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REVIEW ARTICLE

Effects of Brown Adipose Tissue on Human Metabolism and Weight Loss

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ABSTRACT

***BACKGROUND:** Obesity has become an important public health threat that is not contagious but spreads the fastest and affects all physiological functions of the body. Brown adipose tissue, one of these strategies, is found in infancy and is thought to disappear with maturation in adult humans and has an important place in energy expenditure.*

***METHODS:** The literature search was made in databases such as "Academic Google", "Web of Science", "PubMed" and "Ulakbim".*

***RESULTS:** The relative rediscovery of active brown adipose tissue in adult humans has sparked interest in this tissue as a new and viable target to stimulate energy expenditure and control body weight by promoting energy distribution. Studies have shown that BAT activation is increased by estradiol, berberine, melatonin, allicin, leucine, butyrate, fish oil, thyroid hormone and chronic exercise, and sympathetic stimulation is provided.*

***DISCUSSION:** Considering the current literature on the relationship of leptin to brown adipose tissue, the findings suggest that cold-induced BAT activation can reduce 'leptin resistance' in overweight / obese participants. Conclusion: We anticipate that BAT will be used as an alternative method to obesity and metabolic surgery in the future.*

***KEY WORDS:** Adipose tissue, brown adipose tissue, UCP-1, energy*

INTRODUCTION

There are two types of adipose tissue in rodents and humans. These are white adipose tissue (WAT) and brown adipose tissue (BAT). A subtype of adipocyte called "beige" or "brite" (white-brown) adipocytes has been identified in both rodents and humans. BAT is a thermogenic tissue that functions to generate heat in response to cold exposure. It is characterized by high levels of mitochondria, multilocular lipid droplets, high degree of vascularization and sympathetic innervation (1).

BAT activity is very beneficial for mammalian metabolism, considering that it reduces weight gain, improves glucose tolerance and insulin sensitivity, reduces the risk of Type 2 diabetes, lowers free fatty acid levels and high triglycerides in serum, reduces hypercholesterolemia and provides protection (2).

BAT is located in the supraclavicular, paravertebral, cervical, axillary and mediastinal regions in adults. It regulates energy homeostasis by using sources such as fatty acids and glucose, and alsplays an important role in glucose and

lipid metabolism. TNF-α secretes cytokine and hormone-like molecules required for cold adaptation and adrenergic stimulation such as adiponectin, leptin, fibroblast growth factor 21 (FGF-21) (3).

MATERIALS AND METHODS

The literature search was made in databases such as "Academic Google", "Web of Science", "PubMed" and "Ulakbim". The selection of keywords was made on the basis of MesH (medical subject heading) terms and English keywords. The purpose of this review is answer the question "How does brown adipose tissue affect human metabolism and weight loss?"

RESULTS AND DISCUSSION

Adrenergic Stimulation of Thermogenesis and Involvement of UCP1

The capacity of brown adipose tissue to influence energy efficiency is due to its unique ability to dissipate energy as heat and to the expression of uncoupling protein 1 (UCP1) found in brown adipocytes (4). UCP1 is located in the inner membrane of the mitochondria of BAT cells. It separates mitochondrial respiration from ATP synthesis. When activated, BAT causes a leak across the inner mitochondrial membrane during fatty acid oxidation. This leakage results in conversion to ATP by ATP synthase. In conclusion, the presence of active UCP1 leads to a very high rate of fatty acid oxidation that directly generates heat, eliminating the negative feedback inhibition exerted by high ATP and low ADP levels in the mitochondrial Krebs cycle and respiration (5). In situations that require an increase in body temperature, the sympathetic nervous system activates it by secreting norepinephrine (NE) in the brown adipose tissue, close to the postganlionic nerve endings as summarized in Figure 1.

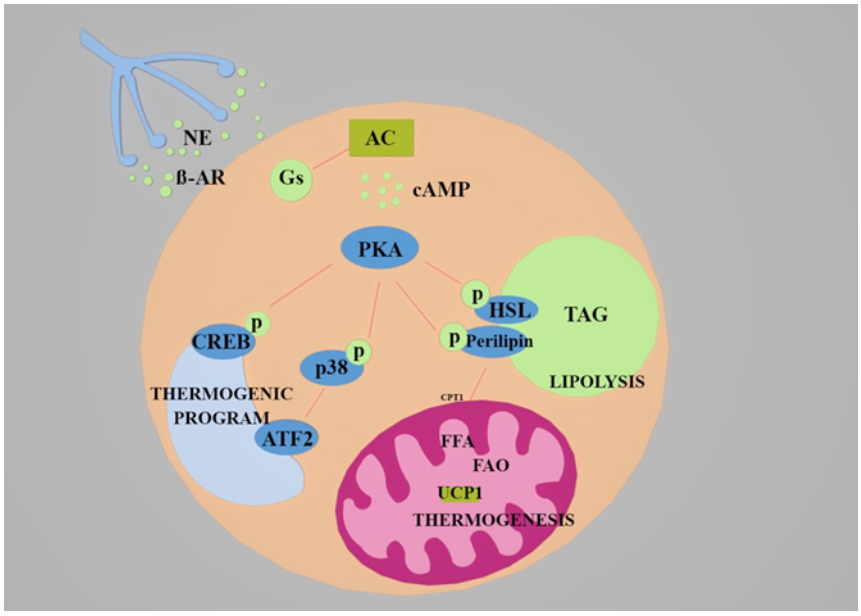

Fig.1. Adrenergic stimulation of thermogenesis.

(AC, adenylate cyclase; ATF2, activating transcription factor 2; CPT1, carnitine palmitoyltransferase 1; CREB, cAMP response element binding protein; FAO, fatty acid oxidation; Gs, Gs a subunit; HSL, hormone-sensitive lipase; NE, norepinephrine; p, phosphate group; PKA, protein kinase A; p38, p38 mitogen-activated protein kinase; TAG, triacylglycerol; UCP1, uncoupling protein 1; b-AR, b-adrenergic receptor.

Norepinephrine promotes intracellular signaling chain by binding to the b3-adrenergic receptor (b3AR) located on the surface of brown adipocytes. Activation of brown adipose tissue requires the mobilization of energy through lipolysis. β3AR binding stimulates cAMP production by adenylate cyclase (AC). Increasing intracellular concentrations of cAMP activates protein kinase A (PKA). PKA; It phosphorylates hormone sensitive lipase (HSL) and perilipin, stimulatind triglyceride hydrolysis. The released fatty acids (FFA) are then transferred to the mitochondria via carnitine palmitoyltransferase 1 (CPT1). In mitochondria, free fatty acids (FFA)activate UCP1 and fatty acid oxidation produces cofactors for the electron transfer chain. UCP1 uses the proton gradient created by ETC to generate heat and therefore dissipates energy (6).

BAT and Glucose Metabolism

In one study, embryonic BAT was transplanted into immunocompetent or deficient mice with severely impaired glucose tolerance and dramatic losses in WAT. Increased BAT has been shown to improve fasting glucose and normalized glucose tolerance, reduce adipose tissue inflammation, and reverse several clinical markers of diabetes, including polyuria, polydipsia, and polyphagia, over a 6-month period post-transplant. Circulating insulin- like growth factor 1 (IGF-1), leptin, and adiponectin were increased as a result of BAT transplantation (1). Since IGF-1 directly activates the insulin receptor, researchers hypothesize that BAT-releasing IGF-1 is the primary mechanism for improving glucose homeostasis. BAT mediates the release of various batokines that act in an endocrine manner to improve metabolic health (7). These batokines are Fibroblast growth factor 21 (FGF21), interleukin-6 (IL-6), insulin growth factor 1 (IGF-1), neuregulin 4 (NRG4). FGF21 has the functions of increasing glucose uptake in adipose tissue and fatty acid oxidation in the liver. It has been seen that BAT regulates the expression and release of FGF21 and induces thermogenic gene expression simultaneously with cAMP-related mechanisms (8). IL-6 has been implicated as a proinflammatory cytokine linked to certain disease states and pathological mechanisms. It has been observed that both exposure to cold and noradrenergic stimulation of BAT increases IL-6 gene expression and secretion. NRG4 is the most abundant batokine in BAT. It is thought that when released from BAT it targets the liver and increases hepatic fatty acid oxidation and suppression of de novo lipogenesis, so it may potentially protect against nonalcoholic fatty liver disease (1).

BAT and Insulin

Under thermoneutral conditions and after prolonged (5-8 hours) exposure to cold (CE) on 7 BAT positive (BAT +) male and 5 BAT negative (BAT-) male, CE showed resting energy consumption, glucose in the whole body, only in the BAT + group. These results indicate a physiologically important role of BAT in human whole-body energy expenditure, glucose homeostasis, and insulin sensitivity, and support the idea that BAT may function as an anti-diabetic tissue in humans (9).

BAT and Obesity

Catecholamine resistance in obesity is characterized by decreased synthesis of norepinephrine and beta-adrenergic (β-AR) receptors and defective intracellular signaling that inhibits protein kinase A (PKA)-mediated cell proliferation. Obesity increases the infiltration of M1 macrophages, which participate in norepinephrine clearance and contribute to the synthesis of proinflammatory cytokines. NF-κB-mediated signaling inhibits the PKA proliferation pathway and suppresses PPARγ and C/EBPs gene expression, which inhibits differentiation and adipogenesis. In addition, TNF-α overexpression triggers cellular apoptosis. The unfolded protein response (UPR) in the endoplasmic reticulum plays a dual role in brown adipocyte differentiation according to the intensity of the signal. Activation of all three branches of the UPR (IRE-1, ATF6 and PERK)

is required for differentiation, while excessive UPR activation (which can be found in severe obesity) triggers proapoptotic mechanisms. Similarly, reactive oxygen species (ROS) are hormetic regulators of cell differentiation and apoptosis. Physiological ROS concentrations promote differentiation-inducing C/EBP expression, while super physiological concentration induces oxidative stress and apoptosis via Wnt signaling (10).

BAT and Estradiol

Estrogen plays an important role in regulating energy homeostasis. Estradiol replacement therapy has been shown to prevent obesity by reducing nutrition and increasing energy expenditure (11). The same hormone replacement therapy is known to reverse the development of obesity and metabolic disorders in postmenopausal women. It has been observed that central estradiol regulates BAT thermogenesis and activation of the sympathetic nervous system by modulating the hypothalamic AMP-activated protein kinase (AMPK), especially in the ventromedial nucleus of the hypothalamus. In a study in rats, estradiol was found to provide weight loss regardless of food. An increase in body temperature was associated with elevated UCP1 protein levels in BAT and a significant increase in skin temperature surrounding interscapular BAT, suggesting increased thermogenesis (12).

BAT and Berberine

Berberine, an active product isolated from a medicinal plant Rhizoma Coptidis, is widely used as an antidiarrheal drug and has also been reported to have antidiabetic and antihyperlipidemic effects in humans. Increased BAT activity is closely associated with metabolic improvement such as weight loss, reduced inflammation, and increased insulin sensitivity. It has been reported that AMPK activation in white adipose tissue of animals given berberine is not as pronounced as in brown adipose tissue. Therefore, the clinical application of berberine in the fight against obesity-related metabolic disorders is shown as promising potential (13).

BAT and Melatonin

Melatonin is a nocturnal pineal hormone that plays a critical role in synchronizing circadian rhythms with known metabolic effects in many animal species. In a study, BAT amounts and activities were compared with 18F-FDG PET method in three experimental groups of Wistar rats (control group, pinealectomy group and pinealectomy group replaced with melatonin) after exposure to room temperature and acute cold. Compared with the other groups, the acute thermogenic capacity was decreased in the pinealectomy group, and also, the expression of UCP1 mRNA was decreased (14).

BAT and Allicin

Allicin is the main bioactive substance of garlic and has many pharmacological functions, including antioxidative stress, antitumor and cholesterol-lowering effects, anti-platelet aggregation, liver protection, cardiovascular disease prevention, and anti-inflammatory capacity (15).

The role of allicin in obesity and energy metabolism was evaluated in a study on high-fat diet-induced obesity and obese mouse models with hereditary leptin receptor deficiency. Allicin treatment improved glucose tolerance and insulin responses, with marked reductions in serum profiles including total cholesterol, triglyceride, low-density lipoprotein (LDL) and non-esterified fatty acid (NEFA) levels. These results show that allicin significantly improves adiposity and maintains glucose homeostasis in mice. Allicin increases whole body energy expenditure by activation of brown adipose tissue. Mice treated with allicin have been shown to have significantly increased oxygen consumption, have higher energy expenditure, induce the expression of genes involved in thermogenesis and energy expenditure, including UCP1, PRDM16, PGC1α/β in BAT, and reduce adiposity in mice. The results clearly demonstrated that the antiobesity role of allicin is more dependent on BAT activation (16).

BAT and Leucine

Chronic leucine supplementation has been shown to promote UCP-1 protein expression in BAT and reduce body weight and fat mass in diet-induced, obese and high-fat/cholesterol diet-fed mice. In contrast, chronic leucine supplementation showed that BAT did not alter UCP-1 expression in the low-fat diet model. Acute leucine administration has been shown to increase circulating insulin and glucose uptake in skeletal muscle. Based on these findings, it was concluded that leucine can increase glucose uptake in BAT through an insulin-mediated route. Stimulation of BAT with leucine can be effective in insulin-resistant conditions (17).

BAT and Butyrate

Studies show that butyrate induces peroxisome proliferator-activated receptor-γ coactivator-1α activity, thereby enhancing mitochondrial function in BAT and significantly promoting energy expenditure. Clinical studies have reported that dietary fiber, namely oligofructose, increases the production of endogenous butyrate and a decrease in energy intake accordingly. Butyrate activates BAT and increases the oxidation of intracellular fatty acids, resulting in a compensatory flux of TG-derived fatty acids. Data from studies show that butyrate also induces sustained satiety and increases fat oxidation, thus effectively preventing diet-induced obesity, insulin resistance, hypertriglyceridemia, and hepatic steatosis without causing any obvious adverse effects. Therefore, oral butyrate administration is recommended as a promising strategy to combat obesity and related cardiometabolic diseases (18,19).

BAT and Fish Oil

In vivo evidence suggests that fish oil activates TRPV1 in the gastrointestinal tract, causing adipose thermogenesis by stimulating sympathetic nerves that innervate fat cells. Activation of AMPK in adipocytes and secretion of apelin are also involved. Numerous studies have shown that feeding rodents with n-3 polyunsaturated fatty acids reduces adiposity. Also, meta-analyses of human diet intervention studies suggest that fish oil (eicosapentaenoic and docosahexaenoic acid) supplementation can reduce waist circumference. A recent study also suggests that browning of white fat stores and activation of respiration in brown fat contribute to these effects. Findings combined with observations in rodents suggest that fish oil may also increase human energy expenditure through activation of thermogenic fat cells (20).

BAT and Thyroid Hormones

Two forms of thyroid hormones, thyroxine (T4) and its active metabolite triiodothyronine (T3), regulate metabolic processes that control energy use. Especially in brown adipose tissue, the T3 form induces thermogenesis by inducing metabolic inefficiency through the induction of mitochondrial spacer protein (UCP1). It is known that during cold exposure, sympathetic stimulation of BAT increases DIO2 expression and increases intracellular T3 concentration. It has been observed that T 3 stimulates thermogenesis by increasing Ucp1 transcription and lipid metabolism in BAT (21).

BAT and Chronic Exercise

In a study examining the ability of chronic exercise to produce energy and improve insulin sensitivity and glucose uptake in brown adipose tissue (BAT). Male Wistar rats were included in a control group and exercise-tested rats (on a motorized treadmill (five times a week for 50 minutes) for 8 weeks). Exercise has been shown to reduce body weight, plasma insulin and oxidized LDL concentrations.In exercise BAT, sirtuin 1 (SIRT1), peroxisome proliferator-activated receptor γ coactivator 1α (PGC1α) and AMP-activated protein kinase (pAMPK) / AMPK ratio) also increased the expression of carnitine palmitoyltransferase II (CPT II), mitochondrial F1 ATP synthase α-chain, mitochondrial malate dehydrogenase 2 (mMDH) and cleavage protein (UCP) 1,2,3 in BAT. It has been reported that chronic exercise can improve the energy profile of BAT in terms of increased mitochondrial function and insulin sensitivity (22).

Effects of Diet on Brown Adipose Tissue in Humans

Rats fed a diet low in protein and high in carbohydrates had increased resting energy expenditure through BAT activation. It is also thought that it may increase cold tolerance by increasing mitochondria in BAT in rodents fed a high-fat diet. This result is partially explained by the evidence that mice fed a ketogenic diet (i.e., high-fat, adequate protein, and low-carb) can double the total number of mitochondria in BAT and UCP1 expression (23). In another study, an 8-week ultra-low-calorie diet reduced the browning formation of subcutaneous white adipose tissue in obese individuals, as measured by UCP1 mRNA. Because of its major homeostatic role in food intake and metabolism, leptin can be considered as an index for measuring BAT activity and the thermal energy of the diet (24). Also, in one of the meta-analyses, it was noticed that the lower the ambient temperature, the higher the resting metabolic rate in response to chronic food consumption. It is thought that the higher resting metabolic rate in cold environments can be explained by higher BAT activity due to cold exposure (23). Therefore, environmental temperature should also be considered in BAT activity measurements in response to food or resting metabolic rate measurements to assess diet-induced thermogenesis (25).

BAT and Polyphenols

Curcumin is a yellow pigment found in the spice turmeric and is also found in the curry spice popular in Indian cuisine. Daily administration of 50 or 100 mg of curcumin/kg to rats for 50 days has been shown to reduce body weight and fat mass, and improve tolerance to cold. It has also been reported to stimulate mitochondrial biogenesis and protein expression of thermogenic genes (UCP1, PGC-1a, PPAR-G and PRD16) in primary adipocytes derived from subcutaneous white adipose tissue (26). The effects of resveratrol on BAT metabolism suggest that treatment of both mice (400mg / kg bodyweight over 8 weeks) and Sprague-Dawley rats (30mg / kg bodyweight for 8 weeks) significantly increased UCP1 and SIRT1 gene expression found in BAT. supported by other studies. A direct effect of flavon-3-ols on BAT has been observed in mice with increased expression of UCP1 after chronic supplementation of cocoa procyanidins (27). Dietary supplementation with 0.5% or 2% cocoa procyanidin (corresponding to an extremely high dose) for 13 weeks has been observed to increase the phosphorylation of AMPK in liver, brown adipose tissue, white adipose tissue, and skeletal muscle and reduce the incidence of obesity (28). Gallic acid is a hydroxybenzoic acid found in significant amounts in red wine, tea, and some fruits. Intraperitoneal administration of gallic acid (10 mg/kg body weight) for 9 weeks has been reported to improve glucose and insulin balance and reduce body weight gain without affecting food intake. An effect on the balance between energy intake and energy expenditure is supported by increased expression of thermogenesis-related genes (UCP1,PGC-1a and 3bAr) in brown adipose tissues of treated mice (29). Also, these increased effects are associated with AMPK phosphorylation and SIRT1 and PGC-1a protein levels, suggesting that gallic acid plays a role in the activation of the AMPK-SIRT1-PGC1a axis (26).

BAT and Appetite

In rodents, many circulating peptides show that BAT influences metabolic regulation, while BAT (sometimes referred to as the "intrascapular gland") secretes signaling molecules that can affect metabolic regulation in other tissues. While studies in humans have also reported the effect of thyroid hormones, beta-adrenergic agonists, glucocorticoids, and insulin on BAT metabolism, data from rodent studies support a link between BAT and peptides secreted from the gastrointestinal tract (GI) involved in appetite regulation (30). However, the relationship (if any) between BAT and key peptides involved in energy homeostasis and appetite regulation is unknown in humans (31). A study of 18 men in thermoneutral conditions and with mild cold (CE) exposure hypothesized

that BAT would be associated with lower systemic concentrations of leptin, ghrelin, and glucagon. Results from the study support that BAT volume is significantly associated with lower leptin, gastric inhibitory polypeptide (GIP) and glucagon concentrations during thermoneutrality, regardless of age and adiposity. When mild CE was used to activate BAT thermogenesis, serum leptin and glucagon concentrations decreased compared to thermoneutral conditions. CE suppresses leptin production in brown adipocytes, while BAT atrophy increases leptin secretion (30). Considering the available literature on the link of leptin to BAT, the findings suggest that cold-induced BAT activation may reduce "leptin resistance" in overweight/obese participants. In addition, BAT volume was associated with greater suppression of serum ghrelin concentration during CE, regardless of age and lubrication. Overall, these results support the link between BAT and peptides involved in basic GI and appetite regulation and energy homeostasis, suggesting a potential endocrine role for BAT in humans (30,32).

CONCLUSION

Increased BAT activation has been shown to improve fasting glucose, glucose tolerance and reverse many clinical manifestations of diabetes. In addition, insulin sensitivity increased significantly with energy expenditure in the whole body. Therefore, we anticipate that in the future, BAT will be used as an alternative method to obesity and metabolic surgery, suppressing appetite and helping weight loss.

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