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The Implication of Brown Adipose Tissue for Humans

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Abstract

We here discuss the role of brown adipose tissue on energy homeostasis and assess its potential as a target for body weight management. Because of their high number of mitochondria and the presence of uncoupling protein 1, brown fat adipocytes can be termed as energy inefficient for adenosine-5′-triphosphate (ATP) production but energy efficient for heat production. Thus, the energy inefficiency of ATP production, despite high energy substrate oxidation, allows brown adipose tissue to generate heat for body temperature regulation. Whether such thermogenic property also plays a role in body weight regulation is still debated. The recent (re)discovery of brown adipose tissue in human adults and a better understanding of brown adipose tissue development have encouraged the quest for new alternatives to treat obesity since obese individuals seem to have less brown adipose tissue mass/activity than do their lean counterparts. In this review, we discuss the physiological relevance of brown adipose tissue on thermogenesis and its potential usefulness on body weight control in humans.

Keywords

adaptive thermogenesis; uncoupling protein; mitochondria; proton leak; obesity

INTRODUCTION

The number of overweight/obese individuals is exceeding the number of lean people in many developed and developing countries, challenging the concept of “body weight normality” in these populations (60). Growing interest exists in finding strategies to reduce excess body weight; however, at present very few—if any—of those strategies have met the essential criteria of being safe and efficacious (86).

Decreasing energy intake seems a difficult goal in societies for which plenty of high-energy foods are available. To tip energy balance toward weight loss, not only should food intake

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be decreased, but also increased energy expenditure may help. Even if increasing physical activity seems the most effective and safe way to enhance energy expenditure, not many people are willing to follow the minimal recommendations to maintain an active lifestyle. As a consequence, the search for a safe and efficacious way to increase metabolic rate has become important.

Until a couple of years ago, a potential role of brown adipose tissue (BAT) in the regulation of body temperature and energy balance in adult humans was dismissed. However, very recently, BAT has been consistently identified in adult humans undergoing positron emission tomography (PET; see sidebar Positron Emission Tomography as a Tool to Measure Brown Adipose Tissue) and computed tomography (CT) technologies (18). This (re)discovery of BAT and its known role in adaptive thermogenesis regulation has opened an interest in activating BAT and enhancing energy expenditure in order to control body weight and prevent metabolic disorders (15, 45, 55, 57, 66, 67, 85, 86). In this review, we discuss the evidence and the putative roles of BAT in the regulation of body weight in humans.

ANATOMICAL, HISTOLOGICAL, AND MOLECULAR CHARACTERISTICS OF BROWN FAT CELLS

From an anatomical point of view, brown fat cells are localized in two types of depots: discrete and diffuse. In humans, BAT of discrete location is found in cervical-supraclavicular (the most common location), perirenal/adrenal, and paravertebral regions around the major vessels (the aorta and its main branches: carotids, subclavian, intercostal, and renal arteries) and is probably present to generate and distribute heat to maintain core temperature (42) (Figure 1). In distinction, diffuse BAT is found in coexistence with white adipose and skeletal muscle tissues.

Brown fat cells are characterized by a polygonal shape with multilocular lipid droplets and an increased number of large and spherical mitochondria, which give their brown coloration (13) (Figure 2). In addition, BAT is highly irrigated with blood vessels and innervated with noradrenergic fibers. Uncoupling protein 1 (UCP1), a highly specialized protein, is expressed in brown fat cells and can therefore be considered as a marker of BAT. Additional genes showing increased expression in these cells are peroxisome proliferator–activated receptor γ coactivator 1α (PGC1α), deiodinase iodothyronine type 2 (DIO2), cytochrome *c*, PR domain containing 16 (PRDM16), and β3 adrenergic receptor (33, 91) (Figure 3). All of these genes are closely related to the main role of brown fat cells, i.e., heat production.

EMBRYONIC ORIGIN OF BROWN FAT CELLS

BAT, dermis, and some skeletal muscle cells are derived from the central dermomyotome, specifically from a group of cells positive for engrailed-1, which is a homeobox transcription factor (5). Indeed, brown but not white fat precursor cells express genes that are characteristics of muscle precursors such as Myf5, an early myogenic transcription factor (33, 82, 93). There is another population of brown fat cells called brite cells, which, in response to cold exposure or chronic catecholamine stimulation, appear in white fat depots.

These cells are not derived from a Myf5-expressing cell lineage (74), thus reinforcing the notion that brown fat cells in discrete locations are from a different lineage than brown fat cells in diffuse locations (82, 100). These newly formed brown adipocytes could derive from existing stem cells in the tissue, from migrating stem cells, or from the direct transformation of differentiated white adipocytes (transdifferentiation) (13, 25, 31). In this regard, Petrovic et al. (62) found that precursors from mouse white adipose tissue treated with rosiglitazone —a PPARγ agonist—promote PGC1α expression, mitochondrial biogenesis, and a noradrenaline-dependent UCP1 gene expression in a subset of cells. However, these cells do not express PRDM16 or myocyte-associated genes (Myf5), typical molecular signatures of brown fat cells found in discrete locations.

REGULATION OF BROWN ADIPOGENESIS

Brown adipogenesis is a highly regulated process, with several growth factors and transcription factors playing significant roles (Figure 4). Bone morphogenetic proteins (BMPs) are main regulators of brown adipogenesis. Indeed, exposure of brown preadipocytes to BMP7 induces a full program of brown fat differentiation, including induction of PRDM16, PGC1α, PPARγ, C/EBPs, and UCP1 genes (87).

POSITRON EMISSION TOMOGRAPHY AS A TOOL TO MEASURE BROWN ADIPOSE TISSUE

Positron emission tomography is a functional imaging technique using specific ligands labeled with positron-emitting isotopes for the monitoring of in vivo molecular processes. The use of a wide range of radioactive elements (such as ^{13}N, ^{11}C, ^{15}O, and ^{18}F) provides a strong basis for molecular imaging using PET. However, the ligands used by PET originate from pharmacological agents that demonstrate specific biochemical interactions. The most widely used PET radioisotope to date is the ^{18}F-labeled glucose analogue known as 2-fluoro-2-deoxy-D-glucose (FDG). FDG allows the monitoring of molecular glucose metabolism since it is taken up and phosphorylated in cells in proportion to the rate of glycolysis (92).

The limitation of FDG PET for BAT activity is that glucose accounts for only a small fraction of the total energy supply to BAT. Differences in BAT glucose uptake and plasma FFA concentration may modify the fuel mix oxidized. As an example, a condition in which GLUT-1-dependent glucose uptake is decreased and plasma FFA concentration is increased will underscore the presence of BAT because less FDG activity will be detected. Therefore, FDG activity represents only a semi-quantitative measure of BAT activity. Whether the presence of excess white adipose tissue impairs the detection of brown adipocytes in obese individuals remains to be established.

At the transcriptional level, several proteins enhance or inhibit brown fat development. PPARγ (8, 58, 62, 70, 84) and the C/EBP family (36) are classical transcription factors promoting both white and brown adipogenesis, which in combination with proteins such as PGC1α and PRDM16 have a critical role on determining brown adipogenesis. Table 1

shows different genetically engineered mouse models having an impact on BAT development.

A master gene involved in BAT development is PGC1α, which plays a critical role in enhancing mitochondrial biogenesis and oxidative metabolic pathways (99). Ectopic expression of PGC1α both in human and mouse white fat cells induces a number of mitochondrial and thermogenic genes including UCP1 (65, 83), whereas genetic ablation of PGC1α in mice reduces cold-induced thermogenesis (CIT) capacity (46). PGC1α activity is regulated through several molecules including RIP140, which binds to PGC1α and antagonizes its transcriptional function of several target gene promoters (27). Genetic ablation of RIP140 causes the emergence of brown fat-like cells in white adipose tissue in mice (44).

The SRC family of proteins also has a regulatory role in PGC1α activity (50). For instance, SRC1 reinforces the coactivation of PGC1α on PPARγ transcriptional activity (63), whereas SRC2 and SRC3 inhibit PGC1α activity. Specifically, SRC2 inhibits the PPARγ-PGC1α interaction (63), while SRC3 promotes PGC1α acetylation (14, 49). Additional inhibitory action on PGC1α activity is accounted for by twist proteins. Twist1 knockout mice showed increased brown fat–related gene expression (94), whereas overexpression represses those genes in a PGC1α-dependent fashion (61).

A recently discovered, critical transcription factor playing a role in brown fat cell differentiation is PRDM16 (Figure 4). This is a potent coactivator of the transcriptional activity of PGC1α and β as well as PPARα and γ (75). PRDM16 directly binds to PGC-1α, PGC-1β, PPARα, PPARγ, p53, and several members of the C/EBP family, resulting in enhanced coactivation of their transcriptional activities (34, 74, 75). The PRDM16-C/EBPβ complex is particularly relevant and appears to control the initiating events of the conversion from myoblastic precursors to brown fat cells. Depletion of C/EBPβ significantly blunts the ability of PRDM16 to induce brown fat differentiation in mice (33). PRDM16 is also a suppressor of specific genes present in white fat (resistin and angiotensinogen) and muscle (myoD, myogenin, and myosin heavy chain) cells. Thus, when PRDM16 is expressed in mouse white fat preadipocytes or white adipocytes, brown fat differentiation is induced, including activation of thermogenic and mitochondrial genes (34, 74, 75). In contrast, depletion of PRDM16 from cultured brown fat cells causes a loss of the brown fat characteristics in parallel with the development of skeletal muscle differentiation features (75). Consistently, BAT from PRDM16$^{-/-}$ mice at embryonic day 17 exhibits decreased expression of thermogenic genes and increased expression of muscle-specific genes (74).

PHYSIOLOGICAL ROLE OF BROWN ADIPOSE TISSUE

In newborns, the sudden change from an intrauterine environment at 37°C to the external environment at lower temperature in combination with a high surface area-to-volume ratio (~twofold higher than in adults) represent an important challenge for thermoregulation (76). As an adaptive mechanism, the appearance of BAT around 150 million years ago allowed mammals to maintain body temperature significantly higher than ambient temperature (18). As mentioned above, the increased capacity to release heat is due to the UCP1. This protein,

located in the inner mitochondrial membrane, allows protons to move down their electrochemical gradient, bypassing adenosine-5′-triphosphate (ATP) synthase and therefore ATP production (52). As a result, brown adipocytes oxidize their own fat stores and circulating substrates at a fast rate, thus releasing heat (Figure 5).

The BAT thermogenic process is mostly induced by noradrenaline. In response to cold [ambient temperature ≤23°C for humans, ≤28°C for rats, and ≤30°C for mice (76)], noradrenaline is secreted by the BAT sympathetic nerve terminals, leading to increased UCP1 expression with concomitant thermogenesis (37). In fact, BAT can be activated and expanded by treatment with β-adrenergic agonists in animals (69) or by cathecolamine-secreting tumors in humans (41). In contrast, when BAT is not adrenergically activated, it loses most of its histological and molecular properties (e.g., multilocular lipid droplets and high UCP1 expression), becoming like a white adipocyte. Interestingly, both cold exposure and cathecolamine stimulation cause the emergence of UCP1-expressing brown fat cells in rat white adipose tissue depots (24). The role of these cells in thermoregulation remains elusive.

Thyroid hormones, particularly triiodothyronine (T_3), also have well known thermogenic properties (51, 76). T_3 availability in brown fat cells is regulated by DIO2, which is highly expressed in BAT (91). For example, brown fat cells from DIO2$^{-/-}$ mice have impaired cathecolamine-stimulated UCP1 expression accompanied by impaired cold tolerance (17). In addition, T_3 action on BAT activity may not be solely restricted to a direct effect at the tissue level. Recently, Lopez et al. (48) showed in rats that direct injection of T_3 into the brain results in activation of sympathetic activity and increased expression of BAT-related markers in parallel with weight loss.

Besides the role of BAT on core temperature regulation, this tissue has also been proposed to play a role in the regulation of body weight (71). For instance, rodents fed a “cafeteria diet” have an expansion and activation of BAT (71). This thermogenic effect in response to hypercaloric diets was proposed to be a defense mechanism against excess energy supply by dissipating part of the energy excess and thus reducing body weight gain and its comorbidities (12, 38, 39, 88, 100). In contrast, genetic ablation of BAT or β-adrenergic receptors causes a propensity toward obesity and metabolic diseases (7, 53), mostly because of hyperphagia. Similarly, deletion of UCP1 in mice causes increased weight gain when mice are housed at thermoneutrality (20) but not at lower temperature (47).

The hypothesized role of BAT on body weight regulation, however, has been strongly refuted. Kozak (40) doubts that BAT evolved to burn off excess calories in mammals—including premodern humans—that rarely had a plethora of food available. In support of this view, increased oxygen consumption in rats fed cafeteria diets was not accounted for by increased BAT oxygen consumption (54). In fact, in response to such a diet, oxygen consumption increased at a comparable rate in UCP1$^{+/+}$ and UCP1$^{-/-}$ mice, indicating that diet-induced thermogenesis (DIT) may be independent of UCP1 expression (4).

In humans, despite easier measures of oxygen consumption, the evidence of the role of BAT in the regulation of body weight is no less controversial. As early as 1902, Neumann

realized that the increase in his body weight was not proportional to the excess energy intake (59). This observation led him to propose that some of the excess energy intake was dissipated as heat or “luxuskonsumption” (59). More than half a century later, Miller et al. (56) revived Neumann’s concept by conducting human overfeeding studies in which they described that only part of the body weight gain was related to increased energy intake, thus implying that some of the excess was dissipated as increased energy expenditure. Such an idea was supported by the findings from the Vermont studies of prisoners in whom almost 50% more energy intake was necessary to maintain their new body weights after long-term overfeeding (77). It is, however, only in the late nineties that Stock (79) confirmed these findings in a careful review of the literature showing that weight gain after overfeeding was quite variable across individuals, up to four times per unit of energy excess. Besides the level dietary compliance, such differences in weight gain can be explained by our inability to assess weight-maintenance energy requirements and therefore the actual energy excess. Differences in digestion and absorption may also modify the amount of bioavailable energy, affecting the actual positive energy balance. The composition of weight gain (fat mass and lean mass) also needs to be considered because the energy cost of protein deposition is higher than that of adipose tissue. Stock also identified that part of the variability in weight gain was related to the dietary composition, particularly to dietary protein content (79). Finally, differences in mitochondrial energy efficiency may also represent an underlying cause of the variability in weight gain. All these confounding factors decrease our chances to isolate any potential role of BAT mass/activity on adaptive thermogenesis and body weight regulation until more reliable methods to assess energy homeostasis become available.

Despite the above caveats in both animal and human studies, there is some evidence that DIT may also be mediated by BAT, mainly in response to adrenergic stimulation, but to a lower extent than CIT (reviewed in 11). This is also indirectly suggested by recent data showing a significant relationship between the magnitude of the increase in energy expenditure in response to cold (CIT) and to overfeeding (DIT) (98).

PRESENCE OF BROWN ADIPOSE TISSUE IN HUMANS

Newborns are particularly dependent on BAT to keep their body temperature within a homeothermic range. In humans, the need for active brown adipocytes decreases after a few months of life, as the surface area-to-volume ratio is reduced in parallel with a reduction in metabolic rate on a body-size basis (Figure 6). For instance, at age 5 months, the surface area-to-volume ratio has decreased by one-third, while in adulthood this ratio goes down to one-half to two-thirds in comparison with newborns. The decreased need to rely on BAT thermogenesis in adults may explain why it has been so difficult to identify BAT in adult humans for a long time. However, the detection by PET of “hot spots” in the neck, roots of the upper limbs, and the intercostal spaces near the spine from adult humans reopened a scientific interest for the search of BAT (2, 28, 81, 95, 101).

Three independent publications reported in a comprehensive manner the presence of BAT in adult humans (16, 89, 91). Virtanen et al. (91) studied five subjects during cold exposure (2 h at 17–19°C; one of the subject’s feet was placed intermittently in ice water 5–9°C for five minutes) and warm conditions using 2-fluoro-2-deoxy-D-glucose (FDG) in combination

with PET/CT technologies. In response to cold, a 15-fold increase in FDG uptake in the supraclavicular area was observed. From three of the volunteers, white adipose tissue and BAT biopsies were taken to measure the expression of informative genes for cellular origin. Increased expression of UCP1, DIO2, PGC1α, PRDM16, β_3 adrenergic receptor, and cytochrome *c* were observed in BAT versus white adipose tissue from surrounding areas (Figure 3).

Van Marken Lichtenbelt et al. (89) used a similar approach in a larger group of subjects (10 lean and 14 overweight or obese volunteers) and found increased FDG uptake potentially attributable to BAT activity in the neck, supraclavicular region, chest, and abdomen. It is noteworthy that the activity of BAT was approximately fourfold higher in the lean group than in the overweight/obese group. However, it will be important to investigate whether the presence of excess white adipose tissue may impair the detection of brown adipocytes in obese individuals before definitively concluding that obese people have lower BAT. Furthermore, the same investigators reported a positive relationship between resting metabolic rate and BAT activity at thermo-neutrality or during cold exposure, while an inverse association between BAT amount/activity and body mass index was found. Similarly, an inverse association between cold-stimulated FDG uptake and body mass index was reported by Saito et al. (72) in healthy volunteers ages 23–65 years. The latter study also pointed out a seasonal variation, with increased cold-activated FDG uptake during winter versus summer, which was later confirmed by others (6). BAT activity was surprisingly more prevalent in women than in men (7% versus 3%) in retrospective readings of FDG PET/CT in approximately 2,000 subjects (16). This sexual dimorphism was recently reported by others under more controlled conditions (42).

Using a histological approach to detect brown fat adipocytes, Zingaretti et al. (103) collected some adipose tissue in the necks of patients undergoing surgery for thyroid diseases. In one-third of the patients, clear evidence of BAT was found. Again, BAT amount was inversely related to age and obesity. At the molecular level, the proportion of UCP1-positive fat cells among all adipocytes in these individuals ranged from 3% to 31% (average 13%). Together, the data show that BAT is indeed present in variable amounts in human adults.

INCREASING BROWN ADIPOSE TISSUE MASS OR ACTIVITY AS A PUTATIVE ALTERNATIVE TO CONTROL BODY WEIGHT

The finding that body mass index and BAT activity are inversely related has encouraged the assessment of the role of BAT on whole-body energy homeostasis, particularly in response to overfeeding. Whether obesity is partially driven by impaired BAT activity as suggested by mouse models (Table 1) or whether decreased BAT activity in obese individuals is due to lower surface area-to-volume ratio and enhanced thermal insulation is unknown (97).

Regarding the effect of BAT on energy expenditure, Virtanen et al. (91) estimated that the size of the supraclavicular BAT depot (both sides included) was 63 g, and the rate of glucose disposal was 2.2 mg/100 g/min, which is equivalent to 1.4 mg/min for the entire depot or approximately 2 g for a day (~8 kcal). Considering that only 10% of the fuel oxidation is derived from glucose in rat brown adipose (53b) and assuming a similar contribution in

humans, one could anticipate a total 80 kcal/d for fully activated BAT. Even if such a small increase in thermogenesis could offset a slightly positive energy balance, it has been clearly established that 80 kcal/d is not sufficient to cause obesity unless the positive energy balance is maintained over time (10, 30, 80, 96). An increased and active mass of BAT could, however, help to maintain body weight, if not contribute to weight loss. This can be particularly relevant in individuals losing weight because they often experience a "metabolic adaptation," i.e., a fall in energy expenditure larger than what can be accounted for by the loss of fat-free mass and fat mass (23, 43, 68).

The notion that body weight could be modified by manipulating energy efficiency is not new. In the 1930s, 2,4-dinitrophenol (a mitochondrial uncoupler) became a popular strategy to lose weight by increasing metabolic rate (up 20% to 30%). However, ingestion of slightly higher doses than prescribed caused serious side effects, sometimes including death (29). The role of energy efficiency was reconsidered when the existence of UCP1 was first described in human BAT (9) and again later, when uncoupling protein 2, a more ubiquitous protein, was proposed to play a role on energy homeostasis (22). However, a lack of differences in metabolic rate between obese and lean individuals decreased the enthusiasm for a potential use of UCPs for boosting energy expenditure (64).

At present, the better understanding of BAT development and regulation has opened a new research avenue that is geared toward finding new targets to increase BAT mass and activity. For example, PPARγ agonists increase the expression of brown fat–selective proteins (e.g., PGC1α, UCP1) both in fat cell lines and in white adipose tissue from mice (62, 90). Consistently, $PPAR\gamma^{+/-}$ mice have a reduced metabolic rate, and their adipose tissue shows an impaired capacity to generate ATP (3). One can therefore hypothesize that PPARγ agonists may increase metabolic rate by stimulating BAT. However, people with type 2 diabetes treated with pioglitazone (a PPARγ agonist; 45 mg/d for 24 weeks) showed no changes in metabolic rate and gained weight (78).

Other strategies to enhance BAT activity may include increasing the activity of BMP7 since mesenchymal progenitor cells treated with BMP7 develop a brown adipocyte phenotype. When such cells were implanted into nude mice, adipose tissue showed a dramatic increase in the amount of brown fat cells (87). Similarly, PRDM16 was shown to induce brown adipocyte differentiation in a fibroblast cell line (75), primary mouse (74), and human myoblasts (34). These findings were accompanied by increased glucose uptake measured by PET scanning and enhanced in vitro respiration (33). Further studies should assess the potential of PRDM16 to increase BAT activity at the whole-body level. Another potential target to increase metabolic rate is to suppress the activity of cell death–inducing DNA fragmentation factor-α-like effector A (CIDEA). This protein increases mitochondrial coupling by suppressing UCP1 expression, which is consistent with the observation that $CIDEA^{-/-}$ mice are resistant to diet-induced obesity (102). In addition, a recent report in humans found an inverse association between adipose tissue CIDEA expression and metabolic rate (26). Sirtuins (NAD-dependent deacetylases) have also been proposed to activate BAT activity via PGC1α (21). After mice were treated with synthetic activators of sirtuin 1, increased PGC1α and enhanced oxidative capacity were observed in skeletal

muscle, liver, and BAT, all associated with higher metabolic rate and reduced weight gain (19, 32).

Finally, it should be considered that increased thermogenesis might still be insufficient to decrease body mass because energy homeostasis is tightly regulated, and compensatory increases in energy intake are likely to happen. Such up-regulation of energy intake would only lead to a new higher energy flux, probably at higher body mass.

CONCLUSIONS

Brown adipose tissue plays a critical role for heat production in mammals, especially in newborns. However, its role in the regulation of body weight remains more controversial, if not unknown. The recent discovery of BAT in adult humans has caused a resurgence of interest in this potential therapeutic target because reports have suggested it may represent a novel strategy in the treatment of obesity. Before conclusions are reached, it will be necessary to investigate:

1. How much variance of the metabolic rate is accounted for by BAT mass/activity in adult humans?
2. What are the behavioral or pharmacological means to increase the amount and activity of human BAT?
3. Is increased BAT mass and activity related to enhanced CIT and/or increased DIT?
4. Does increased energy expenditure (independent of changes in physical activity) represent a way to control body weight?

Only when such questions are answered will it be possible to determine whether strategies to increase the mass and/or activity of BAT can be used to improve the control of body weight.

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Glossary

BAT	brown adipose tissue
PET	positron emission tomography
CT	computed tomography
Core temperature	the defended temperature of the body and its vital organs
UCP1	uncoupling protein 1
PGC1α	peroxisome proliferator–activated receptor γ coactivator 1α

DIO2	deiodinase iodothyronine type 2
PRDM16	PR domain containing 16
Brite cells	brown fat–like white fat cells
Transdifferentiation	process by which white fat cells can turn into brown fat cells in response to hormonal signals
Cold-induced thermogenesis (CIT)	the increase in energy expenditure above basal fasting level during cold exposure
Diet-induced thermogenesis (DIT)	the increase in energy expenditure above basal fasting level divided by the energy content of the food ingested
Energy efficiency	moles of mitochondrial ATP generated relative to moles of oxygen consumed
Adaptive thermogenesis	changes in energy expenditure not attributable to the changes in the size of the body and its tissue composition in response to alterations in energy balance. Those alterations may be caused by excess caloric intake, caloric restriction, increase or decrease in physical activity levels, cold or heat exposure, drugs, and other environmental agents
FDG	2-fluoro-2-deoxy-D-glucose

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SUMMARY POINTS

1. Increasing energy expenditure independent of changes in physical activity may play a role in body weight regulation.
2. The recent confirmation of the presence of brown adipose tissue in adult humans and a better understanding of brown adipose tissue development and activity may increase our potential to enhance energy expenditure.
3. The existence of brown fat cells in white adipose tissue and the reported transdifferentiation from white into brown adipocytes may open a new avenue to boost metabolic rate.
4. The evidence of lower BAT mass/activity in obese and elderly versus lean and young individuals may offer a potential to increase BAT mass/activity and prevent obesity- and aging-related metabolic disorders.

FUTURE ISSUES

Future research is needed on:

1. Improvement in our technical capabilities to determine brown adipose tissue activity.
2. Diet-induced thermogenesis and its relationship to brown adipose tissue activity.
3. Identification of cellular/molecular mechanisms explaining differential BAT mass/activity according to sex, age, and fatness.

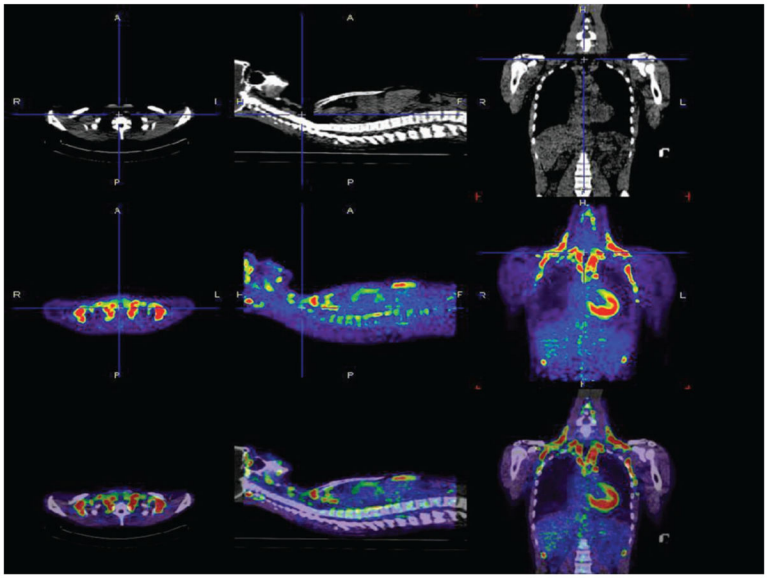

Figure 1.

Anatomical location of discrete brown adipose tissue measured by positron emission tomography (PET). Computed tomography (CT; *upper panel*) and PET (with ^{18}F-fluorodeoxyglucose; *middle panel*) images from the neck and thoracic region in one lean individual. The bottom panel shows the superimposition of the CT and PET scans. In the three panels (from left to right) are (*a*) a transverse slice at the level of the clavicles, (*b*) a sagittal slice at the level of the spine, and (*c*) a coronal slice of the thorax. Activated brown adipose tissue areas (*red* and *green*) are in the cervical-supraclavicular (most common), perirenal/adrenal, and paravertebral regions. Illustration prepared by Dr. Wouter van Marken Lichtenbelt (Maastricht University, The Netherlands).

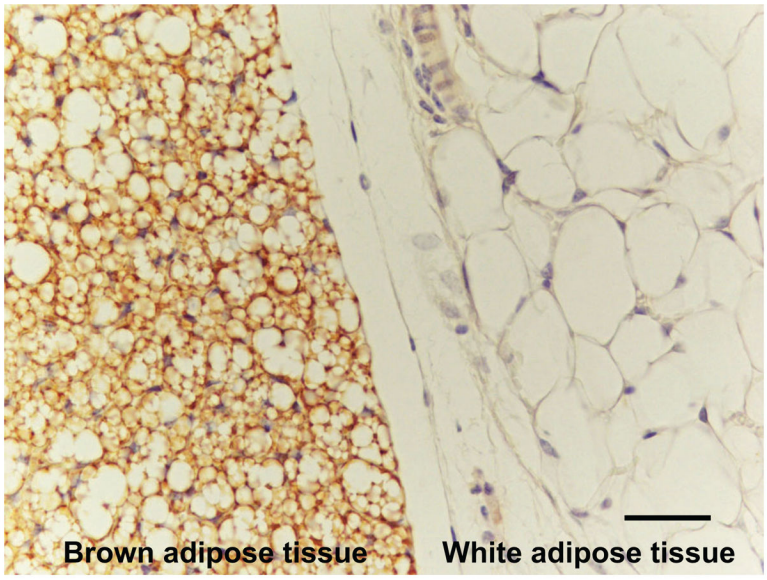

Figure 2.

Histology of brown and white fat cells. Light microscopic image of mouse anterior subcutaneous fat depot in an area where white and brown adipose tissues are close to each other. Uncoupling protein 1 (UCP1)-immunoreactive fat cells corresponding to brown adipose tissue (*left*) and UCP1-negative white fat cells corresponding to white adipose tissue (*right*) are visible. Immunohistochemistry by ABC method. Sheep antirat UCP1 primary antibody diluted 1:500. Antibody kindly provided by Daniel Ricquier (Paris). Bar represents 40 microns. Illustration prepared by Dr. Saverio Cinti (University of Ancona, Italy).

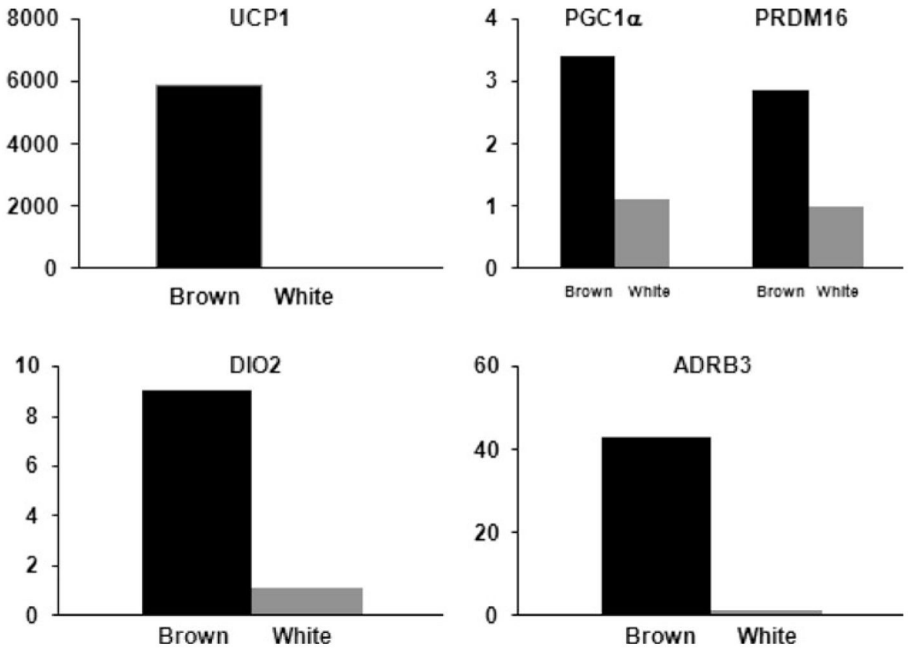

Figure 3.

Gene expression profile in brown and white fat cells. Gene expression unit corresponds to brown adipose tissue as a multiple of white adipose tissue. UCP1, uncoupling protein 1; PGC1α, peroxisome-proliferator–activated receptor γ coactivator 1α; PRDM16, PR domain containing 16; DIO2, deiodinase iodothyronine type 2; ADRB3, β3 adrenergic receptor. Data modified from Virtanen et al. (91).

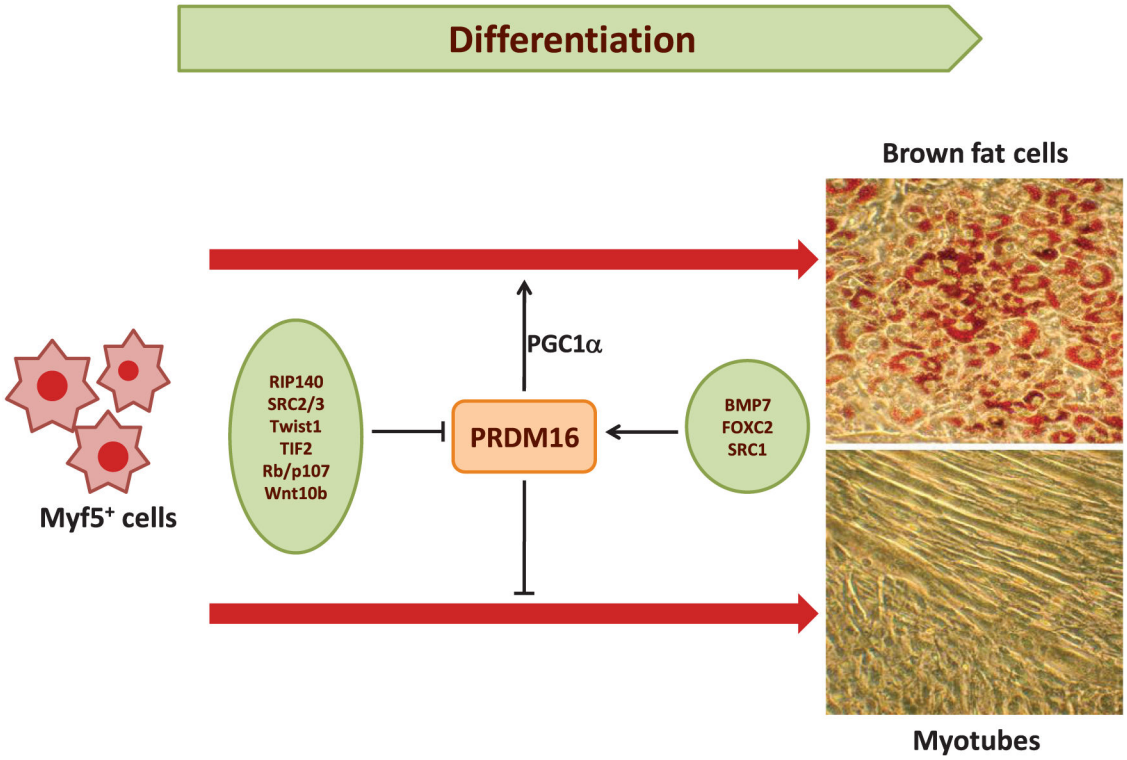

Figure 4.

Regulation of brown adipogenesis. Myf5^{+} cells are early brown fat or muscle cell precursors. Activation of PRDM16 in combination with other proteins such as PGC1α suppresses myocyte differentiation and promotes brown fat cell phenotype. Proteins on the left and right have a negative and positive action on PRDM16 activity, respectively.

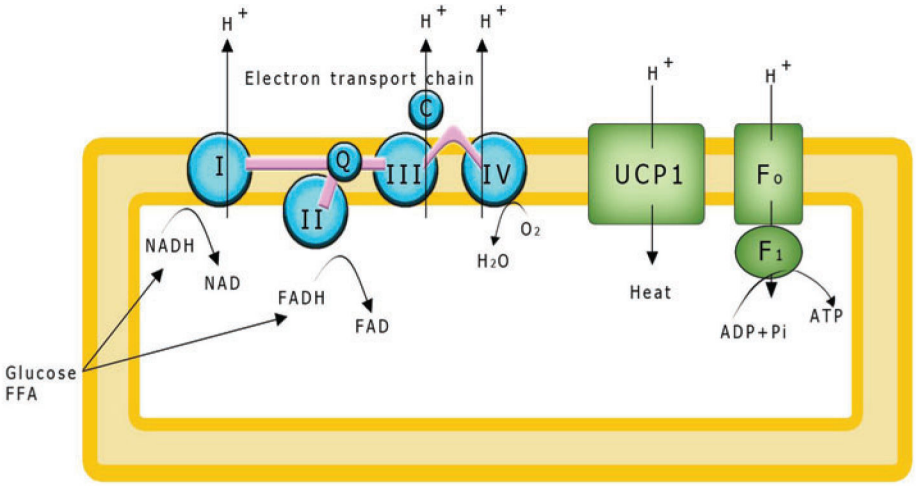

Figure 5.

The role of uncoupling protein 1 (UCP1) on mitochondrial heat production. Free fatty acids and glucose are oxidized to generate nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH)2, which donate electrons to the electron transport chain. At the end of the transport chain, these electrons are accepted by molecular oxygen (O_2). A proton electrochemical potential gradient is created when protons a repumped out. Adenosine-5′-triphosphate (ATP) is generated when protons reenter the mitochondrial matrix through the F0/F1-ATPase. Protons may also reenter through an UCP1, with energy being released in the form of heat.

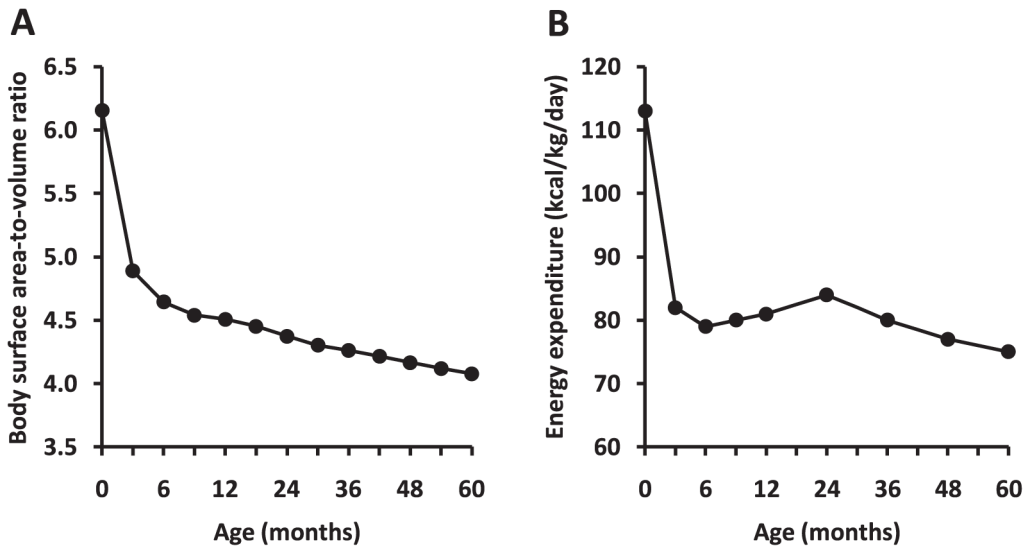

Figure 6.

Change in body surface area-to-volume ratio and metabolic rate during the first five years of life. Body surface area estimated by Dubois's equation [weight $(kg)^{0.425}$ × height $(cm)^{0.725}/1000$]. Body volume was estimated from body weight assuming a body density equal to one. Body weight, height, and energy expenditure measurements were taken from average values reported in children having normal growth (1).

Table 1

Animal models targeting brown adipose tissue–related proteins

Reference	Model (KO/TG)	Changes in brown adipose tissue	Whole-body metabolic phenotype
(12)	TG FoxC2 in fat cells	Higher interscapular BAT and increased expression of C/EBPα, PPARγ, SREBP1, and metabolic rate in TG WAT	Lower HFD-induced weight gain and fat accumulation and improved glucose control
(63)	SRC1 KO	Higher lipid infiltration and lower expression of UCP1 and PGC1α	Higher HFD-induced weight gain, reduced metabolic rate, and body temperature at 4°C
(63)	TIF2 KO	Lower lipid infiltration and higher expression of UCP1 and PGC1α	Lower HFD-induced weight gain and fat accumulation and improved glucose control. Higher metabolic rate and body temperature at 4°C
(14)	SRC3 KO	Lower lipid infiltration and increased mitochondrial number	Lower HFD-induced weight gain and fat accumulation and improved glucose control. Higher metabolic rate, body temperature, and muscle mitochondrial content
(73)	p107 KO	White fat cells with multilocular lipid droplets and high UCP1 and PGC1α levels	Lower WAT mass and increased metabolic rate
(87)	BMP7 KO	Lower BAT mass at birth	Mice are not viable after birth
(87)	BMP7 TG	Increase in brown but not white fat mass	Higher metabolic rate and body temperature and lower weight gain
(44)	RIP140 KO	Higher expression of UCP1 and CPT1b	Lower HFD-induced weight gain and liver fat accumulation. Higher metabolic rate
(35)	UCP1-Wnt10b TG	Lack of functional BAT with lower expression of PGC1α and UCP1	Blunted increase in body temperature after β-agonist stimulation
(61)	Adipose tissue TG twist-1	Lower expression of PGC1α and UCP1. Lower metabolic rate and mitochondrial density. Higher lipid infiltration	Higher HFD-induced weight gain and lower body temperature at night
(61)	Twist-$1^{+/-}$	Lower lipid infiltration. Higher mitochondrial number and metabolic rate	Lower HFD-induced weight gain and higher body temperature at night

Abbreviations: BAT, brown adipose tissue; HFD, high-fat diet; KO, knockout mice; TG, transgenic mice; WAT, white adipose tissue.