ECRONICON OPEN ACCESS

EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Review Article

Brown Adipose Tissue: A Comprehensive Review

Hilary M Holets[1,2†], Nicholas A Kerna[3,4*†], Sudeep Chawla[5], ND Victor Carsrud[6], Dabeluchi Ngwu Onyejerebechi Florence[7], Nicodemus Chidi Okpo[8], Chinwendu Olivia Ayozie[9], Victor P Nkwopara[10], Chizoba Martin Ani[11], Uzoamaka Nwokorie[12] and Obiamaka Pamela Okereke-Ewene[13]

[1]*Beverly Hills Wellness Surgical Institute, USA*

[2]*Orange Partners Surgicenter, USA*

[3]*Independent Global Medical Research Consortium, Thailand*

[4]*First InterHealth Group, Thailand*

[5]*Chawla Health and Research, USA*

[6]*Lakeline Wellness Center, USA*

[7]*Federal Medical Centre, Owerri, Imo State, Nigeria*

[8]*Shaqra General Hospital, Saudi Arabia*

[9]*Madonna University College of Medicine, Elele, Nigeria*

[10]*Olusanya Rufai Medical Center, USA*

[11]*Ave Maria Hospital, Nigeria*

[12]*University of Washington, USA*

[13]*Life is Beautiful, MD., USA*

***Corresponding Author**: Nicholas A Kerna, (mailing address) POB47 Phatphong, Suriwongse Road, Bangkok, Thailand 10500. Contact: medpublab+drkerna@gmail.com. †Indicates co-first author

DOI: 10.31080/ecgds.2022.09.00944

Received: July 17, 2022; **Published**: October 03, 2022

Abstract

Studies on the physiology of different types of fat deposition have increasingly recognized adipocytes as an essential endocrine organ with numerous metabolic activities. Human fat consists of white adipose tissue (WAT) and brown adipose tissue (BAT). WAT helps in energy storage, whereas BAT helps in energy consumption. Increased WAT levels may play a role in the progression of metabolic abnormalities and cardiovascular events. On the contrary, the thermogenic function of BAT allows for significant fatty acid intake due to the activation of uncoupling protein 1 (UCP1) in the internal mitochondrial membrane. In vertebrates, the sympathetic nervous system (SNS) stimulates the thermogenesis of BAT in response to cold, helping to maintain the body temperature. BAT may be a promising new therapeutic target for promoting weight reduction and improving metabolic health. Furthermore, activation of BAT is associated with improved glucose metabolism. This review encompasses the research on human BAT, including its functions and differentiation processes, its potential as a new therapeutic target for managing metabolic illnesses, such as obesity and diabetes, and its possible future applications.

Keywords: *Diabetes; Fatty Acid Intake; Human Fat; Improved Glucose Metabolism; Insulin Resistance; Obesity; Thermogenesis*

Abbreviations

^{18}F-FDG: ^{18}F-Fluorodeoxyglucose; AR: Adrenergic Receptor; BAT: Brown Adipose Tissue; Beta-AR: Beta-Adrenergic Receptor; C/EBP: CCAAT/Enhancer-Binding Protein; BMP: Bone Morphogenic Protein; CIA BAT: Collagen-Induced Arthritis BAT; CT: Computed Tomography;

DDT: Dichlorodiphenyltrichloroethane; DECT: Dual-Energy CT; DiO_2: Iodothyronine Deiodinase 2; EBF2: Early B-Cell Factor 2; ESR1: Estrogen Receptor Alpha; FDG-PET: Fluorodeoxyglucose-Positron Emission Tomography; FF: Fat Fraction; IT: Infrared Thermography; MRI: Magnetic Resonance Imaging; NA: Noradrenaline; OSA: Obstructive Sleep Apnea; PRDM16: Protein 16 of the PR Domain; SNS: Sympathetic Nervous System; sWAT: Subcutaneous WAT; TRL: Triglyceride-Rich Lipoprotein; UCP1: Uncoupling Protein 1; vWAT: Visceral WAT; WAT: White Adipose Tissue

Introduction

The Swiss scientist Conrad Gessner first recognized brown adipose tissue (BAT), often known as brown fat, in 1551, and theories on the functioning of BAT have evolved ever since. Previously called the 'hibernating gland', it has been found to have a multitude of functions, including being a core component of the thymus (1670–1817), an endocrine gland (active in the formation of blood; 1817–1863), a modified version of fat trying to serve as a reservoir of micronutrients (1863–1902) and an endocrine gland (1902–1961) [1]. In 1961, the research identified BAT as a thermogenic organ and the central location of thermoregulatory non-shivering thermogenesis. A decade later, considerable interest, especially by Lindberg's group in Stockholm, was noted in the heat generation mechanism of the tissue. Heat is generally a by-product of metabolic activities but is necessary for brown fat [1,2].

In the second half of the twentieth century and the outset of the 21st century, BAT was thought to be present only in human neonates and began to be involute during infancy [3]. The early BAT in humans was limited to studying the depots around the adrenal bed. The research did not consider the presence of BAT in extra-abdominal sites, underestimating its concentration and distribution in adults. The consensus view at that period did not support a distinct metabolic function of BAT in adult human energy balance, with Rothwell and Stock questioning, "Whither brown fat?" Identifying BAT depots was challenging, and the viewpoint would "remain contentious until a technique for quantitative non-invasive assessment of complete BAT thermogenesis is devised" [2].

Some earlier empirical evidence supported the existence of BAT in adults. However, it was not until fluorodeoxyglucose-positron emission tomography (FDG-PET), an advanced imaging technique that analyzes areas of increased metabolic activity (initially used to check tumor cells), that BAT was identified in at least a subset of the average adult population. This incredible discovery piqued the interest of medical experts in the field. They hypothesized that the presence or absence of BAT could be a causative link in widespread non-transmissible diseases, such as obesity and type 2 diabetes, and a potential therapeutic target because thermoregulation squanders excess energy [3]. Significant advancements in human BAT investigations are outlined in Figure 1 [1,2].

Year	Function
1551-	Role in hibernation by Gessner
1670-1817	Part of the thymus
1817-1863	An endocrine gland—and active in the formation of blood
1863-1902	Modified form of fat tissue which serves as a reservoir for food substances
1902-1961	An endocrine gland once more
1961-	Thermogenic organ—non-shivering thermogenesis
1974-1977	Elucidation of unique bio-energetic properties of brown fat mitochondria (proton leak)
1976-1978	Discovery of UCP1
1978-	Demonstration of quantitative importance to non-shivering thermogenesis in cold-acclimated rodents
1978/9-	Involved in energy balance (diet-induced thermogenesis) and obesity
2002	FDG uptake in cervical/supraclavicular region of PET-CT scan may be BAT
2004	FDG uptake in BAT during PET-CT is influenced by ambient temperature
2006	Inverse relationships between BAT activity and BMI, suggesting the metabolic significance of BAT
2009-	Definitive identification of BAT in adult humans and its metabolic plasticity
2010/12	Discovery of "beige"/"brite" adipocytes
2011/12	Role in glucose disposal and triglyceride clearance – metabolic homeostasis

Figure 1: *Perceptions of BAT's physiological roles and properties over time. Adapted from: [1,2].*

Discussion

Adipose tissue, an essential metabolic organ, plays a critical role in the interaction of nourishment, caloric expenditure, and human health. Adipose tissue, often referred to as fat deposits, is a connective tissue primarily composed of adipocytes (fat cells). The morphology of different types of adipocytes, classified as white, beige, or brown, dictates the functional importance of other adipose reservoirs in energy metabolism and nutritional balance [2]. WAT and BAT differ in their anatomical regions, morphological characteristics, roles, and regulations. On the contrary, beige adipocytes are developed within the WAT in response to cold exposure (Figure 2) [4].

Both WAT and BAT are involved in energy balance. However, WAT is primarily responsible for storing and mobilizing triglycerides, whereas BAT releases energy as heat after cold- or diet-induced thermogenesis [5]. These two cell types differ considerably in the presence of several large mitochondria in brown adipocytes [6]. Moreover, BAT has a higher water-to-fat ratio than WAT [7].

White adipocytes, which range from 25 to 200 μm and feature a unilocular lipid droplet, few mitochondria, and a low oxidative rate, are usually found in WAT (Figure 2) [8]. WAT is present throughout the body, accounting for 3% – 70% of the total body weight in adults. WAT development begins in the late stages (14 – 24 weeks) of pregnancy [9]. Visceral WAT (vWAT) and subcutaneous WAT (sWAT) are the two types of WAT. The sWAT is present beneath the epidermis and in the intramuscular fat found between the skeletal muscles. It protects the muscles against temperature changes. The vWAT, or abdominal fat, is located within the peritoneum and is spread around the internal organs, including the liver, kidneys, and intestines. It offers protective cushioning and is further categorized into mesenteric, retroperitoneal, perigonadal, and omental adipose tissues based on the location [5].

Brown adipocytes, in contrast to white adipocytes, are derived from precursor mesenchymal stem cells in the somites during embryogenesis [10]. They are smaller (15 – 60 μm) and comprise lipids in multiple lipid droplets [8] that shelter the nucleus (Figure 2). They are distinguished by the presence of several mitochondria dispersed across the droplets, contributing to the brown appearance. The brown adipocytes generate heat with the Golgi apparatus, a small number of ribosomes, and the endoplasmic reticulum in the cytoplasm [11,12].

BAT is found in the upper back and shoulders, mainly encompassing the interscapular region, representing approximately 5% of total body mass [13]. It is also present in WAT and skeletal muscles. Histopathological human investigations indicate that brown and white adipocytes are intermingled in all depots [14].

When activated, BAT generates energy up to 300 W/kg compared to most other tissues, which create only up to 1 W/kg. The action mechanism, which constitutes the first reaction required to ensure rapid heat production, is primarily governed by removing the GDP binding sites present within the unique uncoupling protein 1 (UCP1) [15].

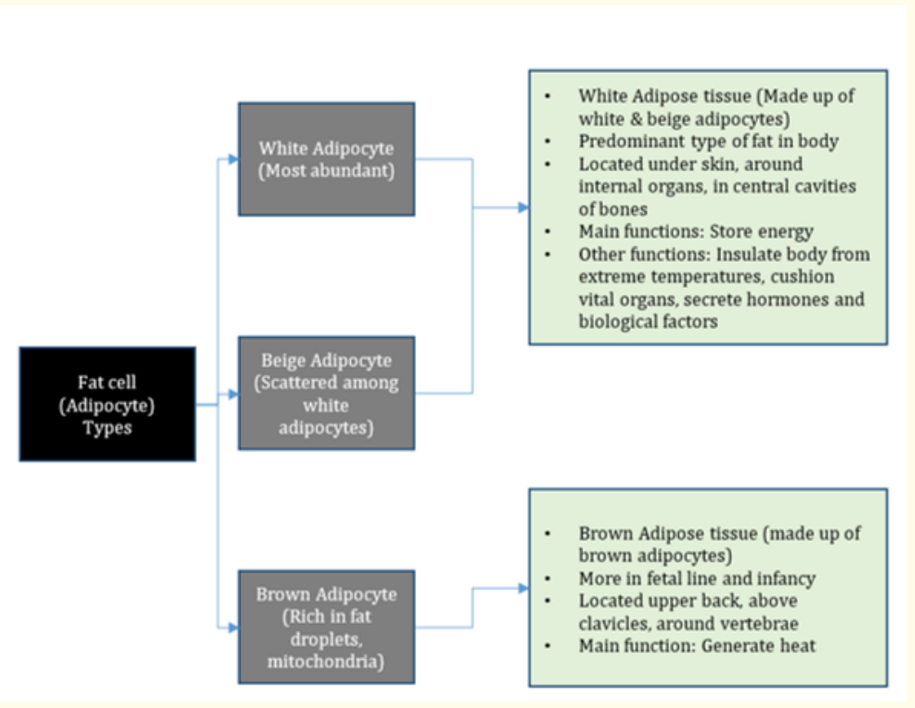

Figure 2: *Different types of adipose tissues and their functions.*

Neonates have a considerably higher proportion of BAT than older individuals. It is broadly spread in other organs until puberty but declines thereafter [16]. In adults, BAT contributes 0.05 to 0.1% of the body mass [17]. However, according to Cypess., *et al*. (2009), women have two times more BAT and larger peripheral fat depots than men [18].

Weight loss benefits

BAT is considered beneficial for weight management because of its unique capacity to transform excess dietary energy into heat energy [19]. Body mass index and body fat percentage are negatively associated with BAT activity [20]. BAT helps to reduce weight by burning considerable calories [21].

In adults, BAT plays a crucial role in maintaining metabolic balance because it is spread uniformly throughout the body. Once the BAT is stimulated, the catecholamine released by sympathetic nerve fibers activates b3-adrenergic receptors (ARs), resulting in high-level expression of UCP1 in the mitochondrial inner membrane. The highly expressed UCP1 burns glucose and essential fats to generate heat via non-shivering thermogenesis [21]. Thermogenesis increases the metabolic rate by catalyzing the consumption of calories and is a lesser-known weight-loss technique. The catalytic process burns calories even when the body is resting and is the quickest way to lose weight [22].

BAT mechanism of action

BAT oxidizes fat and disperses the energy generated as heat, providing the body with a source of heat. The *PRDM16* gene stimulates the differentiation of pre-adipocytes into BAT cells. In addition, the PRDM16 protein (rich in BAT) promotes mitochondrial gene expression and density. Aided by cAMP, PRDM16 enhances the UCP1 expression, significantly increasing uncoupled respiration and heat generation [23].

In BAT, the lack of GRB2-associated binding protein 2 stimulates the development of *UCP1* and other thermogenic genes [24]. On the contrary, a lack of IL10 increases cold intolerance in infants and decreases UCP1-dependent BAT mitochondrial respiration [25].

Identification of BAT in the human body

Magnetic resonance imaging (MRI) is increasingly used to assess BAT functions. However, the degree and direction of cold-induced alterations and density of BAT in an MRI vary depending on the study. In preclinical models, the chemically evaluated fat content of tissues corresponded to the fat mass measured by MRI. Also, the fat fraction (FF) inversely corresponded to the number of UCP1-expressing cells in BAT and favorably compared to the size of the adipocytes [26].

Structurally and functionally, BAT in infants mimics the typical interscapular depot in adults. In addition, BAT in infants has a notable lack of visibly recognizable boundaries, such as the supraclavicular depot, making it difficult to achieve a consensus on the appropriate FF thresholds for specialized BAT imaging. Therefore, FF in human BAT ranges between 60%, 65%, 80%, and 94% in geriatric individuals, and several threshold values of FF have been used to partition BAT [26]. Even for underweight individuals, the total BAT mass is > 60 – 100g, which is a minuscule fraction compared to the WAT mass [3].

Currently, PET–computed tomography (CT) is used to recognize the adipose tissue with a high rate of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) utilization as a putative BAT [18]. However, this procedure is expensive, includes ionizing radiation, and highly depends on activation for detection [3].

This technology led to the hypothesis that the presence or absence of BAT is a possible causative factor in non-communicable illnesses, such as diabetes and obesity, and a potential therapeutic target because thermogenesis squanders excess energy [3]. Infrared thermography (IT), another possible diagnostic alternative, is a non-invasive and inexpensive procedure that uses images to assess skin temperature in different body parts. Obtaining data from IT makes it a potential and valuable technology, as evidenced by Lee P., *et al.*

(2013). In that study, a temperature rise was observed in BAT-correspondent regions in humans after exposure to cold meal intake. Also, a study by Borga., *et al*. (2014) supported the use of dual-energy CT (DECT) as a novel option for BAT detection [3].

Factors affecting BAT regulation

Different human organs generate and emit instructional impulses incorporated into the anatomical sites of brown adipocytes to govern their growth, differentiation, and perhaps thermogenic activity, which ultimately affects the regulation of temperature and overall energy consumption (Figure 3) [27].

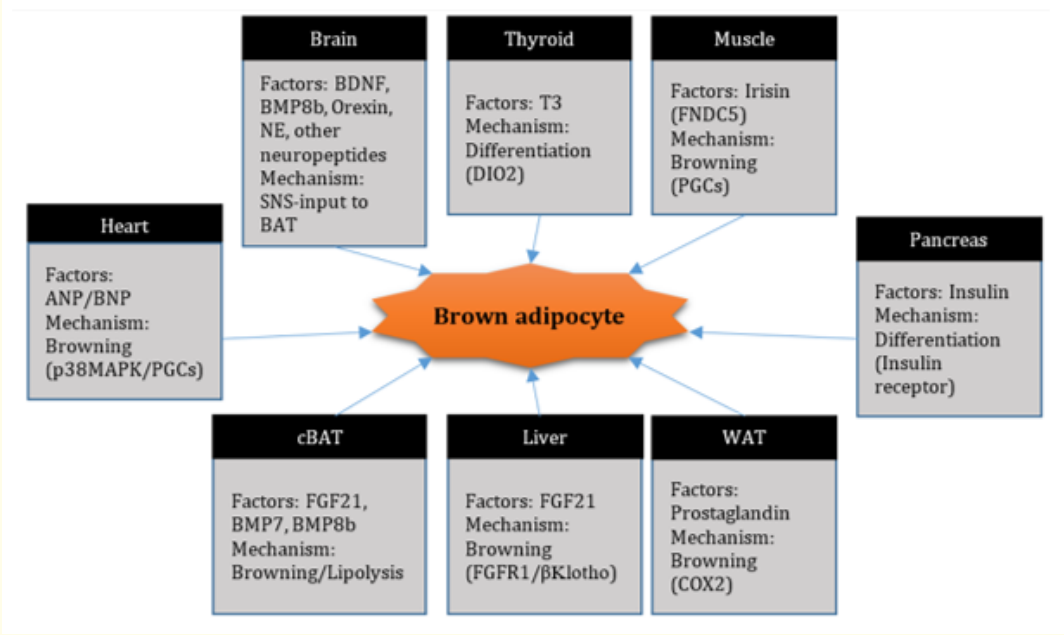

Figure 3: *Factors affecting the physiology of brown adipocytes. Adapted from: [27].*

Moreover, environmental and dietary factors, mediated by the brain and endocrine systems, influence BAT. Some variables influence thermogenic activity and BAT mass; others influence both processes [28]:

- **Cold or hot exposure:** Cold exposure boosts BAT activation. BAT is more prevalent in scans performed in the winter than in the summer. The BAT FDG absorption increases in patients with prescan cooling more than in those with prescan warming. Noradrenaline (NA) secretion from nerve terminals regulates BAT through the hypothalamus. Through beta-adrenergic receptors (beta-ARs), NA modulates the function of brown adipocytes. Circulating catecholamines, in addition to locally produced NA, modulate BAT activity [28].

- **Hormonal factors:** The thyroid hormone plays a crucial role in thermoregulation. It affects the function of the BAT both peripherally and centrally. BAT has Iodothyronine deiodinase 2 (DiO_2), transforming T4 into bioactive T3. Glucocorticoids also increase the feeling of hunger. The hypothesis that glucocorticoid-induced weight gain may be mediated, in part, by reducing BAT activity has received little consideration in humans. BAT has high-affinity glucocorticoid receptors [28].

Sex hormones also regulate body fat mass. Animal studies have demonstrated that progesterone and testosterone influence BAT function. Ovariectomy causes BAT depot atrophy, which is reversed by estrogen replacement, showing that estrogen increases BAT bulk. Insulin is another option for controlling BAT, although it is a complicated action mechanism. Insulin regulates BAT both directly in brown adipocytes and indirectly through the SNS. In isolated brown adipocytes, insulin promotes BAT glucose absorption and lipogenesis [28].

Several peptides, including fibroblast growth factor-21, bone morphogenic proteins (BMP), and cardiac natriuretic peptides (ANP and BNP), have recently been discovered as promoters of fat browning in humans [28]:

- **Dietary factors:** Thermogenesis can also be induced by food consumption. The thermogenic reaction is associated with the caloric amount of a meal. Protein causes a more significant thermogenic reaction than fats or carbohydrates. Capsaicin, a component of chili peppers, induces thermogenesis and decreases fat mass in both animals and people. Capsaicin increases the thermogenesis of BAT through indirect and direct pathways involving vanilloid subtype 1 (TRPV1) receptors [28].

- **Physical activity and irisin**: The discovery of myokine irisin led to the hypothesis that activity may induce WAT browning. Irisin, a peptide generated from the fibronectin type III domain-containing protein 5, causes the browning of WAT in mice [28].

- **Environmental factors:** The potential impact of environmental factors on energy homeostasis and fat development by modifying the thermogenic activity of BAT has been attracting significant interest. Contamination with dichlorodiphenyltrichloroethane (DDT) and its major metabolite dichlorodiphenylethylene is associated with increased metabolic disorders [29]. La Merrill., *et al*. (2014) discovered that perinatal DDT contamination in mice reduces energy expenditure, increases body mass and insulin resistance, and decreases BAT activity in female adult offspring [30].

Studies have found a relationship between environmental pollutants and the development of metabolic disorders [31]. For example, BAT's insulin resistance was associated with mitochondrial dysfunction due to polluted air particles. According to Xu., *et al*. (2011a), prolonged exposure to fine airborne particulates causes insulin resistance and irritation, which is related to a decrease in BAT weight, a significant decline in mitochondrial size in BAT, and a reduction in mitochondrial number in WAT [32].

Environmental pollutants, such as perfluorooctane sulfonic acid and perfluorooctanoic acid, are also associated with a decrease in body mass and adipose mass, which is related to UCP1 activation and improved oxygen uptake in brown fat mitochondria [33]. Oxidative stress is a significant aspect of the relationship between obesity and its consequences. Obesity is caused by oxidative stress by promoting WAT deposition and modifying food intake. Cell culture and animal studies have shown that oxidative stress can promote the proliferation and differentiation of preadipocytes [34].

Sleep concerns, such as insomnia and obstructive sleep apnea (OSA), reduce sleep length and quality, which are associated with a gain in body weight and adiposity [34]. Sleep apnea is prevalent in 40% of obese people, and 70% of patients with OSA are morbidly obese [35]. According to a recent study, breathing problems during sleep are related to increased levels of CRP, regardless of age, basal metabolic index, or body fat percentage, indicating a correlation between low-grade inflammation and sleep disturbances [36].

BAT metabolic functions

The vital role of BAT in metabolic regulation can be attributed to its ability to disperse chemical energy such as heat. Rothwell and Stock (1979) found that BAT thermogenesis was increased in overfed rats. The diet-induced thermogenesis hypothesis states that BAT activation concerning caloric overabundance may impair metabolic efficiency and help reduce weight. Early investigations found that surgical denervation or transgenic ablation of BAT through overexpression of diphtheria toxin A chain exclusively in brown adipocytes led to increased body weight and insulin resistance in treated animals, supporting the hypothesis [37].

BAT importance in cold weather environments

BAT is triggered minutes after exposure to cold, and its energy requirements are satisfied by fast lipolysis of intracellular lipid storage [38]. It takes up free fatty acids produced from triglyceride-rich lipoproteins (TRLs) by lipoprotein lipase in the endothelium of its thick vasculature to replace intracellular triglycerides. BAT stimulation with short-term cold exposure has recently been proven to improve TRL metabolism in mice by managing vascular lipoprotein balance and alleviating hyperlipidemia [39].

Regulation of brown adipocyte development

Brown adipocytes are produced from a multipotent progenitor population of cells in the dermomyotome expressing engrailed 1, paired box 7, myogenic factor 5, skeletal muscle, dorsal dermis, and a small percentage of white adipocytes (Figure 4) [4,40].

Several signaling cascades are linked to the regulation of BAT development. Early B-cell factor 2 (EBF2) identifies dedicated brown preadipocytes and may influence brown adipose lineage determination. Ewing sarcoma breakpoint region 1 (also known as EWS) interacts with the Y-box binding protein 1 (also known as NSEP1) to monitor and control the expression of BMP7, which helps to promote BAT growth. The zinc finger protein 16 of the PR domain (PRDM16) enhances the differentiation of brown adipocytes through interactions with the adipogenic transcription factor CCAAT/enhancer-binding protein (C/EBP). To trigger the brown fat-selective mechanism, EBF2 collaborates with PPAR [4].

Catecholamines and orexin, both potent activators of brown fat production and thermogenic activity, are produced by the central nervous system [41]. By controlling the intracellular location of CRTC3, liver kinase B1, commonly known as serine/threonine kinase 11, regulates the development and thermogenesis of BAT [42].

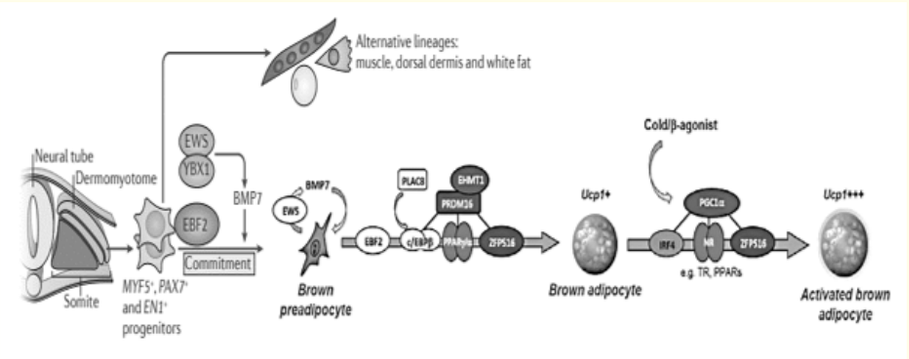

Figure 4: *Brown adipocyte development. Adapted from: [4,40].*

Conversion of WAT to BAT

As UCP1 is only found in BAT, increasing the BAT volume in obese people may help energy dissipation. Transforming white adipocytes into brown-like fat tissue, known as WAT browning, is a strategy to enhance the percentage of functional UCP1-rich cells in AT. Thus, distributed aggregates of brown-like adipocytes, known as beige or brite adipocytes, emerge in WAT. These cells exhibit a multilocular buildup of fat stores are abundant in mitochondria and express high levels of UCP1 and indicators that enhance the transcription of essential thermogenesis proteins, similar to brown adipocytes [43].

The principal causes of WAT browning are sympathetic excitation and interaction of NE with 3-ARs on the cytoplasmic membrane of white adipocytes. This interaction triggers a signaling cascade that results in the upregulation of UCP1 and other thermogenic proteins. Repeated cold stimuli are the most effective sympathetic trigger as the interaction induces a massive thermogenesis response in WAT [44]. Beta-adrenergic receptor promoters (CL316, CL243), PPAR-gamma promoters, miRNAs, and genes such as *PRDM16*, *BMP7*, and *PGC1a* also induce fat browning [45]. Other factors that play a significant role in the development of BAT or the browning of typical WAT storage are detailed in Figure 5 and Table 1.

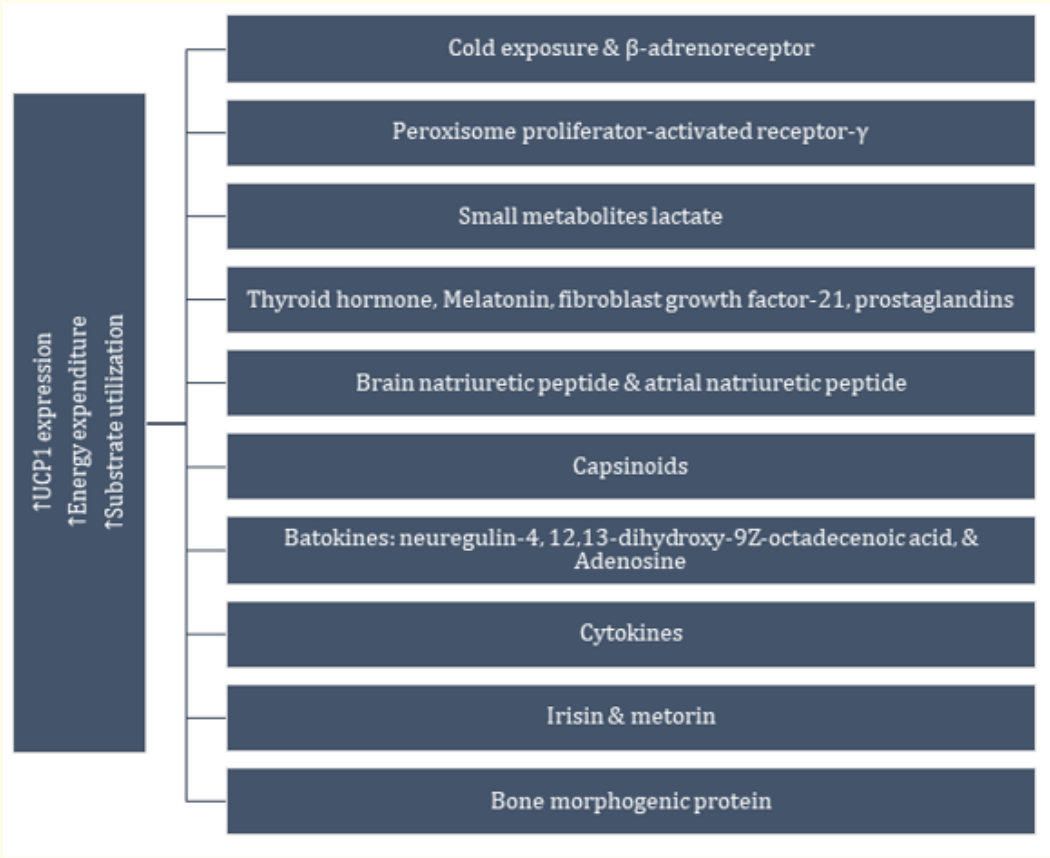

Figure 5: *Factors that induce browning of typical WAT depots. Adapted from: [46].*

Browning factors	Mechanisms of action	Effect
Endogenous factors		
Norepinephrine	cAMP/PKA-dependent signaling pathways activation	↑UCP1 expression
Leptin	Orexigenic NPY/AgRP neuron inhibition Anorexigenic POMC/CART neuron stimulation	Appetite suppression
BDNF	Early regulation of hypothalamic activity	↑sympathetic output
BAIBA	Regulate gene expression	Upregulation of PPARα and UCP1
Interleukin 6	PGC-1α-dependent modulation of gene expression	↑UCP1 expression
Triiodothyronine	Bound of activated TRβ to UCP1 distal enhancer	↑UCP1 expression
Thyroxine	Intracellular conversion to triiodothyronine	↑UCP1 expression
FGF21	Stimulation of p38-MAPK. Autocrine effect on brown adipocytes	↑UCP1 expression
BMP7	Early brown adipocyte programming of Myf5+ progenitor cells	Brown adipocytes differentiation
BMP4	Stimulate p38 MAPK/PGC-1α/ATF2 signaling pathway	Upregulation of glucose and lipid metabolism, expression of brite
ANP and BNP	cGMP/PKG-dependent stimulation of p38 MAPK/PGC-1α signaling pathway	Upregulation of UCP1 and increase of lipolysis
Adiponectin	Polarization promotion and maintenance of resident M2 macrophages after cold-exposure	scWAT browning
Prostaglandin E2	Modulation of cAMP level in the adipocyte Stabilization of white-to-brown transcriptional regulators Interaction with PPARγ	↑ lipolysis WAT browning ↑ WAT browning ↑
Serotonin	POMC neurons activation and NPY/AgRP neurons inhibition Central hypothalamic serotoninergic neurons activation	Appetite suppression WAT browning, regulation of glucose and lipid metabolism
Adenosine	Stimulation of cAMP/PKA-dependent signaling pathway in brown adipocytes	UCP1 upregulation
Pharmacological factors		
Mirabegron	Selective β3-sympathomimetic, weak affinity to other β-adrenoreceptors	↑UCP1 expression
Sibutramine	Inhibition of the reuptake of serotonin and norepinephrine	↓Appetite, ↑ thermogenesis, improvement of blood parameters.
Fenfluramine	Increase of the synaptic release of serotonin	↓Appetite
Fluoxetine	Inhibition of the reuptake of serotonin	UCP1 upregulation, ↑ BAT mass
Tamoxifen	Estrogen receptor agonist	Chronic scWAT browning Modification of lipid and glucose metabolism
Rosiglitazone	Agonist ligand of PPARγ	UCP1 upregulation in preadipocytes and mature adipocytes Downregulation of β3-AR and DIO2
Pioglitazone	Agonist ligand of PPARγ	Modest upregulation of UCP1
Nutritional factors		
L-796568	Selective β3-sympathomimetic	Acute ↑ of thermogenesis
Isopropylnorsynephrine	Selective β3-sympathomimetic	High lipolytic power
Capsicum (Capsaicin)	CaMKII/AMPK/SIRT1-dependent deacetylation of PPARγ and PRDM16	↑UCP1 expression and BMP8B
Fucoxanthin (Edible Seaweeds)	↓Lipogenic enzymes ↑β3-AR and oxidative enzymes	↑UCP1 expression
β-carotene (Red-colored fruits and vegetables)	Conversion into retinoids and apocarotenoids	Indirect WAT browning
Trans retinoic acid	Lipocalin 2-driven regulation of gene transcription	↑UCP1 expression
Eicosapentaenoic acid (Fish oil)	Agonists of PPARα and PPARγ	↑ Glucose and lipid metabolism. ↑UCP1 expression, PPARα and β3-AR
Conjugated linoleic acid (Cow milk)	NE-dependent activation of adipocyte	Selective browning of omWAT
Thymol	Selective β3-sympathomimetic	Promotion of lipolysis and lipid oxidation Upregulation of UCP1 Mitochondrial biogenesis
Curcumin (Curcuma longa)	Activation of AMPK-dependent signal Pathways	↑UCP1 expression and of brite/specific Markers
L-menthol	Ca^{2+}-dependent phosphorylation of PKA and activation of downstream pathways	↑UCP1 expression Mitochondrial biogenesis

Table 1: *Endogenous: pharmacological: and nutritional factors involved in BAT development and WAT browning. Adapted from: [43]. AgRP: Agouti-Related Peptide; AMPK: cAMP-Activated Protein Kinase; ANP: Atrial Natriuretic Peptide; BAIBA: β-Aminoisobutyric Acid; BDNF: Brain-Derived Neurotrophic Factor; BMP: Bone Morphogenetic Protein; cAMP: Cyclic Adenosine Monophosphate; CART: Cocaine-Regulated and Amphetamine-Regulated Transcript; DIO2: Type II Iodothyronine 50-Deiodinase; FGF21: Fibroblast Growth Factor 21; MAPK: p38 Mitogen-Activated Protein Kinase; NPY: Neuropeptide Y; omWAT: Omental WAT; PKA: Protein Kinase A; PGC-1α: PPARγ Coactivator-1α; POMC: Proopiomelanocortin; PPAR: Peroxisome Proliferator-Activated Receptor; TrkB: Tyrosine Kinase Receptor B; PI3K: Phosphatidylinositol-4,5-Biphosphate 3-Kinase; SIRT1: Silent Information Regulator Type 1; scWAT: Subcutaneous WAT; TRPM8: Transient Receptor Potential Cation Channel Subfamily M: Member 8; UCP1: Uncoupling Protein 1.*

Therapeutic applications of BAT

Brown adipogenic thermogenesis as a therapeutic target can be considered for managing obesity and related diseases due to the significant capacity of BAT to accelerate energy [47]. Research suggests that BAT may be a promising pharmacological tool and even a precise controller of energy balance. People living in cold environments have a lower risk of developing diabetes because they have higher BAT levels. Furthermore, the functions of BAT in patients are inversely related to obesity, aging, and impaired glucose tolerance [5]. Increased BAT quantity and activity positively affect glucose homeostasis independent of body weight (Figure 6) [48].

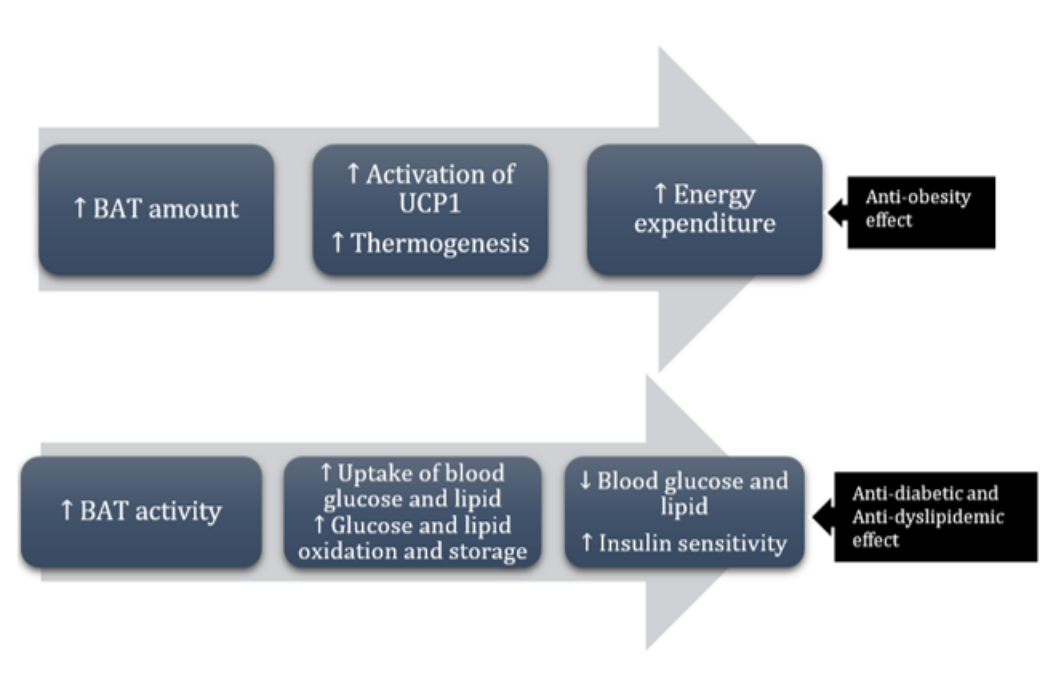

Figure 6: *Obesity and associated metabolic diseases are treated by targeting BAT.*

Activated BAT promotes glucose uptake, and cold-induced stimulation of BAT promotes glucose uptake, whole-body glucose clearance, and glycemic levels in humans [49]. A study involving healthy individuals and using indirect calorimetry and stable isotopes revealed that cold stimulation increased resting metabolic rate by 14% in those with detectable BAT levels, and this increase was fueled by plasma-derived glucose (30%) and free fatty acid oxidation (70%) [50]. Similarly, insulin sensitivity was increased in overweight or diabetic individuals following a periodic cold stimulation treatment. A short-term 10-day cold exposure increased BAT activity and resulted in 43% greater whole-body insulin sensitivity in overweight individuals with diabetes [51].

Stanford., *et al*. (2013) transferred BAT from male donor mice into the visceral cavity of age- and sex-matched recipient mice to evaluate its role in the direct regulation of glucose homeostasis. Glucose and insulin sensitivity increased, body and fat mass decreased, and insulin resistance induced by a high-fat diet was fully restored in recipient mice [52]. Furthermore, β3-adrenoreceptor agonists increase BAT glucose metabolic activity in mice. According to a recent study by Cypess., *et al*. (2015), mirabegron, a selective 3-adrenoreceptor agonist

recommended for the treatment of incontinence, could stimulate BAT in healthy individuals, with a single 200 mg tablet increasing the metabolic rate by 203 kcal/day (e.g., 13%) [53].

Capsinoids have also been a viable therapeutic strategy for treating obesity in mouse studies [54]. They may increase BAT thermogenesis and reduce body fat by activating TRPV1 and the SNS. They have a comparable thermogenic effect in humans [55].

GLP-1 agonism, via hypothalamic AMPK, increases BAT thermogenesis and browning. According to Beiroa., *et al*. (2014), obese patients with T2DM managed with liraglutide (a GLP-1 analog) have increased energy expenditure, possibly because of elevated BAT thermogenesis and WAT browning [56].

Menopausal women tend to gain weight, suggesting the protective role of female sex hormones against obesity. Estrogen receptor alpha promoted WAT browning. Significantly, estrogen receptor signaling increases mitochondrial biogenesis and has been shown to have lipolytic and antilipogenic characteristics. Kim., *et al*. (2020) examined the anti-obesity benefits of coumestrol (phytoestrogen). The researchers found that coumestrol expands BAT and decreases WAT mass. Furthermore, coumestrol administration was found to stimulate AMPK signaling in BAT and mitochondrial biogenesis, dependent on the expression of the estrogen receptor alpha (ESR1) [57].

As BAT is an insulin-sensitive tissue, its stimulation can influence whole-body glucose metabolism postprandially. According to Chondronikola., *et al*. (2014), chronically active BAT (above 70 mL) may dispose of 23g of glucose in 24h [50]. Targeting BAT can potentially be helpful in the treatment of autoimmune disorders. According to Moon., *et al*. (2014), BAT alleviates rheumatoid arthritis by inhibiting Th17 cells. They implanted collagen-induced arthritis mice-derived BAT (CIA BAT) and normal BAT into CIA recipient mice and evaluated their functions.

Normal BAT-transplanted mice had considerably reduced skeletal abnormalities, inflammation, and cartilage degradation levels. The levels of proinflammatory cytokines such as IL-12, IL-17, IL-6, and TNF appeared to decrease in rats transplanted with normal BAT. Furthermore, a microarray study revealed that CIA BAT tissues had considerably higher levels of the PI3K-AKT signaling pathway and IL-17 than normal BAT tissues [58].

Adverse effects of promoting BAT or BAT augmentation

According to a recent study, extra adipose tissue plays a crucial role in the development of obesity, which can cause significant health problems. Obesity increases the possibility of developing T2DM by allowing the body to become insulin-dependent. Individuals with adipose tissue deficit (e.g., lipodystrophy) also have metabolic syndrome [59].

As a person matures, the loss of traditional brown adipocytes and brown-like adipocytes in WAT increases, reducing energy expenditure and contributing to an obesity-prone phenotype. BAT was also affected by impaired brown adipogenic stem/progenitor cell activity. It minimizes the regeneration ability of BAT [60]. Furthermore, few studies have shown that increased sympathetic activity in people with active BAT can induce higher blood pressure levels, contributing to atherogenesis [61].

Typically, the detrimental consequences of brown fat remain largely unclear. For example, uncontrolled brown fat activity may result in incredibly high-temperature levels, although studies are yet to demonstrate this aspect. Furthermore, sympathetic nerve stimulation causes the activation of brown fat, which has been associated with an increase in blood pressure and heart rate. However, these cardiovascular adverse effects may occur independently of brown fat [62]. Adverse outcomes related to the induction of browning are detailed in Figure 7 [63].

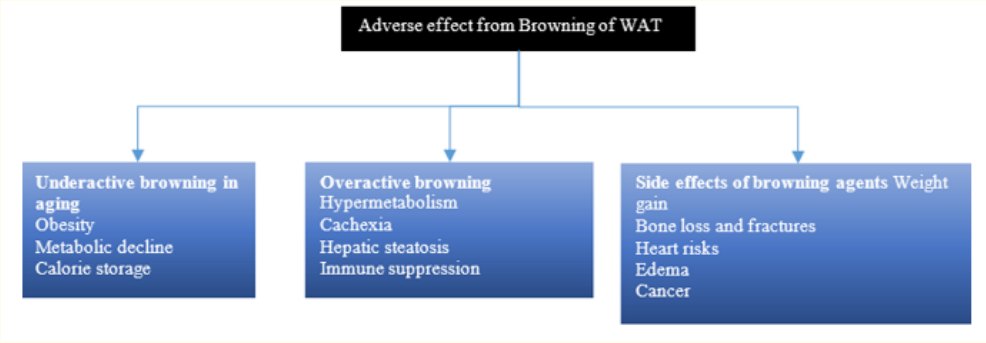

Figure 7: *Adverse outcomes associated with the induction of browning. Adapted from: [63].*

Future of BAT research and its applications

Research on the biology of BAT in living organisms continues. The development of therapeutic techniques to harness BAT requires a thorough understanding of the mechanisms that regulate the function and mass of BAT, as well as the impact of changing the function and mass of BAT on human energy metabolism. Despite being a significant promoter of BAT development, operation and metabolic advantages, it is doubtful that humans widely embrace cold exposure at the cost of personal comfort. Controlling internal housing temperatures to allow for minor cooling of inhabitants, on the contrary, is a feasible and acceptable public health policy at the population level to help combat the obesity epidemic. The efficacy of cold exposure research in managing obesity is necessary [28].

A growing body of evidence suggests that BAT-mediated thermoregulation may significantly affect human energy balance. Stimulating brown fat-mediated thermogenesis may offer therapeutic promise in treating obesity, hyperglycemia, and metabolic syndrome, unlocking new avenues for interventional therapy. However, crucial challenges must be resolved in addition to these significant advances [16].

Several critical concerns that, if addressed, may help in the design of BAT-based therapeutics. For starters, the fidelity of neural stem cells to the thermogenic lineage is unknown. Understanding the processes of brown fat specificity may be highly beneficial in boosting the transition of non-thermogenic cells to brown adipocytes. It is unclear if relying on BAT or beige adipocytes is preferable as a strategy to improve energy expenditure [64].

New areas of BAT involvement, such as epicardial fat, and detection of novel metabolic impacts, such as cardiac NPs, will aid in creating and executing new BAT research ideas. In addition, new locations of involvement of BAT, such as epicardial fat, and detection of novel metabolic impacts, such as cardiac NP, will help create and apply novel perspectives in BAT research [16].

Finally, non-invasive approaches are desired to distinguish alterations in BAT activity from bulk—critical for formulating treatment strategies; for example, drugs that only alter BAT bulk should be supplemented with those that stimulate BAT function to obtain optimal therapeutic advantages [28].

Conclusion

Modern comprehension of the activities of BAT has progressed, and it is clear that the tissue performs several functions beyond temperature regulation. Following substantial proof of its existence and versatility in metabolism in adult humans, there has been a resurgence of interest in BAT over the past decade. According to recent studies, the average adult BAT reacts to cold stimulation in acute

and long-term situations and is controlled by adrenergic activation. In addition, the discovery of beige adipocytes and the phenomenon of WAT browning have contributed to the identification of BAT as a targeted therapy for managing metabolic disorders. The FDG-PET/CT is a routinely used technique for detecting BAT, although additional methods, such as IT and DECT, are being investigated.

Conflict of Interest Statement

The authors declare that this paper was written without any commercial or financial relationship that could be construed as a potential conflict of interest.

References

1. Trayhurn P. "Origins and early development of the concept that brown adipose tissue thermogenesis is linked to energy balance and obesity". *Biochimie* 134 (2017): 62-70. https://pubmed.ncbi.nlm.nih.gov/27621146/

2. Lee P., *et al*. "Brown adipose tissue in adult humans: a metabolic renaissance". *Endocrine Reviews* 34.3 (2013): 413-438. https://pubmed.ncbi.nlm.nih.gov/23550082/

3. Halpern B., *et al*. "Brown adipose tissue: what have we learned since its recent identification in human adults". *Arquivos Brasileiros De Endocrinologia E Metabologia* 58.9 (2014): 889-899. https://pubmed.ncbi.nlm.nih.gov/25627043/

4. Wang W and Seale P. "Control of brown and beige fat development". *Nature Reviews Molecular Cell Biology* 17.11 (2016): 691-702. https://pubmed.ncbi.nlm.nih.gov/27552974/

5. Park A., *et al*. "Distinction of white, beige and brown adipocytes derived from mesenchymal stem cells". *The World Journal of Stem Cells* 6.1 (2014): 33-42. https://pubmed.ncbi.nlm.nih.gov/24567786/

6. Colaianni G., *et al*. "Anatomy and physiology of adipose tissue". In: Multidisciplinary Approach to Obesity. Springer International Publishing (2015): 3-12.

7. Chen YCI., *et al*. "Measurement of human brown adipose tissue volume and activity using anatomic MR imaging and functional MR imaging". *The Journal of Nuclear Medicine* 54.9 (2013): 1584-1587. https://pubmed.ncbi.nlm.nih.gov/23868958/

8. Cedikova M., *et al*. "Mitochondria in white, brown, and beige adipocytes". *Stem Cells International* (2016): 6067349. https://pubmed.ncbi.nlm.nih.gov/27073398/

9. Parlee SD., *et al*. "Quantifying size and number of adipocytes in adipose tissue". *Methods in Enzymology* 537 (2014): 93-122. https://pubmed.ncbi.nlm.nih.gov/24480343/

10. Alcalá M., *et al*. "Mechanisms of impaired brown adipose tissue recruitment in obesity". *Frontiers in Physiology* 10 (2019): 94. https://pubmed.ncbi.nlm.nih.gov/30814954/

11. Luo L and Liu M. "Adipose tissue in control of metabolism". *Journal of Endocrinology* 231.3 (2016): R77-R99. https://pubmed.ncbi.nlm.nih.gov/27935822/

12. Ojha S., *et al*. "Adipocytes in Normal Tissue Biology". In: Pathobiology of Human Disease. Elsevier (2014): 2003-2013. https://www.researchgate.net/publication/300284439_Adipocytes_in_Normal_Tissue_Biology

13. Urisarri A., *et al*. "BMP8 and activated brown adipose tissue in human newborns". *Nature Communications* 12.1 (2021): 5274. https://www.nature.com/articles/s41467-021-25456-z

14. Tam CS., *et al*. "Brown adipose tissue: mechanisms and potential therapeutic targets". *Circulation* 125.22 (2012): 2782-2791. https://pubmed.ncbi.nlm.nih.gov/22665886/

15. Symonds ME. "Brown adipose tissue growth and development". *Scientifica* (2013): 305763. https://pubmed.ncbi.nlm.nih.gov/24278771/

16. Zafrir B. "Brown adipose tissue: research milestones of a potential player in human energy balance and obesity". *Hormone and Metabolic Research* 45.11 (2013): 774-785. https://pubmed.ncbi.nlm.nih.gov/23803970/

17. Chen HJ., *et al*. "The role of brown adipose tissue dysfunction in the development of cardiovascular disease". *Frontiers in Endocrinology* 12 (2021): 652246. https://pubmed.ncbi.nlm.nih.gov/34113316/

18. Cypess AM., *et al*. "Identification and importance of brown adipose tissue in adult humans". *The New England Journal of Medicine* 360.15 (2009): 1509-1517. https://pubmed.ncbi.nlm.nih.gov/19357406/

19. Carpentier AC., *et al*. "Brown adipose tissue energy metabolism in humans". *Frontiers in Endocrinology* 9 (2018): 447. https://pubmed.ncbi.nlm.nih.gov/30131768/

20. Vijgen GHEJ., *et al*. "Increase in brown adipose tissue activity after weight loss in morbidly obese subjects". *The Journal of Clinical Endocrinology and Metabolism* 97.7 (2012): E1229-1233. https://pubmed.ncbi.nlm.nih.gov/22535970/

21. Wu C., *et al*. "Activating brown adipose tissue for weight loss and lowering of blood glucose levels: a microPET study using obese and diabetic model mice". *PLoS One* 9.12 (2014): e113742. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0113742

22. Brown Fat Weight Loss Research: Brown Adipose Tissue (BAT) (2022).

23. Wolf G. "Brown adipose tissue: the molecular mechanism of its formation". *Nutrition Reviews* 67.3 (2009): 167-171. https://www.sciencedirect.com/topics/medicine-and-dentistry/brown-adipose-tissue

24. Wang X., *et al*. "Gab2 deficiency suppresses high-fat diet-induced obesity by reducing adipose tissue inflammation and increasing brown adipose function in mice". *Cell Death and Disease* 12.2 (2021): 212. https://www.nature.com/articles/s41419-021-03519-9

25. De-Lima-Júnior JC., *et al*. "Abnormal brown adipose tissue mitochondrial structure and function in IL10 deficiency". *Ebio Medicine* 39 (2019): 436-447. https://pubmed.ncbi.nlm.nih.gov/30502051/

26. Abreu-Vieira G., *et al*. "Human brown adipose tissue estimated with magnetic resonance imaging undergoes changes in composition after cold exposure: An in vivo MRI study in healthy volunteers". *Frontiers in Endocrinology* 10 (2019): 898. https://www.frontiersin.org/articles/10.3389/fendo.2019.00898/full

27. Schulz TJ and Tseng YH. "Brown adipose tissue: development, metabolism and beyond". *Biochemical Journal* 453.2 (2013): 167-178. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3887508/

28. Thuzar M and Ho KKY. "MECHANISMS IN ENDOCRINOLOGY: Brown adipose tissue in humans: regulation and metabolic significance". *European Journal of Endocrinology* 175.1 (2016): R11-25. https://pubmed.ncbi.nlm.nih.gov/27220620/

29. Di Gregorio I., *et al*. "Environmental pollutants effect on brown adipose tissue". *Frontiers in Physiology* 9 (2018): 1891. https://www.researchgate.net/publication/330249569_Environmental_Pollutants_Effect_on_Brown_Adipose_Tissue

30. La Merrill M., *et al*. "Perinatal exposure of mice to the pesticide DDT impairs energy expenditure and metabolism in adult female offspring". *PLoS One* 9.7 (2014): e103337. https://journals.plos.org/plosone/article/comments?id=10.1371/journal.pone.0103337

31. Araujo JA., *et al*. "Ambient particulate pollutants in the ultrafine range promote early atherosclerosis and systemic oxidative stress". *Circulation Research* 102.5 (2008): 589-596. https://pubmed.ncbi.nlm.nih.gov/18202315/

32. Xu X., *et al*. "Long-term exposure to ambient fine particulate pollution induces insulin resistance and mitochondrial alteration in adipose tissue". *Toxicological Sciences* 124.1 (2011): 88-98. https://pubmed.ncbi.nlm.nih.gov/21873646/

33. Shabalina IG., *et al*. "The environmental pollutants perfluorooctane sulfonate and perfluorooctanoic acid upregulate uncoupling protein 1 (UCP1) in brown-fat mitochondria through a UCP1-dependent reduction in food intake". *Toxicological Sciences* 146.2 (2015): 334-343. https://pubmed.ncbi.nlm.nih.gov/26001964/

34. Manna P and Jain SK. "Obesity, oxidative stress, adipose tissue dysfunction, and the associated health risks: Causes and therapeutic strategies". *Metabolic Syndrome and Related Disorders* 13.10 (2015): 423-444. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4808277/

35. Vgontzas AN., *et al*. "Sleep apnea and sleep disruption in obese patients". *Archives of Internal Medicine* 154.15 (1994): 1705-1711. https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/619157

36. Punjabi NM and Beamer BA. "C-reactive protein is associated with sleep-disordered breathing independent of adiposity". *Sleep* 30.1 (2007): 29-34. https://pubmed.ncbi.nlm.nih.gov/17310862/

37. Lidell ME., *et al*. "Brown adipose tissue and its therapeutic potential". *Journal of Internal Medicine* 276.4 (2014): 364-377. https://onlinelibrary.wiley.com/doi/pdf/10.1111/joim.12255

38. Ouellet V., *et al*. "Brown adipose tissue oxidative metabolism contributes to energy expenditure during acute cold exposure in humans". *Journal of Clinical Investigation* 122.2 (2012): 545-552. https://pubmed.ncbi.nlm.nih.gov/22269323/

39. Bartelt A., *et al*. "Brown adipose tissue activity controls triglyceride clearance". *Nature Medicine* 17.2 (2011): 200-205. https://pubmed.ncbi.nlm.nih.gov/21258337/

40. Kajimura S., *et al*. "Brown and beige fat: Physiological roles beyond heat generation". *Cell Metabolism* 22.4 (2015): 546-559. https://pubmed.ncbi.nlm.nih.gov/26445512/

41. Kajimura S and Saito M. "A new era in brown adipose tissue biology: molecular control of brown fat development and energyy homeostasis". *Annual Review of Physiology* 76.1 (2014): 225-249. https://pubmed.ncbi.nlm.nih.gov/24188710/

42. Shan T., *et al*. "Lkb1 controls brown adipose tissue growth and thermogenesis by regulating the intracellular localization of CRTC3". *Nature Communications* 7.1 (2016): 12205. https://www.nature.com/articles/ncomms12205

43. Montanari T., *et al*. "Factors involved in white-to-brown adipose tissue conversion and in thermogenesis: a review". *Obesity Reviews* 8.5 (2017): 495-513. https://pubmed.ncbi.nlm.nih.gov/28187240/

44. Nedergaard J and Cannon B. "The browning of white adipose tissue: Some burning issues". *Cell Metabolism* 20.3 (2014): 396-407. https://pubmed.ncbi.nlm.nih.gov/25127354/

45. Lu KY., *et al*. "Clinical application potential of small molecules that induce brown adipose tissue thermogenesis by improving fat metabolism". *Cell Transplantation* 29 (2020): 963689720927394. https://pubmed.ncbi.nlm.nih.gov/32854518/

46. McNeill BT., *et al*. "MECHANISMS IN ENDOCRINOLOGY: Human brown adipose tissue as a therapeutic target: warming up or cooling down?" *European Journal of Endocrinology* 184.6 (2021): R243-R259. https://pubmed.ncbi.nlm.nih.gov/33729178/

47. Brandão BB., *et al*. "Thermogenic fat: Development, physiological function, and therapeutic potential". *International Journal of Molecular Sciences* 22.11 (2021): 5906. https://pubmed.ncbi.nlm.nih.gov/34072788/

48. Kim SH and Plutzky J. "Brown fat and browning for the treatment of obesity and related metabolic disorders". *Diabetes and Metabolism Journal* 40.1 (2016): 12-21. https://pubmed.ncbi.nlm.nih.gov/26912151/

49. Marlatt KL and Ravussin E. "Brown adipose tissue: An update on recent findings". *Current Obesity Reports* 6.4 (2017): 389-396. https://pubmed.ncbi.nlm.nih.gov/29101739/

50. Chondronikola M., *et al*. "Brown adipose tissue improves whole-body glucose homeostasis and insulin sensitivity in humans". *Diabetes* 63.12 (2014): 4089-4099. https://pubmed.ncbi.nlm.nih.gov/25056438/

51. Hanssen MJW., *et al*. "Short-term cold acclimation improves insulin sensitivity in patients with type 2 diabetes mellitus". *Nature Medicine* 21.8 (2015): 863-865. https://pubmed.ncbi.nlm.nih.gov/26147760/

52. Stanford KI., *et al*. "Brown adipose tissue regulates glucose homeostasis and insulin sensitivity". *Journal of Clinical Investigation* 123.1 (2013): 215-223. https://pubmed.ncbi.nlm.nih.gov/23221344/

53. Cypess AM., *et al*. "Activation of human brown adipose tissue by a β3-adrenergic receptor agonist". *Cell Metabolism* 21.1 (2015): 33-38. https://pubmed.ncbi.nlm.nih.gov/25565203/

54. Baskaran P., *et al*. "Capsaicin induces browning of white adipose tissue and counters obesity by activating TRPV1 channel-dependent mechanisms: TRPV1 activates browning of WAT to counter obesity". *British Journal of Pharmacology* 173.15 (2016): 2369-2389. https://pubmed.ncbi.nlm.nih.gov/27174467/

55. Saito M and Yoneshiro T. "Capsinoids and related food ingredients activating brown fat thermogenesis and reducing body fat in humans". *Current Opinion in Lipidology* 4.1 (2013): 71-77. https://pubmed.ncbi.nlm.nih.gov/23298960/

56. Beiroa D., *et al*. "GLP-1 agonism stimulates brown adipose tissue thermogenesis and browning through hypothalamic AMPK". *Diabetes* 63.10 (2014): 3346-3358. https://pubmed.ncbi.nlm.nih.gov/24917578/

57. Kim SN., *et al*. "Antiobesity effects of coumestrol through expansion and activation of brown adipose tissue metabolism". *Journal of Nutritional Biochemistry* 76.108300 (2020): 108300. https://europepmc.org/article/med/31812908

58. Moon J., *et al*. "Brown adipose tissue ameliorates autoimmune arthritis via inhibition of Th17 cells". *Scientific Reports* 10.1 (2020): 12374. https://www.nature.com/articles/s41598-020-68749-x

59. Grundy SM. "Adipose tissue and metabolic syndrome: too much, too little or neither". *European Journal of Clinical Investigation* 45.11 (2015): 1209-1217. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5049481/

60. Graja A and Schulz TJ. "Mechanisms of aging-related impairment of brown adipocyte development and function". *Gerontology* 61.3 (2015): 211-217. https://www.karger.com/Article/Fulltext/366557

61. Raiko J., *et al*. "High brown fat activity correlates with cardiovascular risk factor levels cross-sectionally and subclinical atherosclerosis at 5-year follow-up". *Arteriosclerosis, Thrombosis, and Vascular Biology* 40.5 (2020): 1289-1295. https://pubmed.ncbi.nlm.nih.gov/31941384/

62. Exploring brown fat: The long road ahead (2022).

63. Tamucci KA., *et al*. "The dark side of browning". *Protein Cell* 9.2 (2018): 152-163. https://pubmed.ncbi.nlm.nih.gov/28677104/

64. Jung SM., *et al*. "Brown adipose tissue development and metabolism". *The Handbook of Experimental Pharmacology* 251 (2019): 3-36. https://pubmed.ncbi.nlm.nih.gov/30203328/

Volume 9 Issue 9 September 2022