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Brown and Beige Adipose Tissue Activation as a Therapeutic Strategy in Obesity and Diabetes

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ABSTRACT

Obesity and type 2 diabetes mellitus (T2DM) have reached epidemic proportions globally, contributing significantly to the burden of chronic metabolic diseases. Central to these disorders is an imbalance between energy intake and expenditure, often associated with excessive white adipose tissue (WAT) accumulation and impaired glucose metabolism. In contrast to WAT, brown adipose tissue (BAT) and beige adipocytes possess thermogenic properties that can dissipate energy as heat via uncoupling protein 1 (UCP1), thereby enhancing energy expenditure and improving metabolic homeostasis. Recent advances have rekindled interest in exploiting BAT and beige fat activation as therapeutic strategies for combating obesity and T2DM. This review summarizes the developmental origins, molecular regulation, and functional differences between brown, beige, and white adipose tissues. We discuss the mechanisms by which BAT and beige fat are activated, including cold exposure, β-adrenergic signaling, exercise, and pharmacological agents. Furthermore, we evaluate preclinical and clinical evidence supporting the role of thermogenic adipocytes in improving insulin sensitivity, glucose tolerance, and lipid profiles. Finally, we highlight emerging therapeutic strategies aimed at modulating adipose plasticity and thermogenesis, as well as the challenges and future directions in translating these findings into effective interventions. Targeting BAT and beige fat represents a promising, multifaceted approach to addressing obesity-related metabolic dysfunction.

Keywords: Brown adipose tissue, Beige adipocytes, Thermogenesis, Obesity, Type 2 diabetes mellitus

INTRODUCTION

The global prevalence of obesity and type 2 diabetes mellitus (T2DM) continues to escalate at an alarming rate, emerging as a major public health crisis with profound socioeconomic consequences[1–4]. According to recent estimates from the World Health Organization, over 650 million adults worldwide are classified as obese, and more than 500 million people are living with diabetes, the majority of whom have T2DM[5]. These chronic metabolic disorders significantly increase the risk of cardiovascular diseases, renal dysfunction, neuropathies, and other life-threatening complications, imposing a substantial burden on healthcare systems globally[6–9]. The pathogenesis of obesity and T2DM is multifactorial, with contributions from genetic, environmental, behavioral, and metabolic factors. Central to their development is a chronic energy imbalance, where caloric intake consistently exceeds energy expenditure, leading to excess fat accumulation and impaired glucose metabolism.[2, 10]

Historically, adipose tissue was regarded merely as a passive reservoir for energy storage, primarily composed of white adipocytes specialized in the storage of triglycerides[11, 12]. However, advances in metabolic research have drastically reshaped this perception, revealing that adipose tissue is a highly dynamic and heterogeneous endocrine organ[13–15]. It not only stores lipids but also secretes a range of adipokines and cytokines that influence appetite regulation, insulin sensitivity, inflammation, and whole-body energy homeostasis. Within this complex adipose tissue landscape, brown adipose tissue (BAT) and beige adipocytes have garnered considerable attention for their unique thermogenic properties and potential metabolic benefits[16–18].

BAT is characterized by multilocular lipid droplets, dense vascularization, and an abundance of mitochondria, which express uncoupling protein 1 (UCP1). UCP1 disrupts the proton gradient in the mitochondrial inner membrane, leading to the dissipation of energy as heat in a process known as non-shivering thermogenesis[19]. This thermogenic capacity enables BAT to burn calories and generate heat, particularly in response to cold exposure or β-adrenergic stimulation. Beige adipocytes, on the other hand, are inducible thermogenic cells that

arise within white adipose depots under certain stimuli such as chronic cold exposure, exercise, or pharmacological agents. Like classical brown adipocytes, beige cells also express UCP1 and exhibit thermogenic activity, albeit to a lesser extent under basal conditions[20].

The discovery of metabolically active BAT in adult humans once believed to exist only in infants—has revolutionized the understanding of human adipose biology[21]. Imaging studies using ^18F-fluorodeoxyglucose positron emission tomography/computed tomography (^18F-FDG PET/CT) have confirmed the presence of functional BAT in adult individuals, with higher BAT activity associated with improved insulin sensitivity, lower body mass index (BMI), and better lipid profiles[21]. Furthermore, the realization that beige adipocytes can be recruited within white fat depots has opened exciting new avenues for therapeutic strategies aimed at enhancing energy expenditure. This process of "browning" white adipose tissue holds significant promise for combating obesity and metabolic dysfunction by converting energy-storing fat into energy-burning fat[21].

Given the compelling evidence of the beneficial metabolic effects of BAT and beige adipose tissue, considerable research efforts have been directed toward elucidating their cellular and molecular mechanisms, regulatory pathways, and interactions with other metabolic organs. Strategies to activate or increase the mass of thermogenic adipocytes either through lifestyle interventions, pharmacological agents, or gene-based therapies—represent a novel frontier in the treatment of obesity and T2DM[22]. This review comprehensively explores the biological characteristics of brown and beige adipose tissue, their roles in energy metabolism, and the therapeutic potential of targeting these fat depots in metabolic disease management. Understanding the intricate biology of these tissues may pave the way for innovative, physiology-based interventions that go beyond conventional calorie-restriction approaches and directly address the energy expenditure side of the energy balance equation.

Characteristics and Origins of Brown, Beige, and White Adipose Tissues

Adipose tissue, a central regulator of energy balance and metabolic homeostasis, is broadly classified into three main types based on cellular morphology, gene expression profiles, developmental origin, and physiological function: white adipose tissue (WAT), brown adipose tissue (BAT), and beige (or brite) adipose tissue[15, 23, 24]. Each of these adipose depots exhibits distinct structural features and metabolic roles, contributing differently to the maintenance of whole-body energy homeostasis.

White adipose tissue (WAT) is the most abundant form of adipose tissue in adult humans and is primarily responsible for long-term energy storage[25, 26]. It is characterized by large, unilocular adipocytes containing a single, large lipid droplet that occupies the majority of the cytoplasm, pushing the nucleus to the periphery[25]. WAT acts as a major energy reservoir, storing excess calories in the form of triglycerides during times of energy surplus and releasing free fatty acids during fasting or energy deficit. In addition to its role in lipid storage, WAT functions as an endocrine organ by secreting a range of adipokines, such as leptin, adiponectin, resistin, and inflammatory cytokines, which influence appetite regulation, insulin sensitivity, inflammation, and immune responses.

Brown adipose tissue (BAT), in contrast, is specialized for energy expenditure and heat generation, a process known as non-shivering thermogenesis[22, 27, 28]. BAT is composed of smaller, multilocular adipocytes that contain numerous lipid droplets and are densely packed with mitochondria. A defining feature of BAT is its high expression of uncoupling protein 1 (UCP1), a mitochondrial inner membrane protein that uncouples oxidative phosphorylation from ATP synthesis, thereby dissipating energy as heat. This thermogenic capacity is especially crucial for maintaining body temperature in neonates and during cold exposure[22, 29, 30]. Unlike WAT, BAT is relatively limited in adults but can be metabolically active under specific conditions such as chronic cold exposure or pharmacological stimulation. Its presence in humans has been increasingly recognized through imaging studies, particularly in the supraclavicular and paravertebral regions.

Beige adipose tissue represents a unique thermogenic fat subtype that arises within WAT depots under certain physiological or environmental stimuli, including chronic cold exposure, endurance exercise, β3-adrenergic receptor stimulation, and certain dietary components[31, 32]. Beige adipocytes share morphological and functional characteristics with brown adipocytes, such as multilocular lipid droplets and elevated UCP1 expression, yet they are developmentally distinct. While classical brown adipocytes are derived from Myf5-positive precursors, a lineage shared with skeletal muscle cells both WAT and beige adipocytes arise from Myf5-negative mesenchymal precursors[31]. This divergence in developmental origin suggests a complex regulatory network controlling adipocyte fate determination.

One of the most remarkable features of beige adipocytes is their plasticity. Unlike classical brown adipocytes, which are constitutively thermogenic, beige adipocytes exhibit a reversible phenotype. In the absence of external stimuli, beige cells can lose their thermogenic properties and revert to a white adipocyte-like state, a process referred to as "whitening." Conversely, under thermogenic stimulation, white adipocytes within WAT can undergo "browning" or "beiging," wherein they adopt a thermogenic phenotype akin to brown adipocytes[33]. This dynamic behavior offers promising therapeutic opportunities for combating obesity and related metabolic disorders by increasing energy expenditure.

Collectively, the interplay between WAT, BAT, and beige fat reflects a sophisticated system of energy regulation that can adapt to changing metabolic demands. Understanding the molecular and environmental

factors that govern the differentiation, activation, and plasticity of these adipose depots holds substantial promise for the development of novel interventions targeting obesity, insulin resistance, and type 2 diabetes mellitus[34]. As research progresses, beige adipose tissue, in particular, is garnering attention as a potential target for metabolic reprogramming aimed at enhancing thermogenesis and improving metabolic health.

Molecular Regulation of Thermogenic Activation

The activation of brown adipose tissue (BAT) and beige fat is governed by intricate regulatory networks that orchestrate thermogenesis—a process whereby energy is dissipated as heat rather than stored. At the heart of this process lies the uncoupling protein 1 (UCP1), a mitochondrial protein uniquely expressed in BAT and beige fat. UCP1 uncouples oxidative phosphorylation, allowing the mitochondrial proton gradient to be dissipated as thermal energy instead of being harnessed for ATP production[35]. This mechanism forms the cornerstone of non-shivering thermogenesis, particularly in response to cold exposure. The recruitment and activation of thermogenic fat cells involve a tightly coordinated set of signals, ensuring the precise control of energy balance in response to environmental and physiological cues[35].

A central regulatory axis in BAT activation is β-adrenergic signaling. Upon cold exposure, sympathetic nerves release norepinephrine, which binds to β3-adrenergic receptors on brown and beige adipocytes[36]. This interaction activates the cyclic AMP (cAMP) pathway, leading to protein kinase A (PKA) activation, which in turn upregulates UCP1 expression and other thermogenic genes. Additionally, the transcriptional coactivator PGC1α plays a pivotal role by promoting mitochondrial biogenesis and enhancing the expression of genes involved in energy metabolism[36]. Another critical player is PRDM16, a master transcriptional regulator that drives the differentiation of precursor cells into brown and beige adipocytes while modulating thermogenic gene programs. These factors operate in concert to initiate and maintain the thermogenic capacity of adipose tissue, allowing for adaptive responses to environmental stimuli and metabolic demands[36].

Endocrine and paracrine factors further augment the thermogenic programming of adipose tissue. Irisin, a myokine secreted by skeletal muscle during physical activity, and fibroblast growth factor 21 (FGF21), a hormone from the liver, are known to induce the browning of white adipose tissue by promoting the development of beige adipocytes[37]. Bone morphogenetic proteins such as BMP7 and BMP8b also contribute by stimulating brown adipogenesis and enhancing UCP1 expression. These signaling molecules underscore the systemic regulation of thermogenic fat and highlight potential therapeutic avenues. Pharmacological strategies aimed at modulating these pathways hold promise in boosting energy expenditure, improving insulin sensitivity, and combating metabolic disorders such as obesity and type 2 diabetes[37]. Understanding and leveraging the molecular underpinnings of BAT and beige fat activation could pave the way for novel interventions in metabolic disease management.

Physiological Roles in Energy and Glucose Homeostasis

Brown adipose tissue (BAT) and beige adipocytes play vital roles in systemic metabolism that extend well beyond their classical function in non-shivering thermogenesis[29, 37]. When activated, these thermogenic fat depots significantly enhance energy expenditure by increasing substrate oxidation, thereby reducing overall adiposity. This energy-consuming process helps counteract the chronic energy surplus characteristic of obesity. By dissipating energy as heat through mitochondrial uncoupling mediated by UCP1, thermogenic adipocytes offer a means of increasing basal metabolic rate, which not only helps with weight control but also prevents lipid accumulation in non-adipose tissues, a key feature of metabolic dysfunction[8].

Beyond energy expenditure, BAT and beige fat are critically involved in glucose metabolism. Upon activation, these tissues exhibit elevated glucose uptake, primarily through the upregulation of GLUT4 and GLUT1 glucose transporters[38]. This capacity allows thermogenic fat to serve as a significant sink for circulating glucose, thereby contributing to improved glucose homeostasis. Such glucose utilization reduces insulin resistance—a hallmark of type 2 diabetes mellitus (T2DM)—and lowers fasting blood glucose levels. Consequently, the recruitment and activation of thermogenic adipocytes can directly modulate glycemic control and insulin sensitivity, representing a promising target for therapeutic intervention in diabetes[38].

Lipid metabolism is another domain where BAT and beige adipocytes exert substantial influence. These thermogenic cells actively clear triglyceride-rich lipoproteins from the circulation by hydrolyzing triglycerides into free fatty acids, which are then oxidized to fuel thermogenesis[39]. This lipid-clearing function not only prevents ectopic fat deposition but also improves plasma lipid profiles, thereby alleviating dyslipidemia—a common comorbidity of obesity and T2DM. As such, BAT activation can contribute to cardiovascular protection by modulating lipid handling and improving the balance between lipid storage and oxidation[40].

Importantly, beige adipocyte induction also exhibits potent anti-inflammatory effects. The expansion of white adipose tissue (WAT) in obesity is often accompanied by chronic, low-grade inflammation, which exacerbates insulin resistance and metabolic dysfunction[41]. Beige fat, however, is associated with reduced secretion of pro-inflammatory cytokines and enhanced anti-inflammatory signaling, both locally within adipose depots and systemically[41]. These immunomodulatory properties further underscore the therapeutic potential of thermogenic adipocytes in metabolic disease. Collectively, the metabolic, glycemic, lipid-regulating, and anti-inflammatory actions of BAT and beige fat firmly establish them as central players in mitigating the pathophysiological consequences of obesity and type 2 diabetes [42].

Pharmacological and Lifestyle Interventions Targeting BAT and Beige Fat

Several strategies have been explored to activate thermogenic adipocytes in humans:

Cold Exposure

Repeated cold exposure is one of the most well-characterized physiological stimuli for activating brown adipose tissue (BAT) and promoting the browning of white adipose tissue (WAT), resulting in increased energy expenditure and improved metabolic function[43]. When exposed to cold temperatures, the sympathetic nervous system becomes activated, releasing norepinephrine, which binds to β3-adrenergic receptors on adipocytes. This cascade leads to the upregulation of uncoupling protein 1 (UCP1), a hallmark of thermogenic function, which uncouples oxidative phosphorylation in mitochondria to generate heat instead of ATP. Consequently, substrate oxidation increases, leading to a reduction in fat mass and improved glucose metabolism[43]. Human studies have demonstrated that individuals acclimated to mild cold exposure (e.g., 17–19°C for several hours per day) show a significant increase in BAT activity, as evidenced by increased glucose uptake in thermogenic fat depots on PET-CT imaging. Additionally, cold exposure improves insulin sensitivity and lipid profiles, especially in overweight or obese individuals[44]. This intervention is non-invasive and does not rely on pharmacological agents, making it a potentially accessible adjunctive strategy for metabolic disease management. However, challenges such as individual tolerance, adherence, and environmental feasibility limit its widespread adoption. Innovations such as localized cooling devices or wearable cold suits are being investigated to enhance the practicality of this approach[44]. Moreover, identifying optimal exposure duration, temperature thresholds, and long-term metabolic benefits remains an area of active research. Overall, cold exposure is a physiologically relevant and evidence-backed method for stimulating endogenous thermogenesis through BAT and beige fat activation.

Pharmacological Agents

Numerous pharmacological agents have been explored for their capacity to activate thermogenic adipose tissue and replicate the metabolic benefits of cold-induced thermogenesis. One of the most promising classes includes β3-adrenergic agonists, such as mirabegron[45]. These agents mimic sympathetic activation by stimulating β3-adrenergic receptors on BAT and beige adipocytes, leading to increased UCP1 expression and enhanced glucose uptake, lipid oxidation, and energy expenditure[45]. Clinical studies with mirabegron have shown elevated BAT activity and improved insulin sensitivity in humans, though side effects like elevated blood pressure raise concerns about long-term use[46]. Another category includes thiazolidinediones (TZDs), which are PPARγ agonists. Although primarily used as insulin sensitizers in type 2 diabetes, TZDs also promote the differentiation of beige adipocytes in WAT depots, contributing to increased thermogenic capacity[47]. Natural compounds such as capsaicin (found in chili peppers) and menthol (from mint) activate transient receptor potential (TRP) channels, particularly TRPV1 and TRPM8, which can simulate the effects of cold exposure and stimulate sympathetic outflow to thermogenic adipose tissue. Furthermore, fibroblast growth factor 21 (FGF21) and its analogs have gained attention due to their ability to enhance BAT thermogenic activity and improve systemic glucose and lipid metabolism[48]. These agents act through the FGFR1/β-Klotho complex and modulate the expression of thermogenic and metabolic genes. While these pharmacological interventions are promising, their long-term efficacy, safety profiles, and tissue specificity remain under investigation. A combination of agents or targeted delivery systems may overcome some of these hurdles and pave the way for safe and effective BAT-activating therapies.

Exercise and Hormonal Modulators

Exercise is a well-established intervention for improving metabolic health, and recent findings suggest it also contributes to the activation of thermogenic adipose tissues[49]. Physical activity induces the secretion of several muscle-derived cytokines, or myokines, which can influence adipose tissue remodeling and function. Among these, irisin, a cleavage product of the membrane protein FNDC5, has been shown to promote the browning of WAT by inducing UCP1 expression and mitochondrial biogenesis[50]. Elevated circulating irisin levels following aerobic and resistance exercise are associated with improved insulin sensitivity and reduced fat mass in both animal models and humans[49]. Another myokine, meteorin-like (METRNL), has been implicated in stimulating eosinophil-mediated activation of type 2 immune responses in adipose tissue, thereby enhancing beige fat recruitment. These hormonal changes not only improve energy expenditure but also contribute to reductions in inflammation and lipid accumulation. Furthermore, exercise impacts the hypothalamic-pituitary axis, leading to the release of systemic hormones such as growth hormone and catecholamines, which may further influence BAT activity through β-adrenergic pathways[51]. Exercise also enhances mitochondrial function and increases AMPK activity, which promotes fatty acid oxidation in multiple tissues including BAT. Although the precise mechanisms by which exercise induces browning are still being elucidated, its role as a non-pharmacological and accessible means to enhance thermogenic potential is well supported[51]. Combining exercise with other browning strategies such as nutritional or pharmacologic agents may provide synergistic benefits. Continued research into exercise-induced endocrine signals holds promise for identifying novel targets for metabolic disease intervention through adipose tissue modulation.

Nutritional Approaches

Dietary components have emerged as potent modulators of thermogenic adipose tissue, offering a non-invasive approach to enhance energy expenditure and improve metabolic health. Among these, polyphenols—naturally

occurring compounds found in fruits, vegetables, tea, and wine—have demonstrated promising thermogenic and anti-obesity properties[52, 53]. Resveratrol, a polyphenol found in red grapes, activates AMP-activated protein kinase (AMPK) and sirtuin 1 (SIRT1), both of which are crucial regulators of mitochondrial biogenesis and UCP1 expression in adipocytes[54, 55]. These effects mimic those of caloric restriction and exercise, promoting energy dissipation and reducing adiposity. Similarly, catechins from green tea and curcumin from turmeric have been shown to enhance thermogenesis via sympathetic activation and increased β-oxidation[56–58]. Omega-3 fatty acids, especially EPA and DHA, also play a role in promoting BAT activation and beige adipocyte formation by modulating PPAR signaling and reducing chronic inflammation in adipose tissues[59, 60]. These fatty acids may improve mitochondrial efficiency and contribute to lipid clearance and insulin sensitivity. In addition to these bioactives, dietary amino acids such as arginine and leucine have been implicated in promoting browning through nitric oxide and mTOR pathways, respectively. Importantly, the gut microbiota mediates the bioavailability and systemic effects of many of these nutrients, suggesting that nutritional strategies may need to be personalized based on individual microbiome profile[53, 61, 62]s. While preclinical data are robust, human studies remain limited and sometimes inconsistent due to variations in dose, bioavailability, and study design. Nonetheless, nutrition-based interventions targeting thermogenesis hold considerable translational potential and may complement other strategies in the holistic management of obesity and metabolic diseases.

Clinical Evidence and Translational Potential

Clinical studies over the past decade have confirmed that functional brown adipose tissue is present in adult humans, particularly in regions such as the supraclavicular, cervical, and paraspinal areas[63]. These depots are metabolically active and responsive to environmental stimuli such as cold exposure. Using 18F-FDG PET/CT imaging, researchers have demonstrated that mild cold stimulation significantly increases glucose uptake in BAT, correlating with elevated energy expenditure and improved insulin sensitivity. In overweight and obese individuals, cold-induced BAT activation has been associated with reductions in fat mass and enhancements in lipid profiles[64]. Pharmacologically, β3-adrenergic receptor agonists like mirabegron have shown promise in stimulating BAT activity and improving metabolic outcomes. Human trials with mirabegron have demonstrated increases in thermogenic gene expression, glucose uptake, and energy expenditure[64]. However, concerns remain regarding its cardiovascular side effects, particularly tachycardia and hypertension, which limit its use in certain populations. Other agents, such as FGF21 analogs, are currently being investigated in clinical trials for their ability to induce thermogenesis and enhance insulin sensitivity without adverse effects[64]. Despite these promising findings, inter-individual variability in BAT activity remains a major hurdle for clinical translation. Factors such as age, sex, BMI, genetic background, and prior exposure to cold influence the abundance and responsiveness of BAT. Additionally, standardized methods for assessing BAT activity, such as improved imaging modalities and reliable biomarkers, are lacking. These limitations must be addressed to develop personalized and scalable therapies. Nevertheless, the cumulative clinical evidence underscores the therapeutic potential of targeting BAT and beige fat in the fight against metabolic diseases.

Challenges and Future Directions

While the activation of brown and beige adipose tissue represents a promising avenue for combating obesity and type 2 diabetes, several challenges must be overcome before these strategies can be widely adopted in clinical settings. A primary concern is the safety and specificity of thermogenic agents. Many pharmacological compounds that stimulate BAT activity also affect other tissues, leading to unintended side effects such as increased heart rate or blood pressure. Ensuring tissue-specific targeting and long-term safety remains a major hurdle. Another issue is the considerable inter-individual variability in BAT mass and activity, influenced by factors such as age, sex, body composition, and environmental exposure. This variability complicates treatment standardization and highlights the need for personalized approaches to thermogenic therapy. Furthermore, quantifying BAT reliably in clinical populations remains difficult. Current imaging techniques like PET/CT are expensive and expose patients to radiation, while alternative methods lack the sensitivity and specificity needed for routine use. There is also the challenge of sustaining BAT activation over time. Transient responses to cold or drugs may not provide lasting metabolic benefits unless combined with lifestyle or nutritional interventions. Future research should focus on identifying novel molecular targets, improving delivery systems for thermogenic agents, and integrating personalized medicine frameworks to optimize outcomes. Additionally, development of non-invasive biomarkers for BAT activity could revolutionize monitoring and diagnosis. Finally, multidisciplinary efforts that combine insights from endocrinology, bioengineering, nutrition, and computational biology will be essential to translate bench-side discoveries into effective, scalable, and safe clinical interventions for obesity and metabolic diseases.

CONCLUSION

Brown and beige adipose tissues represent dynamic regulators of energy and glucose metabolism. Their capacity to dissipate energy and modulate systemic metabolic processes offers a compelling therapeutic avenue for obesity and T2DM. Advances in understanding their developmental origins, molecular regulators, and activation strategies provide a foundation for novel interventions. While challenges remain in clinical translation, targeting thermogenic adipocytes holds great promise for addressing the growing burden of metabolic disease.

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