loss in knockout mice than wildtype mice at the end of the 11 days. Wildtype mice also experienced a significantly larger drop in core temperature than the knockout mice, indicating that knockout mice were more cold tolerant. Further exploration was also conducted into the ways that the knockout of CCL5/CCR5 might impact metabolism and inflammatory pathways (Chan et al., 2022).

Deletion of CCL5/CCR5 was linked with both an increase in the expression of genes necessary for lipid metabolism and an inhibition of inflammatory pathways during cold exposure. More notably, at room temperature, knockout mice had significantly upregulated levels of UCP1 within BAT whereas wildtype mice had barely detectable levels. Given UCP1's role in BAT activation, this indicates that knockout of CCL5/CCR5 may be a viable possibility to increase BAT activation in a clinical setting. Further exemplifying the viability of CCL5/CCR5 clinically, the increased lipid metabolism found within experimentation may be especially beneficial in the treatment of obesity (Chan et al., 2022).

Leptin and Sh2b1 Stimulate BAT Activation

Leptin is a hormone that is released from adipose tissue, which is a major regulatory of weight and metabolism. Therefore, disruption of leptin signaling results in obesity and metabolic disease, but its pathway is widely unknown. Knockout of Sh2b1, which enhances the activity of leptin, explored possible pathways of leptin and its effects within the body. Deficiency in Sh2b1 was found to cause mice to develop obesity, insulin resistance, and liver steatosis. Further, Sh2b1knockout stopped leptin's ability to stimulate BAT via sympathetic nerves, leading to BAT dysfunction. This contributed to a reduced core body temperature in addition to the increased incidence of obesity, type 2 diabetes, and liver steatosis. The exact mechanism

between leptin, Sh2b1, the sympathetic system, and BAT remains unknown but is a vital relationship given the detrimental effects of knocking out part of the pathway (Jiang et al., 2020).

BRL37344 Stimulates BAT Activation

Wu et al. (2014) explored the use of a β3 adrenergic agonist called BRL37344 in the activation of BAT in mice. All mice began the experiment healthy and had no significant differences in BAT deposits at the baseline imaging. Obesity and diabetes mellitus were induced in some of the mice. Images were taken again, which showed a decrease in BAT deposits in the obese mice and mice with diabetes mellitus compared to the healthy mice. Eight obese mice, six mice with diabetes mellitus, and six control mice were injected with BRL3744 three times a week for two weeks with dosage based on their weight. Nine mice received no treatment and were monitored for control purposes. After the two weeks of treatment, BAT deposits within obese mice and mice with diabetes mellitus were found to be significantly increased. Further, BRL37344 treatment in the healthy mice also served to increase BAT deposits. BRL37344 may serve as a potential activator of BAT for both treatment and a prevention method (Wu et al., 2014).

Transplantation of BAT Stimulates BAT Activation

Perhaps the most revolutionary option for increased activation of BAT activity currently being explored is the direct transplantation of BAT. Payab et al. (2021) conducted a systematic review of literature on BAT transplantation. Based on the 10 studies which made it into the final review, BAT transplantation was found to reduce weight gain and decrease adipose tissue hypertrophy even in mice that were fed high fat diets overall. BAT transplantation has also been associated with reduced size of WAT and liver mass. It has also been suggested that BAT transplantation both enhances glucose homeostasis and tolerance as well as reverses clinical

signs of diabetes. However, despite these appealing findings, BAT transplantation has been found to have varying success based on the location of transplantation (Payab et al. 2021).

Cai et al. (2021) evaluated the success of BAT transplantation based on subcutaneous versus sub-muscular placement of BAT. Findings indicated that location of transplantation drastically changes the outcome of BAT transplantation success. In fact, subcutaneous grafts were found to have features of WAT and oil cysts after 16 weeks compared with sub-muscular grafts retained normal BAT features. Mice with sub-muscular grafts also did not gain as much weight as those who underwent subcutaneous grafting. Further, while initially both graft groups showed a decrease in blood glucose levels, only those who received the sub-muscular grafts maintained low blood glucose levels for the entire 16 weeks whereas mice who received subcutaneous grafts showed a gradual increase back to levels of the control mice. Evidently, while BAT transplantation is a promising treatment for obesity and diabetes, attention must be given to the most advantageous location for successful BAT activation (Cai et al., 2014).

Possible Therapeutic Targets of Brown Adipose Tissue (BAT)

Increased energy expenditure is associated with increased heat generation. BAT thermogenesis therefore has a primary role in the maintenance of body temperature. More importantly, the increased energy expenditure produced by the activation of BAT has also been shown to improve glucose and lipid metabolism. Further, BAT has been found to play an endocrine function via BATokines, which are adipokines released from BAT. These BATokines have been found to contribute further to improvements in metabolism when BAT is activated. These metabolic improvements and increased energy expenditure via BAT activation could be applied to the treatment of obesity and diabetes, both of which would benefit from improved glucose and lipid metabolism (Osuna-Prieto et al., 2021).

Therapeutic Possibility of BAT Activation in Obesity

Deng et al. (2017) found that MRIs of BAT could differentiate between the obese and nonobese individuals within their study. They found that generally, nonobese individuals had higher levels of active BAT. Only one obese individual had high amounts of BAT, but the activation capacity of this BAT was less in comparison to the nonobese individuals. This indicates that the activation of or transplantation of BAT into obese individuals could lead to a lower weight (Deng et al., 2017).

In support of this, BAT transplantation has tended to decrease triglycerides, total cholesterol, and low-density lipoprotein (Payab et al., 2021). All of these are typically elevated in obese individuals, supporting the potential of BAT transplantation to counter these elevated lipids within obese individuals (Payab et al., 2021). Further, BAT transplantation has been found to lower pro-inflammatory genes and increase anti-inflammatory genes. Inflammation plays a major role in both obesity and diabetes (Payab et al., 2021). Therefore, decreasing inflammation would have a positive therapeutic effect on the treatment of obesity and its associated diseases (Payab et al., 2021). Activation of BAT would be a less invasive and yet still effective way to combat obesity too. BAT activation alone has been found to increase oxidative capacity and decrease body fat mass (Betz & Enerbäck, 2018).

Wu et al. (2014) found that injections of BRL37344 significantly decreased the weight of obese mice compared to control mice. This significant decrease in body weight correlated directly with an increase in BAT deposits within treated mice. From this, it appeared that BRL37344 injections increased BAT deposits and increased the activity of those BAT deposits, making it a potential treatment of obesity (Wu et al., 2014).

Therapeutic Possibility of BAT Activation in Diabetes

Increased BAT and BAT activation has also been associated with increased insulin sensitivity and decreased body fat mass, making it a potential treatment for diabetic individuals (Betz & Enerbäck, 2018). Enhanced energy expenditure, which is possible through BAT activation, has also been associated with improved glucose homeostasis and adipose tissue inflammation (Xie et al., 2021). Further, individuals with higher levels of BAT have been found to correlate with lower incidences of type 2 diabetes, dyslipidemia, coronary artery disease, cerebrovascular disease, congestive heart failure, and hypertension (Becher et al., 2021). Increased BAT and BAT activation has correlated with higher metabolic health due to its tendency to lessen inflammation and improve blood glucose, so it could therefore contribute to an innovative treatment for diabetes (Omran & Christian, 2020; Becher et al., 2021).

Wu et al. (2014) found that BRL37344 injections correlated with an increase in BAT deposits in mice with diabetes mellitus compared to control mice. After two weeks of treatment with BRL37344, the mice with diabetes had significantly lower level of fasting glucose levels compared to before treatment began. Therefore, fasting glucose levels were found to negatively correlate with BAT deposits and BAT activation via BRL37344 injections, indicating a potential for treatment of diabetes mellitus (Wu et al., 2014).

The Future of BAT Research

Questions remain about BAT, involving localization, the BATokines that it releases, and whether there are adverse effects within the body especially with transplantation. For a long time, it was accepted that BAT location in humans was similar to BAT location in mice. However, BAT is in the subcutaneous area below WAT in mice and beneath the trapezius muscle in humans. Therefore, this raises the possibility of further localizations of BAT in

humans that is inconsistent with mice BAT localization. BAT has been found to release numerous factors that play various endocrine functions. Further research into the role of known BATokines released and the exploration of novel BATokines would be beneficial among future studies. Finally, it is vital that exploration is focused on transplantation occurring in the most beneficial areas and that BAT is not overactivated. Overactivation has been found to exacerbate diseases related to atherosclerotic plaques (Nishio & Saeki, 2020). Taking these remaining mysteries into account, future studies have the potential to identify revolutionary novel treatments for obesity, diabetes, and other metabolic conditions.

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