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Brown Adipose Tissue, Thermogenesis, and Obesity: A Review of Literature

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***Abstract*--** The white adipose tissue (WAT) mass in adult humans ranges between 10-35 kg. The cells are normally sensitive to insulin in the fed state, and to glucagon and adrenaline in fasting or during exercise. Well-fed sedentary individuals are prone to weight gain as they fall victims to the anabolic mechanisms led mainly by insulin. Brown adipose tissue (BAT), by contrast, stores smaller amounts of triglycerides in multi-locular droplets, is highly vascularized and its cells are rich in unique mitochondria which are capable of uncoupling oxidation from phosphorylation or ATP formation. The tissue is innerved by the sympathetic nervous system and is highly sensitive to iodothyronines. It releases heat in the body in response to sympathetic activity. BAT unique mitochondria express numerous cristae and, unlike ordinary mitochondria on other body cells including WAT cells, they express uncoupling protein-1 (UCP-1, or thermogenin). UCP-1 allows the mitochondria to oxidize more fat and glucose as they escape the controlling mechanisms that depend on the coupling of oxidation to the demand for ATP, i.e., uncouples oxidative phosphorylation. Thermogenin (UCP-1) is a natural un-coupler of oxidative phosphorylation as it dissipates the proton gradient generated across the inner mitochondrial membrane, which is required to attain a certain level for the activation of ATP synthesis in mitochondrial matrix. In BAT, ATP synthesis is inhibited, as the protons are dissipated, and most energy is released as heat. The different proportions and activity of BAT and WAT in different individuals might explain why some people are more prone to weight gain, and find it difficult to lose weight, than others; and also explains the tendency for weight gain as individuals get older. New approaches in the battle against obesity, metabolic syndrome and type 2 diabetes mellitus are expected through better understanding of how this balance between WAT and BAT is controlled. Interestingly, long term adrenergic stimulation of WAT induces browning of some white adipocytes, and the tissue gradually turns into "beige" adipose tissue, which shares characteristics of brown adipose tissue like thermogenesis, larger number of mitochondria and smaller lipid droplets, all developing in a gradual way. The adipose tissue interconverts its cell types in order to adapt for the changing metabolic balance and other stimuli. This phenomenon is currently incompletely understood, albeit significant for our understanding of obesity, metabolic syndrome and type 2 diabetes mellitus and many consequent complications of insulin resistance. Moreover, the nervous system is involved in the regulation of WAT and BAT through effects on fat cell proliferation, differentiation, trans-differentiation and apoptosis. The brain interacts with different adipocytes and adipokines in the pathogenesis of obesity, type 2 diabetes mellitus, anorexia, cachexia and other syndromes. This review will target many of these aspects in an attempt to draw more attention in the direction of this major health issue.

Keywords: Brown Adipose Tissue, Thermogenesis, Obesity

1. INTRODUCTION

Adipose tissue is traditionally classified into either white adipose tissue (WAT) or brown adipose tissue (BAT), with different morphology, biochemical activities, and physiological functions [1]. WAT is the more abundant subtype, representing at least 10% of the bodyweight of healthy adult humans. It usually ranges between 10-35 kg in adults, although it might rise to 100 kg or more in obese individuals (Figure 1 and Figure 2).WAT is primarily located in the subcutaneous and visceral depots and is able to store energy as triacylglycerols (triglycerides) and to modulate energy homeostasis through its own activity [2]. The cells clearly demonstrate a large fat vacuole in the cytoplasm, a marginal flattened cytoplasm and a flattened nucleus. The subcellular organelles, particularly the mitochondria, are very few and the vasculature is very limited. The main function is to store fat and the cells are sensitive to insulin in the fed state, and to glucagon and adrenaline in fasting or during exercise [3]. The white adipose tissue can take up dietary or liver synthesized free fatty acids from the blood capillaries when released by lipoprotein lipase from chylomicrons or very low-density lipoproteins, respectively. The lipoprotein lipase is an insulin activated enzyme in the wall of blood capillaries. In addition, the white adipose tissue cells are active in converting glucose into fatty acids and using them to synthesize triacylglycerols and storing them in the cytoplasmic fat globule in the fed state. WAT is therefore a tissue that is designed to capture, build and store fat in the fed state, in the presence of insulin. Well-fed sedentary individuals are therefore prone to weight gain as they fall victims to these anabolic mechanisms lead by insulin [4] (Figure 3).

However, not everyone is prone to obesity as other

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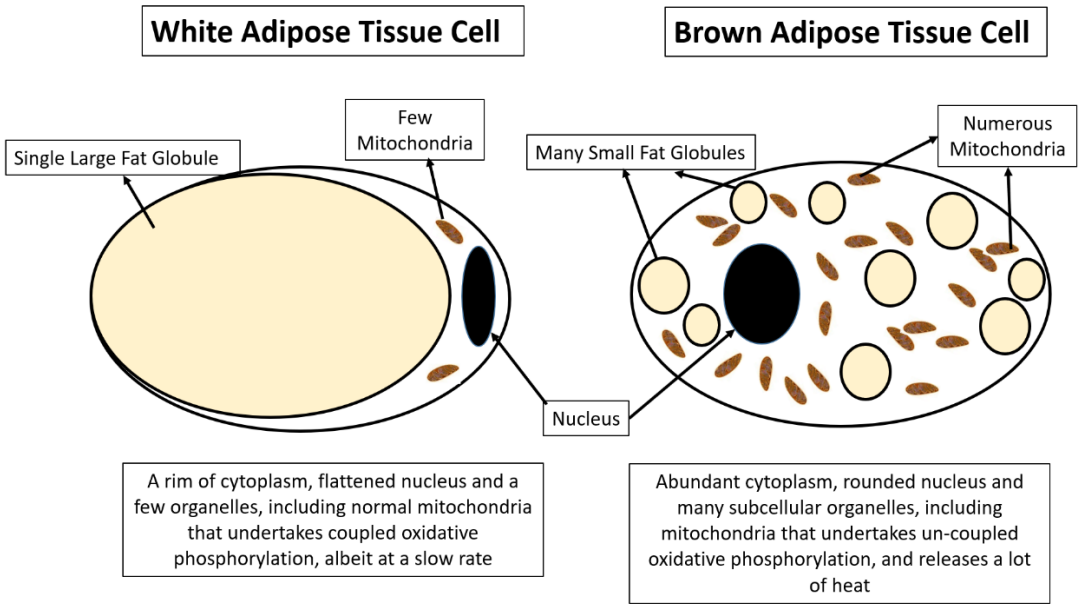

Figure 1. White and Brown Adipose Tissue Cells.

individuals are, and there are many ethnic, racial and altitude (average annual temperature) factors that might affect the lean/fat balance in the human body [5, 6]. At least part of this controversy might open up to rationale when we consider BAT which stores lipids in multi-locular lipid droplets in the cells (Figures 1 and 2). The tissue itself is highly vascularized and innerved by the sympathetic nervous system. BAT provides heat to the body in response to sympathetic nerve activity, and the heat is distributed all over the body via the bloodstream. In addition, BAT cells have unique cellular and molecular characteristics, with the thermogenic activity of BAT carried out in its unique mitochondria [7]. BAT mitochondria express numerous cristae and, unlike ordinary mitochondria in WAT and other body cells, they express uncoupling protein-1 (UCP-1), also known as thermogenin [8, 9]. UCP1 is found only on BAT adipocyte mitochondria, and constitutes the ultimate marker of BAT cells. The presence of this inner mitochondrial membrane protein in BAT allows these subcellular organelles to oxidize more fat and glucose as they escape the controlling mechanisms that depend on coupling of oxidation to the demand for ATP or energy, through the tight coupling of oxidation and phosphorylation or ATP formation. Thermogenin (UCP-1) is an un-coupler of oxidative phosphorylation as it dissipates the proton gradient generated across the inner mitochondrial membrane, which is required for the activation of ATP synthesis in the mitochondria. As a result, ATP synthesis is inhibited and excess energy is released as heat. The different proportions and activity of BAT in certain individuals might, at least in part, explain why some people are more prone to weight gain than others, (Figure 3). In 2009, van Marken-Lichtenbelt et al. demonstrated much higher BAT activity in lean than in obese adult humans. They also demonstrated an exponential negative relationship between BAT activity and BMI in the same individuals [10] (Figures 4 and 5).

The sympathetic nervous system innervates BAT through beta-3 adrenergic receptors which are abundant on the surface of BAT cells [11, 12, 13]. The cells respond to nor-adrenaline by four mechanisms:

1. Lipolysis or breakdown of triacylglycerols into free fatty acids and glycerol.
2. The released fatty acids activate thermogenin (UCP-1) which dissipates the proton gradient across the inner mitochondrial membrane and uncouples oxidation of fatty acids and glucose from ATP formation. This allows oxidation to keep going longer, as it is normally inhibited by ATP accumulation, and stimulated by elevated AMP.
3. Release of most of the generated energy as heat, a phenomenon known as non-shivering thermogenesis.
4. Increased glucose uptake, independently from the above effects, as human BAT expresses high levels of the glucose transporter GLUT4; and in the fed state, insulin effectively stimulates glucose uptake into the tissue, which is then used for lipogenesis. Insulin also increases sympathetic activity mediated by the hypothalamus, which further activates BAT [14, 15].

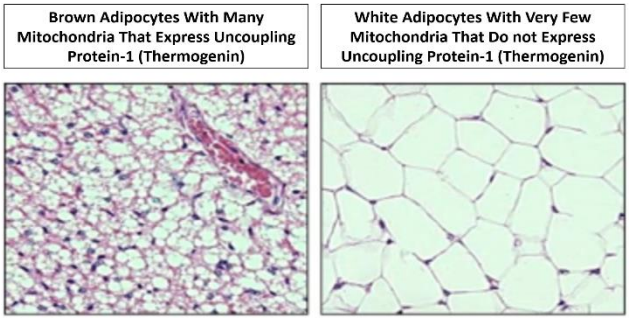

Figure 2. Haematoxylin and Eosin stained natural slides of brown adipose tissue and white adipose tissue.

Some metabolic fluxes in WAT are coordinated by factors secreted by BAT and other peripheral tissues through paracrine and endocrine effects. Some examples are listed below:

o BAT-derived IL-6 enhances insulin sensitivity and glucose homeostasis [16, 17].

o The fibroblast growth factor 21 (FGF-21) is induced in BAT by cold exposure. It promotes hepatic fat oxidation, improves glucose homeostasis, and stimulates WAT browning and thermogenesis [18, 19].

o Neuregulin 4 (NRG4) is a BAT secreted factor that attenuates hepatic lipogenic signaling during diet-induced obesity [20].

The above reports indicate that BAT significantly contributes to the homeostasis of lipids and glucose.

Furthermore, the adrenergic stimulation of BAT induces mechanical changes in the cells' cytoskeletal actin/ myosin elements, expressed as stiffening of BAT cells by a factor of two, in a way comparable to isometric muscle contraction. The activity of thermogenin (UCP-1) increases in the stiff status of BAT cells and is reduced upon relieving the tension [21, 22].

Interestingly, long-term adrenergic stimulation of WAT induces “browning” of the adipocytes, and the tissue gradually turns into "beige" adipose tissue, which shares many characteristics of BAT, like thermogenesis, increasing number of mitochondria and smaller lipid droplets [23]. In 2002, it was demonstrated that fully differentiated white adipocytes can trans-differentiate into brown adipocytes and vice versa [24]. The author concluded that the ability of the adipose organ to interconvert its cell types in order to adapt for the ever-changing metabolic needs is significant for our understanding of the problems of obesity and how they could be managed. In 2000, the importance of the nervous system in the regulation of the WAT and BAT has been emphasized by Penicaud et al., who discussed how it affects the proliferation, differentiation, trans-differentiation and apoptosis of adipocytes [25]. The authors emphasized the interaction between the brain and different adipocytes in the pathophysiology of obesity, type 2 diabetes mellitus, anorexia and cachexia. Moreover, it has been demonstrated in adult humans that adrenergic stimulation enhances the transformation of WAT into BAT adipocytes, with UCP-1 immunoreactivity appearing on the mitochondria and pauci-locular fat droplet pattern developing in the cytoplasm [26]. Lipid droplet proteins (LDs) such as Perilipin A (PLIN1) and fat Specific protein 27 (Fsp27) localize to the lipid droplet and may regulate lipid storage and BAT biology [27]. Genetic deletion of Fsp27 in knock-out mice results in decreased adiposity, increased energy expenditure, higher mitochondria number and activity and up-regulation of several BAT genes in WAT adipocytes [28]. In addition, omental WAT might have distinct trans-differentiation abilities compared to subcutaneous WAT, as in murine models, the over-expression of PRDM16 induced the formation of brown-like adipocytes only in subcutaneous WAT [29]. Likewise, BAT adipocytes can also transform into WAT adipocytes when the energy balance is positive and the adipose organ acquires increased storage capacity [30, 31], a common phenomenon with increasing age (Figure 6). One might argue that a dynamic balance exists between BAT and WAT that controls a two-way trans-differentiation of adipocytes between the two tissues, with aging favoring the BAT to WAT transformation (Figure 6).

Further research is needed to establish the key players that control the proposed balance, with potential clinical and academic implications. Some of the currently known modulators of browning are listed below:

BAT enhancing factors:

• Exercise, which induces myokines like irisin that reverses diet-induced obesity and diabetes by stimulating BAT-like thermogenesis in murine WAT [32, 33].

• Cold exposure: chronic cold exposure promotes BAT hypertrophy and WAT browning. The amount of activated BAT increases during winter compared to summer and following sleeping in a cold room, which might indicate the ability of human BAT to adapt to the environment [34, 35].

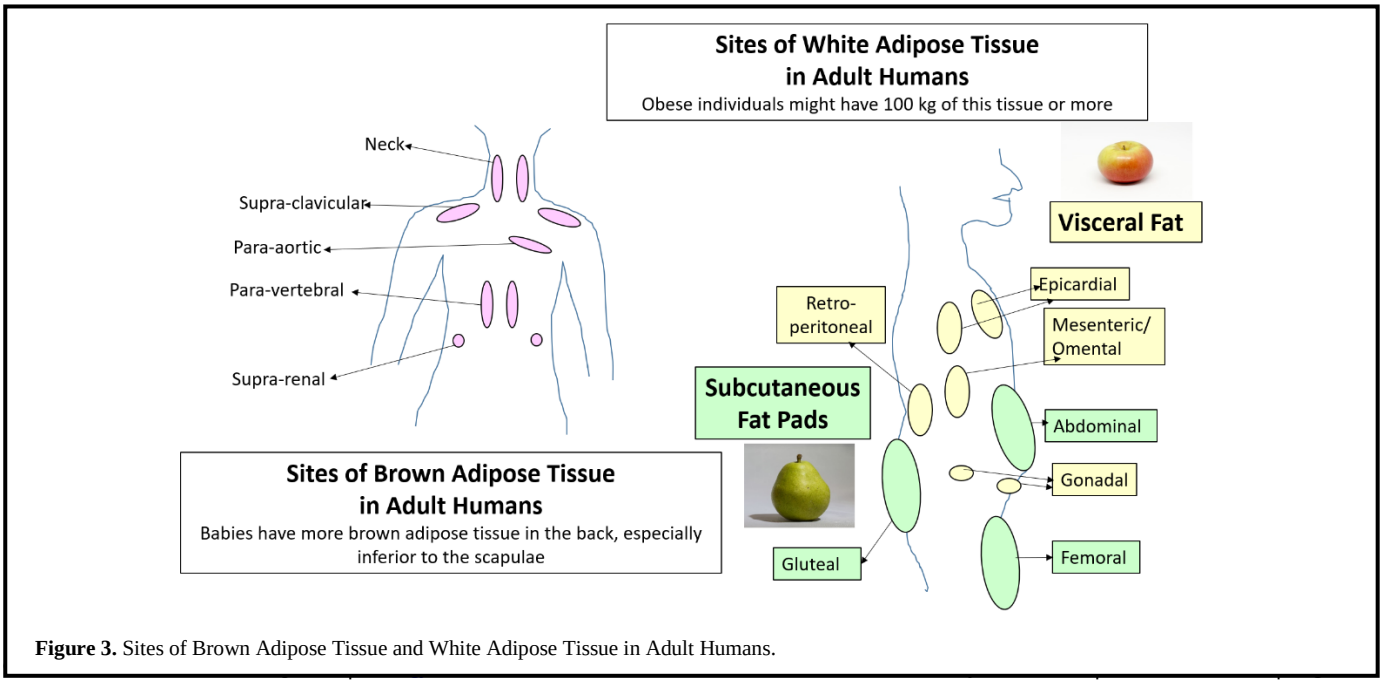

Figure 3. Sites of Brown Adipose Tissue and White Adipose Tissue in Adult Humans.

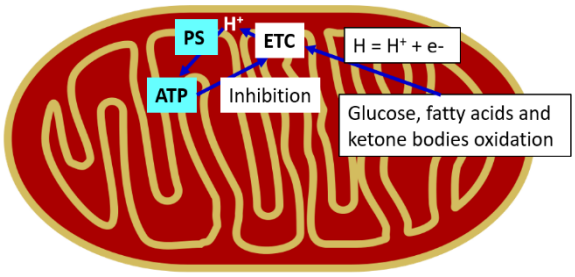

Figure 4. White Adipose Tissue (or Skeletal Muscle) Mitochondria and Coupled Oxidative Phosphorylation.

In white adipose tissue (and skeletal muscles) food oxidation provides protons and electrons to the electron transport chain (ETC) which pumps protons into the space between inner and outer mitochondrial membrane. When enough energy (in the form of electrical potential and pH/ osmotic differences) is generated activation of the phosphorylating unit (PS) occurs, which produces ATP from ADP. When enough ATP is produced the reaction of the ETC slow down and food is stored as fat.

- High fat diet [36].
- Thyroid hormones: T3 or tri-iodothyronine promotes mitochondrial biogenesis, expression of UCP-1 and thermogenesis in BAT which is rich in thyroid hormone receptors and deiodenase-2, the enzyme that activates T4 into T3. Hyperthyroidism is known to be associated with increased BAT thermogenesis and weight loss [37, 38, 39].
- Beta-3-adrenergic receptor stimulation leads to BAT activation and browning, with enhanced energy expenditure and reduced food intake in mice, [40]. However, selective beta-3 adrenergic receptor agonists such as L-796568 had no effect on human BAT activity [41]. Further research is needed to elaborate this discrepancy.
- "Peroxisome proliferator-activated receptor gamma" (PPAR-gamma) is a nuclear receptor expressed in WAT, BAT, skeletal muscles and liver cells, which is a significant player in glucose homeostasis and lipogenesis [42]. Its agonists include polyunsaturated fatty acids eicosapentenoic and docosahexenoic acids, which are twenty, and twenty-two, carbon atom fatty acids with 5, and 6, double bonds, respectively, all in the cis-configuration. These acids are prevalent in oily fish like sardine, salmon and seabream. The antidiabetic drug thiazolidinedione is another effective agonist. These agonists activate the browning of WAT. Further human studies are being undertaken in the field of clinical nutrition.
- The adipokine "fibroblast growth factor 21" (FGF-21) activates BAT, and its administration in obese rodents reduces adiposity and improves glucose tolerance [43]. It induces heat production in human adipocytes [44], but in vivo effects have not yet been reported, although it is being clinically tried in the treatment of obesity.
- "Bile acid receptor TGR5" activation induces the intestinal release of glucagon-like peptide-1 and increases energy expenditure in BAT. The receptor is expressed in WAT and BAT, with the level of expression correlated with resting metabolic rate and obesity [45, 46]. However, plasma bile acid concentrations are normally very low which strongly argue against a role for this receptor, outside intestinal or omental adipose tissue.
- Many phytochemicals are known to have potential in beneficially altering the WAT metabolism and enhancing thermogenesis, e.g., caffeine which enhances the release of free fatty acids from WAT [47]. Capsaicin is also effective, although lack of compliance with intended doses is a significant problem with clinical trials [48]. Curcumin promotes the browning of WAT and enhances thermogenesis [49].

BAT inhibiting factors:

- Increasing age is associated with decreased cold-activated BAT and accumulation of WAT in healthy humans [50]; (Figure 6).
- Obesity/overweight: BAT activity is much lower in patients with obesity and it increases in this group after weight loss is induced by bariatric surgery [51]. Reduced BAT activity contributes to the development of obesity and insulin resistance [52], and whitening of BAT is involved in the pathogenesis of insulin resistance and the metabolic syndrome.
- High fasting glucose, as it has been demonstrated that BAT atrophy takes place in mice in line with reduced beta-cell mass in the pancreatic Islets of Langerhans, decreased basal and stimulated insulin secretion and impaired glucose intolerance [53]. Further research is expected to clarify the exact role of BAT/WAT balance on insulin resistance. Some currently available details are presented below.

2. BAT AND INSULIN SENSITIVITY

BAT in adult humans actively uptakes glucose, although fatty acids derived from intracellular triglycerides are the main energy substrate [54]. Simultaneous uptake of systemic free fatty acids and glucose has been demonstrated. Therefore, the activation of brown fat is an attractive strategy for counteracting the metabolic syndrome and obesity. A study confirmed the beneficial effects of BAT in the regulation of glucose homeostasis and insulin resistance [55].

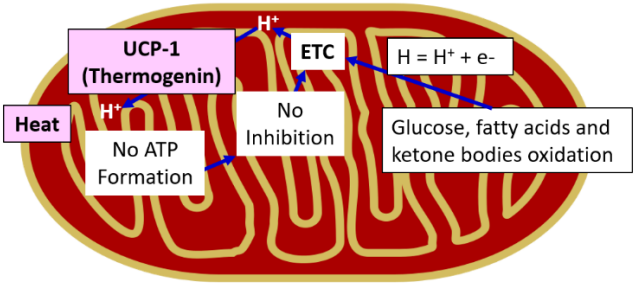

Figure 5. Brown Adipose Tissue Mitochondria and Un-coupled Oxidative Phosphorylation.

In brown adipose tissue food oxidation provides protons and electrons to the electron transport chain (ETC) which pumps protons into the space between inner and outer mitochondrial membrane. No energy is allowed to build up, as protons are dissipated back across the inner mitochondrial membrane and energy is released as heat. No activation of the phosphorylating unit (PS) occurs and no ATP is produced from ADP. ETC is not inhibited and it continues to allow nutrient oxidation. More heat is released and no storage as fat occurs.

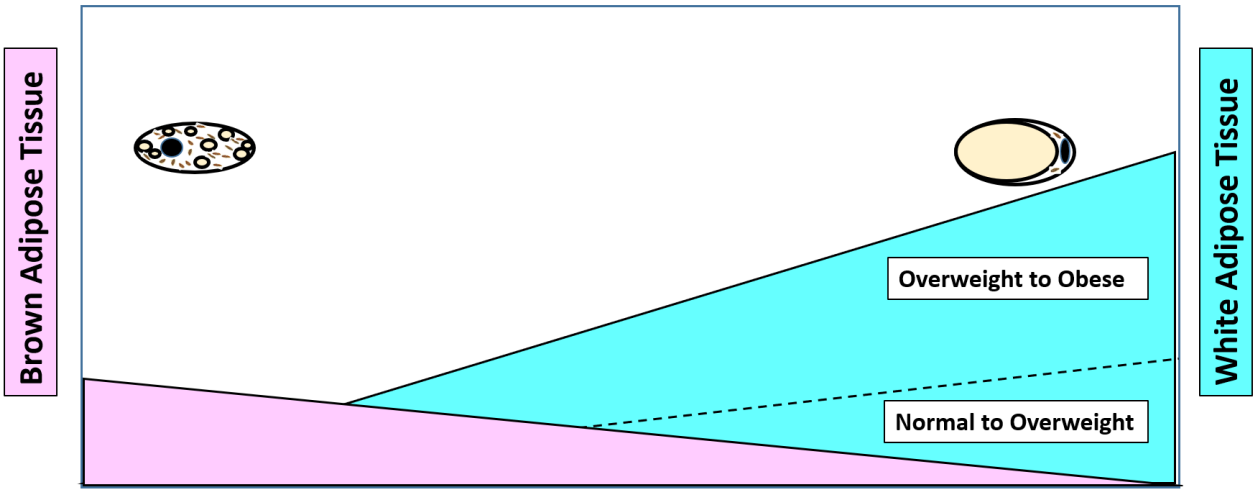

Figure 6. Effect of Increasing Age on the Relative Proportions of Brown and White Adipose Tissue.
Evidence suggests that exercise might slow down the change through browning of the white adipose tissue. Increasing age is associated with reduced brown adipose tissue and increased white adipose tissue: a phenomenon that might explain the slowdown in metabolic activities with age, increased likelihood of overweight and increased onset of type 2 diabetes mellitus.

BAT transplantation induced positive effects on body composition, insulin-sensitivity, and glucose tolerance possibly due to increased circulating levels of IL-6 [56]. Chronic BAT activation like in acclimatization to low temperature or cold enhances glucose uptake in BAT and increases insulin sensitivity. People suffering from obesity or type 2 diabetes experience an increased insulin sensitivity following a cold stimulation protocol [57]. Moreover, BAT volume is correlated with adipose tissue insulin sensitivity in over-weight and obese subjects. A pharmacological study using beta-3-agonist, "mirabegron" demonstrated an increased resting metabolic rate mediated by the increased activation of human BAT [58]. However, none of the cold acclimatization studies performed in humans have demonstrated any loss of total body weight, although body fat mass has decreased [59]. The lack of weight loss in response to increased BAT activation, despite an increased metabolic rate, might be due to the extent and the limited duration of the interventions or it might reflect altered fat to lean tissue proportions. Further studies are required to explore these academic possibilities and how to clinically benefit from their applications.

A reduction in BAT thermogenesis contributes to the positive energy balance of several obese mutant mice, such as the leptin deficient ob/ob mouse [60], and the leptin resistant db/db mouse [61]. Some reports demonstrated the increased extent of fat accumulation in mice lacking BAT or UCP1 [62]. Furthermore, UCP1-knock-out mice showed a marked increase in their fat gain associated with a reduced BAT adaptive thermogenic response only when they were housed at a temperature insuring thermo-neutrality [63]. Further series of experiments are needed to elaborate these significant reports.

3. Thyroid Hormones, Hypothyroidism and BAT Thermogenesis

Hypothyroidism suppresses the oxidative capacity and thermogenesis in rat mitochondria. Morphological and functional studies have demonstrated reduced mitochondrial content and respiration, enlarged cells and lipid droplets, and increased number of uni-locular cells within adipose tissue [64]. Di-iodothyronine (T2) is a thyroid hormone derivative that effectively activates BAT thermogenesis in rats. In vivo administration of T2 to hypothyroid rats activates BAT thermogenesis by enhancing mitochondrial respiration and increasing the sympathetic innervation and vascularization of the tissue [65, 66]. In vivo administration of T2 leads to an increase in the peroxisome proliferator-activated receptor γ coactivator- 1 (PGC-1) level in nuclei and mitochondria, thereby suggesting enhanced mitochondrial biogenesis and BAT thermogenesis [67]. Likewise, T2 increases BAT oxidative capacity in vitro when added to BAT homogenates from hypothyroid rats [67]. The inhibition of mitochondrial respiration by GDP and its reactivation by fatty acids were greater in mitochondria from T2-treated hypothyroid rats than untreated hypothyroid rats. In addition, BAT from hypothyroid rats have reduced oxidative capacity and mitochondrial thermogenesis compared to euthyroid rats, which reflects reduced mitochondrial numbers, respiration rate, and reduced mitochondrial protein content in the tissues. The antioxidant capacity was lower in hyperthyroid than in hypothyroid state, and mitochondria from hyperthyroid liver have a high capacity for H2O2 removal [68]. In addition, immunoreactivity for thermogenin (UCP-1) are also reduced in hypothyroid tissues [66]. Hypothyroid rats have more lipid-replete BAT adipocytes and increased number of unilocular adipocytes, which are typical of WAT. Administration of T2 to hypothyroid rats activates BAT thermogenesis and increases cyclo-oxygenase (COX) activity, which is an index of the maximal oxidative capacity of a tissue. In addition, inhibition of mitochondrial thermogenesis by GDP and its reactivation by arachidonic acid, a twenty carbon atom essential fatty acid with four double bonds, were both greater in mitochondria from T2-treated hypothyroid rats than in those from untreated hypothyroid animals. The ability of T2 to

activate BAT thermogenesis is associated with changes in adipocyte morphology as T2 administration reverses the "whitening" of "brown" adipocytes induced by hypothyroidism through increasing the percentage of multilocular cells and decreasing that of unilocular ones, decreasing the lipid droplet diameter, and increasing the mitochondrial content [65].

The thermal response of BAT to noradrenaline administration is drastically reduced in hypothyroid mice compared with euthyroid animals. As the classical function of BAT is to generate heat for thermoregulatory purposes, the enhanced sympathetic innervation and vascularization observed in hypothyroid versus euthyroid rats could represent a form of compensation for the impaired capacity of BAT to produce heat. Higher BAT vascularization would facilitate the distribution of heat produced that is decreased with hypothyroidism. By promoting sympathetic tone activation, administration of T2 to hypothyroid rats would lead to an increase in BAT adipocytes, which are well innervated and properly vascularized [66].

BAT may undertake at least part of the observed effect of T2 on rat energy expenditure. However, although T2 administration normalizes most of the thermogenic parameters depressed by hypothyroidism in rats, i.e., mitochondrial content, respiration, maximal oxidative capacity, it does not normalize overall energy expenditure. One of the main contributors to rat energy expenditure in skeletal muscles, the mitochondrial proton conductance which is an index of mitochondrial thermogenesis, is markedly reduced by hypothyroidism. One-week administration of T2 significantly enhances its level albeit does not fully restore it to the euthyroid levels [69].

The transcriptional co-activator PGC-1 alpha is considered as a major regulator of BAT function and the activation of thermogenesis [70]. PGC-1alpha has also been implicated as a central regulator of mitochondrial gene expression and as an essential component of mitochondrial biogenesis. Indeed, nuclear PGC-1 alpha co-activates nuclear respiratory factors-1 and -2, which regulate the expression of mitochondrial transcription factor A (mt-TFA), a nuclear-encoded transcription factor essential for replication, maintenance, and transcription of mitochondrial DNA (mt-DNA). PGC-1 alpha may mediate the effect of T2 on BAT activation, since an increase in PGC-1 alpha protein levels was observed both in the nucleus (at 1 h) and in the mitochondria (after 1 week) in hypothyroid-T2 treated rats. This suggests that T2 promotes mitochondrial biogenesis and BAT thermogenesis, with PGC-1 alpha involved in the effect. The effect exerted by T2 on BAT PGC-1 alpha seems to mimic that induced by T3 the most potent form of thyroid hormone.

Using a diet-induced obese mice model, Zhang et al. [71] demonstrated thyro-mimetic effects of T2 on mice body composition and energy metabolism, thus supporting previous data concerning the effects induced by T2 on high fat fed rats. Thyro-mimetic effects of T2 on hypothalamo-pituitary-thyroid axis, hepatic and pituitary gene expression, heart rate and weight have also been demonstrated. However, differences in animal models, housing temperature, diet, dose or duration of T2 administered might explain differences in the drawn conclusions. An important point to consider when administering iodothyronines in vivo is the possibility of their conversion to other metabolites with varying biological activities. For instance, T3 can be converted to T2, while T2 can be further converted to monoiodo-L-tyrosine, iodothyronamine (T1AM), or 3, 5-diiodothyroacetic acid (DIAC) [72]. The use of inhibitors of deiodinases is a helpful tool when "in vivo" experiments are contemplated. The discovery of functional BAT in adult humans, its significant involvement in energy metabolism and potential control of triglyceride clearance and glucose disposal suggest that T2 may be able to counteract metabolic dysfunction and related diseases in humans. It may also facilitate weight loss during caloric restriction, which causes a reduction in T3 levels that antagonize further weight loss. Since T2, contrary to T3, is not associated with thyro-toxicity or undesirable cardiovascular side effects, its supplementation while dieting could enhance weight loss when clinically intended [73].

4. Conclusions

The balance between the brown adipose tissue and white adipose tissue is critical for understanding many health and disease processes in Man, including obesity, diabetes, metabolic syndrome, hyperlipidaemia, thyroid illness, ischaemic heart disease, stroke, peripheral arterial diseases and others. A better understanding of this balance and how it is affected by browning or whitening factors might open significant avenues into a better understanding of the aging processes and common chronic illnesses. These potential advances need extensive future research and exploration with novel strategies and dynamic approaches. Collaborative research between biochemistry, physiology, histology, pharmacology and related clinical specialties is core for genuine achievements in understanding how to favourably tip the BAT/ WAT balance in favor of improved quality of human life and longevity.

Conflict of Interest Statement: To the best of the authors knowledge, there is no conflict of interest in relation to the article entitled: Brown adipose tissue, thermogenesis and obesity: a literature review.

Author contributions: HA: critical manuscript writing, preparing or designing the graphs. NR: preparing and systematically classifying the references. AA: preparing the source material and planning the skeleton of the article content in a preliminary draft. SR: helping with the references organization and proof-reading the paper.

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