Geliş Tarihi:02.04.2018
Kabul Tarihi:30.09.2018
SPORMETRE, 2018,16(3),28-38
DOI: 10.1501/Sporm_0000000373

BROWN ADIPOSE TISSUE AND METABOLIC WINTER HYPOTHESIS: A KEY TO SOLVING OBESITY?*

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Abstract: Brown Adipose Tissue (BAT) present only in mammals play a significant role in maintaining body temperature through non-shivering thermogenesis during the early days of extra-uterine life. "Metabolic Winter Hypothesis", suggests that cold exposure is one the most powerful and physiological stimulus for BAT activation resulting in weight loss through increased thermogenesis. The objective of this study was to review the relationship between cold stress (metabolic winter hypothesis) and related factors in energy metabolism through activation of brown adipose tissue.
Literature search was conducted using Science direct, Medline, Scopus data bases, 59 studies were included in this review. Mitochondrion rich BAT are unique in the sense that they bypass adenosine triphosphate (ATP) production and instead create heat by activating uncoupling protein 1 (UCP-1). Repeated stimulation by cold (16-18°C) few hours per day for a period of 6 weeks in human adults resulted in hyperplasia of brown adipocytes and increased tissue mass. Increased stimulation from sympathetic nerve endings also resulted in increased UCP-1 activity as found in studies performed with rodents and humans. Melatonin, a hormone associated with sleep, acting to lower the core body temperature, increased BAT activity and improved glucose metabolism. New studies suggest that Sirtuins (Sır-2) proteins and exercise-induced production of Irisin causes an increase in BAT activity by stimulating mitochondrial biogenesis in brown adipocytes leading to increased energy expenditure. Further studies are required to elucidate the novel relationship between cold stress and altered energy metabolism, promising a solution to obesity related progressive metabolic diseases.

Key words: BAT, Metabolic Winter Hypothesis, Cold Stress, Melatonin, Irisin

**This work was shared as an oral presentation at 4th International Conference on Computational and Experimental Science and Engineering, held between 04.10.2017 to 08.10.2017 at Side - Antalya, Turkey*

INTRODUCTION

Mammals have two types of adipose tissues namely white and brown, possessing separate roles in energy metabolism of the body. While white adipose tissue (WAT) is for energy storage, brown adipose tissue (BAT) is responsible for cold- and diet-induced thermogenesis, which significantly contributes to the control of body temperature and energy expenditure owing to the presence of a mitochondrial protein called uncoupling protein (UCP1) or thermogenin (Cannon and Nedergaard, 2004; Scheelea et al., 2017). Although all skeletal muscle cells are associated with adaptive (shivering) thermogenesis, BAT plays a significant role in maintaining body temperature through "non-shivering thermogenesis" in the neonates during the early days of extra-uterine life. During the first decade of life there appears to be a wide distribution of active brown fat in all areas of the body. This gradually disappears with advancing years. Recent reports on BAT detected by MRI and PET/CT-scan technologies indicate that the amount of active brown fat declines with age and restricted to the area around neck vessels, intercostal vessels, para-aortic and peri-renal region (Chen et al., 2013; Rasmussen et al., 2013). However,

BAT appears to play a protective role against obesity/adiposity risk and metabolic dysfunction (Fenzl and Kiefer, 2014; Attie and Scherer, 2009; Trayhurn, 2007).

In response to cold, BAT is activated through sympathetic signalling. Norepinephrine activates β3-adrenergic receptors on the brown adipocytes, initiating lipolysis of the intracellular triglyceride storage. Free fatty acids are released as substrate, triggering mitochondrial respiration, which generates a mitochondrial membrane potential. However, instead of producing ATP, the mitochondrial membrane potential is uncoupled through mitochondrial UCP1, resulting in dissipation of the energy as heat (Saito et al., 2009). Thus, through this mechanism brown fat consumes energy and has thereby become an attractive target in the battle against obesity as suggested by the metabolic winter hypothesis (Cronise et al., 2014). Increased stimulation from sympathetic nerve endings also result in increased UCP-1 activity as found in studies performed with rodents and humans (Bartness et al., 2010). Apart from cold stress, exercise-induced production of irisin is also suggested to cause an increase in BAT and an associated increase in energy expenditure (Sanchez-Delgado et al., 2015). Melatonin, a hormone associated with onset and quality of sleep, acts to lower the core body temperature and helps in energy regulation through improved glucose metabolism (Cronise et al., 2014). Oral melatonin administration in young zucker diabetic rats have been shown to ameliorate glucose homeostasis rats by improving both insulin action and B-cell function (Agil et al., 2012) as well restoring insulin-induced vasodilation to skeletal muscle, a major site of glucose utilization (Sartori et al., 2009).

The objective of this study was to review the relationship between cold stress (metabolic winter hypothesis) and related factors in energy metabolism through activation of brown adipose tissue.

MATERIAL AND METHODS

This study was executed as per criteria established in the preferred reporting items for systematic review and meta-analysis (PRISMA) (Moher et al., 2014). No design limit was imposed on search of articles, although publications only in English language were included within the scope of the research. Original research articles on human and animal models as well as review studies pertaining to the subject mostly within the last 10 years were taken under review. The articles selected were investigated under three categories. (i) brown adipose tissue (BAT) and its role in thermogenesis (ii) effect of cold exposure/stress (metabolic winter hypothesis) on BAT metabolism and obesity (iii) other related factors that play a role in energy metabolism through activation of BAT. For the first category the search process was conducted using the keywords “Brown adipose tissue (BAT)”, “obesity”, “ glucose homeostasis”, “weight loss”. For the second and third category, additional key words such as “metabolic winter”, “cold stress”, “irisin”, “melatonin”, “sirtuins” were used for literature review.

MEDLINE, Pubmed, Elseiver Journal, Science Direct and Springer Link was searched for publications in English documenting BAT’s role in energy metabolism and management of obesity through non-shivering thermogenesis, as well as understand the the role of other factors as irisin hormone secreted during exercise, melatonin hormone related with sleep, sirtuin proteins in BAT metabolism. Literature search was conducted during the month of July 2017. Titles and abstracts of all articles possessing the mentioned keywords were first assessed, most suitable ones that would contribute to the review were

fully downloaded and utilized for the review study. One of the objectives of this study was to elucidate the term "metabolic winter" suggested by Cronise et al. in their review study published in 2014 (Cronise et al., 2014). This term was not encountered elsewhere during the search however, metabolism of brown adipose tissue was shown to be primarily affected by cold stress and other factores like exercise induced irisin, sleep hormone melatonin and sirtuins thus altering energy metabolism of the body, glucose homeostatis and adiposity. Literature search was therefore conducted using keywords related to these topics. Finally a total of 44 original research and 15 review articles were included within the scope of this study.

Due to the nature of the review, no request was sought for approval from the ethics committee.

RESULTS AND DISCUSSION

Brown Adipose Tissue (BAT) and its Role in Thermogenesis

Apart from the role of Brown adipose tissue in heat production through non-shivering thermogenesis, involvement of the tissue for diverse types of metabolic inefficiency (i.e, as a possible antiobesity organ) has only been discussed for the last two decades (Cannon and Nedergaard, 2004; Fenzl and Kiefer, 2014; Attie and Scherer, 2009; Trayhurn, 2007). The uncoupling protein UCP1 also known as thermogenin is a member of the mitochondrial carrier proteins present in BAT and is responsible for its unique function. The tissue is surrounded by capillaries enabling adequate supply of substrates and dissipation of heat, nerve endings and pre-adipocytes that, under conditions of increased thermogenic demand, will divide and differentiate to form new brown adipocytes. Information on body temperature, feeding status, and body energy reserves is coordinated in the ventromedial hypothalamic nucleus (VMN). When there is reason to increase the rate of food combustion (decrease metabolic efficiency) or increase the rate of heat production, a signal is transmitted via the sympathetic nervous system to the individual brown adipocytes. The released transmitter, norepinephrine (NE), initiates triglyceride breakdown in the brown adipocytes, primarily via beta-3-adrenergic receptors. The intracellular signal is transmitted via cAMP and protein kinase A, leading to the release from triglycerides (TG) of fatty acids (FFA) that are both the acute substrate for thermogenesis. UCP1 enables mitochondrial combustion of substrates, uncoupled from the production of ATP (uncoupled respiration), by functionally being a H ion transporter leading to an increased heat production termed as non-shivering thermogenesis (Cannon and Nedergaard, 2004; Fenzl and Kiefer, 2014; Cronise et al., 2014).

Adipose tissue present in the body are of three types namely, white, brown and beige.White adipose tissue (WAT) mainly consists of mature white adipocytes, which can store excess energy in the form of triglycerides that can be released as free fatty acids into the circulation in times of high energy demand. Moreover, WAT serves as a thermal insulator, protects organs against mechanical damage and secretes adipokines that are implicated in inflammation, angiogenesis, and metabolism (Attie and Scherer, 2009; Trayhurn, 2007). Visceral WAT is closely associated with inflammation, insulin resistance, and type 2 diabetes (Trayhurn, 2007); whereas subcutaneous WAT has been shown to be less inflammatory but more susceptible to acquiring brown fat characteristics (Fenzl and Kiefer, 2014; Wu et al., 2012). Brown fat tissue in infants (iBAT) functions as a thermogenic organ consisting of classical brown adipocytes that is essential for the

survival of small mammals in a cold environment. iBAT was identified not only in the supraclavicular region but also in interscapular region using fat fraction methods (Lidell et al., 2013). In addition, it was also suggested that there are two distinct types of brown fat: classical brown fat derived from a myf-5 cellular lineage and UCP1-positive cells that emerge in white fat from a nonmyf-5 lineage called beige or brite cells (Wu et al., 2012; Lidell et al., 2013). Beige cells resemble white fat cells in having extremely low basal expression of UCP1, but, like classical brown fat, they respond to cyclic AMP stimulation with high UCP1 expression and respiration rates. Beige adipose cells are shown to be sensitive to the exercise induced polypeptide hormone irisin (Wu et al., 2012; Lidell et al., 2013). White adipose tissue (WAT) depots possess the capacity to acquire brown fat characteristics in response
to prolonged cold exposure, β-adrenergic stimulation, increased energy expenditure, and protection against obesity and type 2 diabetes. The induction of a BAT-like cellular and molecular program in WAT has been termed as "browning" or "beiging"(Wu et al., 2012).

When exposed to low environmental temperatures, warm blooded animals exhibit thermogenesis which compensates for the increased heat loss and defends body temperature. Thermogenesis may be differentiated as "shivering" and "non-shivering". Shivering is an involuntary, spontaneous, oscillatory mechanical activity of skeletal muscle associated with increased oxygen consumption (Honarmand and Safavi, 2008). Shivering can be divided into thermoregulatory and nonthermoregulatory in nature. Thermoregulatory shivering occurs as a consequence of hypothermia, and inorder to maintain normothermia, vasoconstriction. Non thermoregulatory shivering is less well understood and may be associated with postoperative pain, release of endogenous pyrogens, uninhibited spinal reflexes and adrenal suppression (Padayachee, 2013; Golembiewski, 2015). Non-shivering thermogenesis occurs as a result of chronic cold exposure and beta (β_3) adrenergic agonisits which is entirely brown adipose tissue dependent. In a study performed by Saito et al 17 of 32 subjects aged 23-35 years showed a substantial fluoro-deoxy glucose (FDG) uptake when subjected to cold temperatures (19°C for 2 hours) detected by positron emission tomography (PET) indicating increased metabolic activity of brown adipose tissue in the supraclavicular and paraspinal regions. On the other hand, they showed no detectable uptake when kept warm (27°C). The authors suggested an unexpected high incidence of cold-activated BAT in adult healthy humans and suggest a role in the regulation of metabolic thermogenesis and body fat content (Saito et al., 2009). whereas resting metabolic rate had a significant positive correlation (Lichtenbelt et al., 2009).

Effect of cold exposure/stress (metabolic winter hypothesis) on BAT metabolism and obesity

"Metabolic Winter Hypothesis" suggested by Cronise et al dwells on human body's nutritional and caloric energy balance, and driving weight loss through basic thermodynamic principles, in an age of calorie excess, chronic overnutrition and increasing prevalence of nutritionally related diseases (Cronise, 2014).

Obesity is characterized by an increase in adipose tissue mass. Unlike white adipose tisse, the brown adipose is inversely correlated with BMI in humans. Moreover, BAT consumes large amounts of energy for thermogenesis and may play a fundamental role in the maintenance of a leaner and more metabolically healthy phenotype (Saito et al., 2009; Cypess et al., 2009). BAT is a highly energetic organ that not only utilizes its unique

expression of uncoupling protein 1 (UCP1) for uncoupling of respiration (i.e., cold or diet-induced thermogenesis), but is also a mitochondrially rich tissue that uses glucose and fatty acids as a fuel. BAT activity induced by short-term cold exposure was found to accelerate plasma clearance of triglycerides as a result of increased uptake into BAT, correcting hyperlipidemia and improving deleterious effects of insulin resistance (Bartelt et al., 2011). Therefore it was suggested that substantial depots of metabolically active BAT may play a fundamental role in the maintenance of a leaner and more metabolically healthy phenotype (Bartelt et al., 2011; Stanford et al., 2013).

In a study performed to moniter whether increasing BAT mass by transplantation would improve whole-body and tissue-specific metabolism in mice, 8–12 weeks following transplantation, recipient mice had improved glucose tolerance, increased insulin sensitivity, lower body weight, decreased fat mass, and a complete reversal of high-fat diet–induced insulin resistance. Increasing the mass of transplanted tissue improved the results. The mechanism for this effect was suggested to involves BAT-derived IL-6, as transplantation of BAT from *Il6*-knockout mice failed to significantly improve glucose homeostasis and insulin sensitivity (Stanford et al., 2013).

Perfusion rate is generally matched to the oxygen consumption of a tissue and in the case of BAT, determination of perfusion rate could be used to estimate thermogenesis (Orava et al., 2011). In a study performed in healthy human subjects, cold-induced and insulin-stimulated glucose uptake was induced 12-fold in BAT as compared to white adipose tissue, accompanied by doubling of perfusion (Chondronikola et al., 2014). Furthermore, a positive association between whole-body energy expenditure and BAT perfusion was observed. Insulin was found to enhance glucose uptake 5-fold in BAT independently of its perfusion, while the effect on WAT was weaker. The gene expression level of insulin sensitive glucose transporter GLUT4 was also higher in BAT as compared to WAT. The authors suggested that BAT appeared to be activated differently by insulin and cold. In response to insulin, BAT displayed high glucose uptake without increased perfusion, but when activated by cold, it dissipated energy in a perfusion-dependent manner (Chondronikola et al., 2014).

In another study performed to investigate whether BAT activation altered whole-body glucose homeostasis and insulin sensitivity in humans, individuals with detectable BAT (BAT+) BAT positive or nondetectable BAT (BAT-) BAT negative (BAT-), glucose metabolism markers were evaluated following the individuals'subjection to thermoneutral conditions and prolonged (5–8 hours) of cold exposure (CE). CE significantly increased resting energy expenditure, whole-body glucose disposal, plasma glucose oxidation, and insulin sensitivity in the BAT+ group only (Segal, 2005).

BAT decreases with age and thereby accelerates age-related accumulation of body fat in humans. The effects of repeated stimulation by cold and capsinoids (nonpungent capsaicin analogs) in healthy human subjects with low BAT activity was investigated (Yoneshiro et al., 2013). Acute cold exposure at 19°C for 2 hours increased energy expenditure (EE). Cold-induced increments of EE (CIT) strongly correlated with BAT activity independently of age and fat-free mass. Daily 2-hour cold exposure at 17°C for 6 weeks resulted in a parallel increase in BAT activity and CIT and a concomitant decrease in body fat mass. Changes in BAT activity and body fat mass were negatively correlated. Similarly, daily consumption of capsinoids for 6 weeks increased CIT. These results

demonstrated that human BAT could be recruited even in individuals with decreased BAT activity, thereby contributing to body fat reduction (Yoneshiro et al., 2013).

Other related factors that play a role in energy metabolism through activation of BAT

Irisin

In humans, body fat makes up a larger percentage of weight at birth as compared to any other mammal which is an adaptive mechanism against adverse conditions as starvation and cold stress (Enerback, 2010). Brown adipose tissue which plays a significant role in maintaining body temperature through "non-shivering thermogenesis" during the early days of extra-uterine life was thought to be lost by adulthood until recently (Cronise et al., 2014). New studies suggest that not only can adults have significant amounts of BAT (Kuzawa, 2010; Yoneshiro et al., 2011) but also noted in mice and cell cultures (Swick et al., 2013). Irisin, derived from FNDC5 drives brown-fat-like thermogenesis in murine white fat. In addition, cold exposure was reported to be an afferent signal for irisin secretion in humans and and compared with FGF21, a brown adipokine in rodents. Cold exposure increased circulating irisin and FGF21. An induction of irisin secretion proportional to shivering intensity, in magnitude similar to exercise-stimulated secretion. FNDC5 and/or FGF21 treatment upregulated human adipocyte brown fat gene/protein expression and thermogenesis in a depot-specific manner. The authors suggested that exercise-induced irisin secretion could have evolved from shivering related muscle contraction, serving to augment brown fat thermogenesis in concert with FGF21 (Lee et al., 2014). Furthermore, Irisin levels are reported to be decreased in patients with type 2 diabetes, while positively correlated with BMI, fat mass and muscle mass across a very broad spectrum of body weight (Stengel et al., 2013) . These findings support the notion that modern humans evolved to cope with seasonally cool temperatures or cold stress, and during periods of calorie restriction (Cronise et al., 2014).

Melatonin

Melatonin (N-acetyl-5-methoxytryptamine or, according to IUPAC, N-[2-(5-methoxy-1H-indol-3-yl) ethyl] acetamide) is an ancient molecule ubiquitously present in nature including both plant and animals (Stehle et al., 2013; Gomez et al., 2012; Byeon et al., 2012, Migliori et al., 2012). A connection between sleep and metabolic dysfunction has been reported in ancient Roman medicine (Cronise et al., 2014), scarce sleep is associated with obesity and many cardiometabolic diseases (Cappuccio et al., 2011; Cappuccio et al., 2008). There is increasing evidence showing that sleep has an influence on eating behaviors. Short sleep duration, poor sleep quality, and later bedtimes are all associated with increased food intake, poor diet quality, and excess body weight. Insufficient sleep seems to facilitate the ingestion of calories when exposed to the modern obesogenic environment of readily accessible food. Lack of sleep has been shown to increase snacking, the number of meals consumed per day, and the preference for energy-rich foods (Chaput, 2014). The sleep hormone melatonin largely provided by the pineal gland where it is produced and directly released to the blood and cerebrospinal fluid (Reiter et al., 2014). Melatonin acts to lower the core body temperature, and a steep rate of decline in core body temperature is associated with both sleep onset and quality (Cronise et al., 2014). Moreover, melatonin is known to possess anti-obesogenic and weight-reducing effects depending on several mechanisms of action (Cipolla-Neto et al., 2014).

Experimental evidence demonstrates that melatonin is necessary for the proper synthesis, secretion, and action of insulin. Melatonin acts by increasing insülin sensitivity and regulating GLUT4 expression and/or triggering, via its G-protein-coupled membrane receptors, the phosphorylation of the insulin receptor and its intracellular substrates mobilizing the insülin signaling pathway (Cipolla-Neto et al., 2014; Zanuto et al., 2013). Melatonin is a powerful chronobiotic being responsible, in part, by the daily distribution of metabolic processes so that the feeding phase is associated with high insulin sensitivity and fasting phase is synchronized to the insulin-resistant metabolic phase of the day (Cipolla-Neto et al., 2014). Furthermore, melatonin is responsible for the establishment of an adequate energy balance mainly through the activation of brown adipose tissue and participating in the browning process of white adipose tissue (Jimenez-Aranda et al., 2013). Increased light exposure has been associated with obesity in both humans and mice. It was reported that prolonging daily light exposure increases adiposity by decreasing energy expenditure rather than increasing food intake or activity. This was due to light-exposure period dependent alleviation of the noradrenergic activation of brown adipose tissue (Kooijman et al., 2015). The reduction in melatonin production, as in aging, shift-work or illuminated environments, induces insulin resistance, glucose intolerance, sleep disturbance, and metabolic circadian disorganization characterizing a state of chrono-disruption. (Cipolla-Neto et al., 2014; Kooijman et al., 2015).

Importantly, perturbations of the internal clock system and sleep are established risk factors for obesity, diabetes mellitus, and cardiovascular disease and are associated with metabolic dysfunction (Cronise et al., 2014). Thus melatonin, a naturally occuring substance with no reported toxicity may be considered to serve as a novel approach for treatment of obesity. In this respect, because of the availability of artificial light sources, excessive light exposure after the onset of darkness in modern societies should be considered a potential contributory factor to human obesity as light at night dramatically reduces endogenous melatonin production (Tan et al., 2011).

Sirtuins

The sirtuins family of proteins are highly conserved NAD^+-dependent protein deacetylases and/or ADP-ribosyl transferases that target histones, transcription factors, co-regulators, as well as metabolic enzymes to adapt gene expression and metabolic activity in response to the cellular energy state in organisms (Schug, 2011). Mammals have seven sirtuins (SIRT1-7), each characterized by differences in subcellular localization, substrate preference, and biological function. While it is unclear whether sirtuins regulate aging in mammals, it is clear that sirtuins influence diverse aspects of their metabolism.

Recent studies involving SIRT1, the most intensely studied sirtuin family member, have shown that it regulates many metabolic adaptations linked with obesity (Lomb et al., 2010). SIRT1 promotes oxidation of fatty acids in liver and skeletal muscle, cholesterol metabolism in liver, and lipid mobilization in white adipose tissue. Moreover, small-molecule activators of SIRT1 have recently been shown to protect mice from the negative effects of a high-fat diet (Lomb et al., 2010; Metoyer and Pruitt, 2008). SIRT1 has been shown to regulate the expression of adipokines, repress the activity of factors required for maturation of fat cells, regulate insulin secretion, modulate plasma glucose levels and insulin sensitivity and alter mitochondrial capacity. Moreover, some investigators have suggested that altering SIRT1 activity may be a promising new therapy for type 2 diabetes

(Metoyer and Pruitt, 2008). Sirtuins link nutrient availability and energy metabolism. Calorie restriction, which increases lifespan and is beneficial in age-related disorders, activates sirtuin. Apart from that resveratrol is the most potent natural compound able to activate SIRT1, mimicking the positive effect of calorie restriction (Schug, 2011; Allcain and Villalba, 2009). Animals treated with resveratrol showed increased insulin sensitivity, reduced IGF-1 levels, activation of AMPK and PGC-1α, and increased mitochondrial number (Lomb et al., 2010).

Cold exposure increases SIRT2 and SIRT3 expression in BAT, whereas elevated temperatures decrease the expression of these genes. Although SIRT2 and SIRT3 may both influence BAT function, only SIRT3 has been investigated in this respect. Overexpression of SIRT3 in HIB1B cells, a brown adipocyte precursor cell line has been observed that increases the expression of PPARγ coactivator 1 α (PGC-1α), a master regulator of mitochondrial biogenesis and gene expression of the uncoupling protein UCP1 in BAT (Shi et al., 2005; Wang and Tong, 2009).

CONCLUSION AND FUTURE PERSPECTIVES

There has been an alarming rise in the obesity trend worldwide in recent years and has become a major global health challenge owing to the established health risks associated with it (Seidell and Halberstadt, 2015). Worldwide, the proportion of adults with a body-mass index (BMI) of 25 kg/m²or greater increased between 1980 and 2013 from 28.8% to 36.9% in men, and from 29.8% to 38.0% in women (Marie Ng et al., 2014). It has been demonstrated that daily energy expenditure of traditional hunter-gatherers was no different than that of modern day Western (United States and European) counterparts after controlling for body size (Pontzer et al., 2012). Furthermore, a recent study even demonstrated that energy expenditure from physical activity in humans has not declined since the 1980s (Westerterp and Speakman, 2008). As physical activity expenditure has not declined over the same period that obesity rates have increased dramatically, it is unlikely that decreased expenditure has fuelled the obesity epidemic. On the other hand in a nationwide food consumption survey study performed in US between 1977 and 2006, an increase in total energy intake (+570 kcal/day) and portion sizes (15 kcal/day/age in years) was recorded (Duffey and Popkin, 2011). Although it seems reasonable to assume that obesity is a result of less activity, simply increasing activity through exercise in the absence of a significant lifestyle and dietary modification, is unlikely to have a significant impact. On the other hand, lifestyle modifications involving diet alone can significantly impact both obesity and chronic disease (Hall et al., 2011). Nevertheless, health benefits of physical activity may be considered as adaptive responses related to cold stress and shivering (Cronise et al., 2014; Tansey and Johnson, 2015).

In this study the relationship between cold stress (metabolic winter hypothesis) and related factors in energy metabolism, metabolic syndrome and diabetes through activation of brown adipose tissue has been reviewed. Furthermore, role of other factors on brown adipose tissue metabolism such as sleep hormone melatonin, exercise induced irisin and sirtuins group of proteins have also been discussed briefly. Further studies with human subjects are required to elucidate the novel relationship between cold stress and altered energy metabolism, promising a solution to obesity related progressive metabolic diseases.

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