Obesity is a significant health challenge, with the latest projections estimating that there will be 2.16 billion overweight and 1.12 billion obese individuals globally by 2030. In addition to social stigmatization and impaired quality of life, obese people are faced with significantly increased risk of cardiovascular disease, type 2 diabetes mellitus, and a number of cancers. Weight gain results from a sustained imbalance between energy intake (calories consumed) and energy expenditure (calories burned), resulting in positive energy balance. To tip energy balance toward weight loss, not only should food intake be decreased, but increasing physical activity may help. It is important to realize, however, that the secular rises in obesity over the past 3 to 4 decades can be explained by both physiological and environmental drivers and a number of putative factors (Figure 1).1,2 At one level, the obesity epidemic is a classic gene-environment interaction in which the human genotype is susceptible to environmental influences that affect energy intake and expenditure, with the obesogenic environment being dominant. These environmental factors include the 2 obvious explanations, ie, reduced physical activity and increased energy intake from high-calorie food and drinks, with the latter likely being the dominant factor.1 However, other less studied factors have been implicated, including longer time spent awake, increased mean age of mothers at first birth, decreased prevalence of smoking, presence of environmental pollutants, ingestion of many novel medications, and reduction in the variability of seasonal ambient temperature owing to the presence of almost ubiquitous air conditioning.4 Fundamentally, the obesity epidemic is explained by a dysregulation of energy balance in our obesogenic environment. Understanding the cause of obesity requires the study of how genetic and environmental factors interact to produce long-term positive energy balance.

As a consequence of the obesogenic environment, the treatment of obesity requires intensive lifestyle modification. However, lifestyle modification in obese individuals tends to provide only transient success, and pharmacological treatment of obesity has often been disappointing and is very contentious because of the many safety concerns. Other approaches such as bariatric surgery are costly and not without risk. Thus, there is a concerted effort to find novel strategies to reduce excess body weight. This includes the potential of increasing energy expenditure via the stimulation of brown adipose tissue (BAT), now known to be present in adult humans. We would expect that such physiological or pharmacological stimulation of thermogenesis (heat production) would lead to dissipation of at least some excess ingested calories. This review provides a historical overview on the research on BAT, highlights recent developments in the field, and concludes with a discussion of the relevant issues that need to be addressed before BAT is considered a therapeutic option for human obesity.

**Characteristics of BAT**

The majority of adipose tissue in the human body is white adipose tissue (WAT), which acts as a passive depot for energy storage and is an active endocrine organ, releasing free fatty acids and adipokines (Figure 2). However, small amounts of BAT may be found in the neck; in the supraclavicular and axillary regions; in the paravertebral, perirenal, adrenal, and paravascular regions; and around the major vessels (the aorta and its main branches: carotids, subclavian, intercostals, and renal arteries; Figure 3). BAT can also be found within WAT and skeletal muscle tissues.5 Notably, the histological studies described in humans thus far suggest that brown and white adipocytes are mixed together in all depots.6–8 Brown fat cells are characterized by multilocular lipid droplets and an increased number of mitochondria, expressing uncoupling protein 1 (UCP1). UCP1 is located in the inner membrane of the mitochondria, which express uncoupling protein 1 (UCP1). UCP1 is located in the inner membrane of the mitochondria and uncouples the rates of substrate oxidation and ATP production by favoring a loss of protons and thus energy release. Genes such as peroxisome proliferator–activated receptor γ coactivator 1α, cytochrome c, deiodothyronine type 2, β3-adrenergic receptor, and PR domain containing 16 (PRDM16) are highly expressed in brown adipose cells and highlight the common features and physiology of BAT, namely high oxidative capacity, activation by thyroid hormones and catecholamines, and cell differentiation from skeletal muscle precursor cells.9

**A Historical Perspective on BAT**

Traditionally, BAT was considered a thermogenic organ for maintaining core temperature during cold exposure in small mammals and newborns. In humans, BAT was believed to disappear rapidly with age. The notion that BAT thermogen-
Figure 1. The effects of genes and environment on adiposity. Effects of genes and environment on adiposity assessed here by body mass index (BMI). Some of the concepts described in this figure were proposed by Bouchard et al and Keith et al. Our environment has evolved over the past century from a traditional environment to a new Westernized environment. The left side presents the long-lasting traditional environment in which food is scarce and energy expenditure is high mostly as a result of occupational physical activity. Such an environment leads to leptogenic behaviors in which the variability of BMI will depend on the individual’s genetic propensity to weight gain. On the right side, the more recent modern social and built environment leads to obesogenic behaviors characterized by plenty of cheap, high-calorie food and little need for physical activity. The variability in BMI will also depend on the genetic propensity of the individual to weight gain. On the right side, the more recent modern social and built environment leads to obesogenic behaviors characterized by plenty of cheap, high-calorie food and little need for physical activity.

The effects of genes and environment on adiposity. Effects of genes and environment on adiposity. We show the potential effect of genes and environment on adiposity assessed here by body mass index (BMI). Some of the concepts described in this figure were proposed by Bouchard et al and Keith et al. Our environment has evolved over the past century from a traditional environment to a new Westernized environment. The left side presents the long-lasting traditional environment in which food is scarce and energy expenditure is high mostly as a result of occupational physical activity. Such an environment leads to leptogenic behaviors in which the variability of BMI will depend on the individual’s genetic propensity to weight gain. On the right side, the more recent modern social and built environment leads to obesogenic behaviors characterized by plenty of cheap, high-calorie food and little need for physical activity. The variability in BMI will also depend on the genetic propensity of the individual to weight gain, but the obesogenic environment exerts a much stronger influence. The distribution of BMI will have a higher mean and higher standard error in the obesogenic environment than in the leptogenic environment. Such a paradigm can be applied to populations with similar genetic backgrounds living in drastically different environments like the Pima Indians in Arizona and in Mexico.
A recent study supports the role of BAT-mediated energy expenditure in pheochromocytoma patients because, after resection of the tumor, fluorodeoxyglucose (FDG) uptake in BAT was no longer apparent in 25 patients.21 Wang et al20 reported that 6 of 14 subjects with pheochromocytoma had BAT detected by 18F-FDG position emission tomography (PET) with computed tomography (CT) and that circulating metanephrine, a surrogate measure of plasma catecholamines, was associated with the presence of BAT. Despite the lack of association between catecholamine levels and the presence of BAT in 1 study,17 together these observations provide evidence that excessive catecholamines secreted by adrenal tumors stimulate thermogenesis in BAT, thereby increasing total energy expenditure and leading to the lean phenotype characteristic of patients with pheochromocytoma. In a broader context, examining patients with pheochromocytoma provides a unique integrated physiological model for over-stimulation of BAT (mass and activity) and fat mass loss. However, pheochromocytoma-associated weight loss can be attributed not only to BAT activation but also to the impact of catecholamines on other tissues such as skeletal muscle, the liver, and even the central nervous system.

In the 1990s, pharmaceutical companies developed compounds targeting adipose tissue–selective β3-adrenoceptors as a putative pharmacological strategy to increase energy expenditure by BAT activation and thus reduce body weight. In humans, β3-adrenoceptors are located predominantly on BAT with few or no receptors on WAT. β3-Agonists showed some positive metabolic effects such as improved insulin action and increased fat oxidation but in general failed to increase 24-hour energy expenditure and likely BAT activity.22 More recently, a novel β3-adrenoceptor (TAK-677) was shown to marginally increase 24-hour energy expenditure compared with placebo but also caused an increase in heart rate of 9 bpm.23 Less specific β3-agonists also had undesired side effects such as tremors or tachycardia, mediated by their affinity for β1- and β2-adrenoceptors.24–26

The (Re)Discovery of BAT in Humans
In the early 2000s, studies in nuclear medicine using 18F-FDG PET/CT scanning revealed the presence of BAT in adult humans. This pattern of FDG uptake, initially called “USA” (uptake in supraclavicular area) fat, was initially considered an artifact by radiologists who were interested in identifying active tumors. Importantly, the radiologists noticed that the
The presence of BAT was related to ambient outdoor temperature and, unlike in tumors, 18F-FDG uptake could be blocked pharmacologically by β-blockers in rats and humans. Then, in 2009, 5 independent groups used 18F-FDG PET/CT to identify and characterize the presence and relevance of BAT in adult humans. All 5 groups showed major depots of metabolically active BAT in the cervical-supravacular regions, and some confirmed the presence of true BAT by the expression of UCP1 and histological characteristics. Cypress et al reported 3640 consecutive 18F-FDG PET/CT scans from 1972 patients and reported positive BAT scans in 7.5% of women and 3.1% of men. Virtanen et al reported that exposure to cold (2 hours in a 17°C–19°C room and intermittent dipping of 1 foot in ice water) increased glucose uptake 15-fold in paracervical and supravacular adipose tissue. Adipose tissue biopsies were obtained from 3 out of 5 participants and UCP1 mRNA and protein levels immunohistochemistry confirmed that the tissue identified in the PET/CT scans was true BAT. Similarly, van Marken Lichtenbelt et al used 18F-FDG PET/CT to study 24 men under thermoneutral conditions (22°C) and during mild cold exposure (15°C for 2 hours). BAT activity was observed in 23 of 24 subjects during cold exposure but in no participants during thermoneutral conditions. The same investigators reported a positive relationship between resting metabolic rate and BAT activity at thermoneutrality or during cold exposure, whereas an inverse association between BAT amount/activity and body mass index was found. Finally, Saito et al observed that cold-induced BAT (measured with 18F-FDG PET/CT) was more prevalent in young (53%) than in elderly (8%) subjects and was less active with increasing metabolic diseases.

Using a more direct approach, Zingaretti et al examined adipose tissue taken from the neck of patients 18 to 82 years of age undergoing surgery for thyroid diseases. In 20 of 35 patients (57%), they observed distinct islands of UCP1-positive staining that was richly sympathetically innervated. Moreover, within the UCP1-positive islands, there was evidence of brown adipocyte precursors, implying that it may be possible to recruit BAT by promoting the proliferation and differentiation of these cells. Studies over the past 3 years have led to a paradigm shift in our understanding of BAT in adult humans, fueling a resurgence of interest in the potential of activating BAT to enhance energy expenditure, therefore assisting in controlling body weight and possibly preventing metabolic diseases.

**Limitations of PET/CT and Alternative Approaches for Assessing BAT**

According to studies using PET/CT techniques, the prevalence of BAT in adults varies between 2% and 100%. Such variability may be attributed to most measurements being performed at thermoneutral conditions and in a fasting state when we expect BAT activity to be reduced or even minimal. For example, when the assessment of BAT was performed after a 2-hour mild cold exposure, a condition known to induce BAT activity, the prevalence of BAT increased to 96%, whereas no BAT was observed at thermoneutral conditions.

Alternatively, this variability may be due to the inability of PET/CT scans to discriminate between the presence of BAT and its activity (FDG uptake). This point is highlighted by several studies showing poor reproducibility from subjects having multiple PET/CT scans. Lee et al reported that the average probability of obtaining subsequent positive PET/CT scans among patients with BAT was 13%. Similarly, in 33 subjects who each had 5 PET/CT scans, Rousseau et al showed that FDG uptake was identical on all 5 scans in only 5 patients, ie, a 15% reproducibility. No association was found between FDG uptake and outdoor temperature in that study. However, another study with poor BAT reproducibility from multiple PET/CT scans (16% reproducibility) showed that FDG uptake was inversely associated with outdoor temperature. To disentangle the discrepancies between PET/CT and histological methods of defining BAT, Lee et al compared adipose tissue biopsies taken from 3 subjects in whom PET/CT was positive versus 14 subjects in whom PET/CT was negative. Regardless of PET/CT status, signature transcripts of BAT (ABDR1, ADRB2, ADRB3) were present in all patients, and UCP1 staining was seen in all but 1 PET/CT-negative patient. Together, these findings suggest that the prevalence of BAT reported in retrospective PET/CT studies may be largely underestimated, suggesting that BAT is highly prevalent in adult humans.

Currently, 18F-FDG PET/CT scanning is the only “noninvasive” method for examining the presence of BAT. However, this technique is limited by poor reproducibility, high cost, and the radiation exposure during the scan, which generally precludes the inclusion of healthy subjects in such studies. Therefore, there is a need to develop alternative noninvasive techniques for measuring the presence of BAT and, most important, BAT activity in humans. Recent advances in magnetic resonance imaging (MRI) have led to the development of techniques such as the iterative decomposition with echo asymmetry and least-squares estimation (IDEAL) MRI. This method distinguishes WAT and BAT on the basis of their unique lipid compositions because WAT contains greater lipid than BAT. Hu et al demonstrated the feasibility of using IDEAL MRI to distinguish WAT from BAT in excised samples from mice carcasses. To date, there have been no published studies using IDEAL MRI to examine BAT in humans. Another approach is to use the negative Hounsfield units from computer-assisted tomography to differentiate between WAT and BAT. Hu et al examined PET/CT scans from 101 pediatric and adolescent patients and identified that regions of metabolic active tissue (BAT) had more positive Hounsfield units than inactive (WAT) fat. The feasibility of infrared thermography as another noninvasive approach for measuring BAT in humans was recently published in a pilot study of 87 subjects. Using infrared thermography in 1 subject, Lee et al found that the highest skin temperature was localized to the supravacular fossae, which corresponds to the most common location of BAT. After cold exposure, supravacular skin temperature was decreased by only 0.9°C compared with a reference skin area where temperature was decreased by 2°C. Even without a change in core temperature in cold, energy expenditure increased by 14%, an increase similar to that reported in
studies using PET/CT. 

Recently, several new compounds have shown promising results for the detection and quantification of BAT. 41 Bartelt et al43 demonstrated the feasibility of measuring active BAT by MRI and the incorporation of superparamagnetic iron oxide nanocrystals into the lipoprotein cores as tracers. However, this technique, although promising because of its low toxicity, may not be sensitive enough to detect inactive BAT. In contrast to 18F-FDG, another innovative compound, 4,18F-fluorobenzyltriphenyl phosphonium (18F-FbnTP), may provide a unique opportunity to detect and quantify both inactive and active BAT depots.44 By targeting the electro-chemical gradients, 18F-FbnTP accumulates in mitochondria as a function of their uncoupling state and is washed out in relationship to mitochondrial thermogenic activity.44 This unique physical property of 18F-FbnTP warrants a new direction in the noninvasive investigation of BAT in both humans and rodents. Although measures of BAT by 18F-FDG glucose uptake and PET/CT have so far been considered the gold standard, will these novel approaches lead to a better understanding of the physiological role of BAT in humans? The ability to detect inactive BAT by IDEAL MRI or PET/CT with 18F-FbnTP will certainly provide new insights into the “true” prevalence of BAT in humans and its metabolic role and allow us to start examining its plasticity in vivo.

Associations Between the Presence of BAT and Clinical Variables

Higher BAT Prevalence in Women Versus Men

Most analyses from retrospective studies using PET/CT show that the prevalence of BAT is higher in women than in men.31,35,45,66 Nedergaard et al64 speculated that this is attributed to the fact that women experience cold sensations at higher temperatures than men. As a consequence, the chance of detecting BAT during a PET/CT scan may be increased in women. However, this explanation overlooks studies in rodents that strongly suggest that BAT metabolism is sex dependent with more BAT in female rats.47–50 For instance, compared with male rats, female rats have higher UCP1 content, greater multilocular lipid arrangement, and both longer and denser cristae in their mitochondria, indicating higher thermogenic capacity and activity.49 Furthermore, this is accompanied by a more sensitive β3-adrenoceptor response to norepinephrine stimulation in female rats.49 Testosterone- or progesterone-treated brown adipocytes have opposite actions on UCP1 expression, with testosterone-treated cells showing fewer and smaller lipid droplets with a dose-dependent inhibition of UCP1 mRNA expression under adrenergic stimulation by norepinephrine.48 On the other hand, progesterone and 17-β-estradiol-treated cells showed larger lipid droplets and progesterone-stimulated norepinephrine-induced UCP1 mRNA expression.48 These findings, albeit in rodents, suggest that BAT metabolism is sex dependent and influenced by the hormonal environment, giving potential insight into why women have greater reported BAT prevalence than men.

BAT Is Inversely Associated With Aging

BAT was traditionally believed to be present only in newborns and to decline with age owing to a decreased need for thermogenesis. As early as 1972, Heaton et al7 observed that interscapular BAT was consistently present in the first decade of life, disappearing gradually up to 30 years of age with a sharp decline thereafter. We now know that BAT is present in adulthood, with numerous studies reporting a decline in BAT prevalence with age.35,39,51 However, the exact timing of this age-related decline in BAT is unclear. When BAT-positive subjects were stratified into age tertiles, BAT was 3 times more likely to be detected in subjects <50 years of age compared with those >64 years.31 Interestingly, body mass index (BMI) was not correlated with the presence of BAT, but when multivariate analysis was performed, BMI became a significant negative predictor with increasing age.31 Similar findings were obtained by Pfannenberg et al,45 who showed that age was the strongest negative determinant of BAT mass. Furthermore, their analysis suggested that the metabolic effect of BAT, as reflected by its relationship with BMI, declines with age in men but not women. Whether BAT has a protective role in age-related obesity remains to be established.

The decline in BAT activity with aging appears to be related to the decrease in the amount of BAT depots rather than activity. Using immunohistochemistry7,52 or PET/CT,46 there is a notable decrease in BAT after adolescence that is maintained from 20 to 80 years of age before a steep decline after 80 years of age. It is also very likely that following the initial drop in BAT after adolescence, both the function and sensitivity of BAT diminish during adulthood.53 Such observations may explain why the presence of cold-activated BAT is >50% in subjects in their 20s but <10% in subjects in their 50s or 60s.54 Consistent with this hypothesis, Zingaretti et al6 proposed that at “a certain age, humans switch from a phenotype characterized by leanness, small white adipocytes and the presence of brown adipocytes to a phenotype characterized by increasing obesity, large adipocytes and the absence of brown adipocytes.”

BAT and Measures of Body Composition

The inverse association between the amount of active BAT and BMI is well accepted.31–33,45 However, only 4 studies have examined associations between BAT and more specific measures of body composition.20,32,33,54 In 23 of 24 healthy men, van Marken Lichtenbelt et al32 observed a strong negative association between cold-induced BAT and percent body fat measured by dual-energy x-ray absorptiometry. Interestingly, the 1 subject who did not have cold-induced BAT activation had the highest percent body fat (and BMI) of the cohort.32 Similarly, Saito et al33 reported strong negative correlations between cold-induced BAT and total and visceral
fat measured by CT. However, when subjects who were BAT positive were compared with those who were BAT negative, there were no significant differences in fat deposition, although this may have been due to the fact that the BAT-positive subjects were younger. These findings suggest that the relationships between the presence of BAT, obesity, and age are innately intertwined because BAT is generally observed in younger, leaner subjects. Yoneshiro et al. attempted to disentangle these associations by testing the idea that decreased BAT was associated with body fat accumulation with age. In both sexes, significant positive correlations between age and all adiposity parameters (percent fat, visceral and subcutaneous fat) were observed only in BAT-negative subjects, leading to the hypothesis that the presence of BAT may be protective of age-associated body fat accumulation. Nevertheless, this recent finding in humans reinforces the association between BAT activity and visceral fat. Given that decreased BAT was associated with body fat accumulation with age, these group differences may have been even more pronounced if BAT had been measured after cold exposure. Nevertheless, this recent finding in humans reinforces the data from the 1980s showing relationships between BAT activity and body composition in rodents. Whether BAT can be activated by \( \beta \)-adrenergic agonists or catecholamines degradation by catechol-O-methyl transferase and a surrogate measure of plasma catecholamine concentrations, was elevated. On the contrary, there was no detectable BAT in patients without elevated metanephrine and normal control subjects. Interestingly, there was a positive association between BAT activity and total metanephrine and an inverse association between BAT activity and visceral fat. Given that BAT activity was measured by PET/CT in thermoneutral conditions, these group differences may have been even more pronounced if BAT had been measured after cold exposure. Nevertheless, this recent finding in humans reinforces the data from the 1980s showing relationships between BAT activity and body composition in rodents. Whether BAT can be activated by \( \beta \)-adrenergic agonists or catecholamines in classic depots of white fat remains to be investigated.

**BAT and Outdoor Temperature**

One of the major indications that BAT is present in adulthood and activated by cold exposure was provided by Huttunen et al., who found BAT-positive depots in neck necropsies obtained from Finnish outdoor workers in the cold. In recent years, the association between BAT and outdoor temperature has been well described by many groups, although only 1 study has specifically examined seasonal differences in the detection of BAT. Saito et al. performed FDG PET/CT scans in the same 8 subjects in summer and winter. The presence of BAT was observed in only 2 of the 8 subjects in summer but increased to 6 of the 8 subjects in winter. Yoneshiro et al. showed that short-term cold exposure (2-hour) resulted in a significant increase in energy expenditure only in BAT-positive, not BAT-negative, male subjects. Whether this finding suggests that BAT is actively recruited during cold exposure in humans is uncertain. Mice and rats that undergo long-term cold exposure have hyperplasia of BAT and increased 2-deoxyglucose uptake. Moreover, cold acclimation in rodents has been shown to induce a transdifferentiation of WAT to BAT. It is unknown whether long-term cold exposure in humans will induce changes in the amount of BAT and metabolic activity.

**Is There a Relevant Role for BAT in Obesity Therapy?**

As described above, the last few years have heralded a renaissance in the study of BAT and consequently (re)ignited the hypothesis that BAT thermogenic potential could be targeted to increase energy expenditure and thus have an antiobesity effect. However, numerous areas still require thorough investigation before the exploitation of BAT for obesity therapy is considered. In a broad context, both total abundance and activity need to be stimulated, resulting in increased energy expenditure. Approaches that may lead to increased BAT activity (and possibly abundance) include cold exposure, stimulation of the sympathetic nervous system, and/or increasing the activity of the thyroid axis. Other more invasive approaches include BAT transplantation and/or the stimulation of non-BAT progenitor cells to differentiate into brown adipocytes. Transcriptional regulators of brown adipocyte differentiation include bone morphometric protein 7, PRDM16, Mir193b-365, orexin, forkhead Box C2, Plac8, and RIP140, all of which have been described in rodents (see Figure 4). Transcriptional regulators of brown adipocyte differentiation in humans are largely unknown and may depend on whether BAT is in a diffuse or a discrete location. Indeed, given that BAT and WAT are both present in various adipose tissue depots in humans, some authors suggest that under certain conditions WAT could transdifferentiate to BAT and vice versa. Accordingly, these transdifferentiating cells have been described as “brite” or “beige.” Regardless of the method by which upregulation of BAT thermogenesis occurs, a fundamental question remains: How would an “overactive” BAT operate at the whole-body level, and would upregulation be sufficient to induce negative energy balance and thus weight loss?

In a simplified integrated model, BAT thermogenesis occurs mainly through the interaction of 2 components: short-term (ie, minutes or hours) modulation of the activity of the sympathetic nervous system in response to meals, physical activity, or variations in temperature and long-term changes in thyroid hormones in response to changes in energy balance (Figure 5). These interactions are likely to regulate both BAT thermogenesis and the fuel supply to BAT. Indeed, the sympathetic and thyroid axes are involved in peripheral (WAT) and local (BAT) lipolysis and in the regulation of plasma glucose by the liver. Therefore, BAT becomes important to dissipate excess energy intake by potentially increasing energy expenditure to match energy intake. In response to food intake, insulin and gut hormones are transiently increased, thereby promoting substrate disposal and norepinephrine-induced BAT thermogenesis, whereas other hormones involved in the long-term regulation of energy balance (thyroid hormones and leptin) would hardly be affected. As a consequence, short-term excess energy intake (meals) may be only partially buffered by activation of BAT. However, it is assumed that for weight control (which requires long-term regulation) one needs long-term stimulation of BAT (increased amount and optimal activity). This simplified model
fits with observations that in subjects with active BAT (as assessed by PET/CT), BAT mass and activity are associated with BMI. However, a chronically active BAT would likely affect glucose and adipose tissue regulation, triggering counterregulatory mechanisms that may ultimately downregulate its activity (Figure 5C).

The model of human pheochromocytoma provides an example of the potential of long-term BAT thermogenesis to decrease body weight. This idea is also supported by rodent models in which increased BAT activity and uncoupling lead to a reduction in body weight. However, in such a model, the constant increase in BAT metabolic activity with extra stimulation in response to meals, cold exposure, or stress may trigger compensatory mechanisms that may ultimately downregulate its activity (Figure 5C).

Long-term cold exposure may represent a relatively easy method for stimulating BAT thermogenic capacity in humans, even if there is clear interindividual variability in the response to cold-induced energy expenditure. Furthermore, a significant lowering in ambient temperature may not be well tolerated by many individuals, who will compensate by wearing extra layers of clothes. Whether daily short-term (ie, several minutes) exposure to cold (a "cold pill") may be sufficient to stimulate BAT mass and responsiveness remains to be tested. Apart from the reports of high BAT mass and likely activity in lumberjacks working long term in extreme cold temperatures, recent studies reported seasonal differences in BAT activity, with higher BAT prevalence in winter versus summer. In Western countries, occupations are mostly performed indoors and thus in thermoneutral conditions. Only short exposures to cold are experienced during the winter months. It is therefore likely that the reported increase in BAT activity is induced by only daily short cold exposures. However, some data indicate that the seasonal changes in the photoperiod may be more important than the outdoor tem-
temperature in the stimulation of BAT activity. Nevertheless, to what extent such a regimen would be able to induce BAT and to help increase heat dissipation (and therefore caloric excess) in response to food intake is unknown.

Although controversial, a link between BAT activity and diet-induced thermogenesis in humans has recently been reported recently. Furthermore, other studies indicate a role for BAT in facultative thermogenesis and body weight regulation. Wijers et al examined 10 lean and 10 obese subjects exposed to 48 hours of mild cold (16°C) while living in a respiratory chamber. On cold exposure, lean subjects had significantly higher mean daytime energy expenditure, a greater change in distal temperature, and a smaller decrease in proximal skin temperature compared with the obese subjects. In this study, cold-induced thermogenesis and diet-induced thermogenesis were correlated in lean subjects. Similar increases in energy expenditure after exposure to mild cold (22°C) for 30 hours were observed in lean women. These findings, albeit in a small number of subjects, indicate that lean individuals are able to counteract changes to cold by increasing energy expenditure, whereas obese subjects experience a change in temperature distribution and therefore an increase in insulation.

Recent data point to the role of thyroid hormones in the regulation of energy expenditure and, more specifically, BAT thermogenesis through the modulation of hypothalamic fat metabolism. Besides the new insights into the central effects of hyperthyroidism, this newly identified pathway by which metabolic inefficiency can be manipulated may provide a new target for obesity.

Novel approaches aimed at increasing BAT mass have been proposed. The discovery of transcription factors and microRNA implicated in the differentiation of progenitor cells into BAT bring us 1 step closer to the induction of BAT tissue in vivo and/or its transplantation to increase thermogenesis to limit weight gain. In addition to the limitations and caveats already pointed out by Nedergaard and Cannon and Kozak, the prevalence of BAT appears to be higher than reported in retrospective studies in >90% of the subjects investigated. If true, is it necessary to increase BAT mass? Instead, increasing the responsiveness of the BAT already present in the organism by acute sympathetic stimulation will likely be more efficacious. The development and validation of measurement techniques such as IDEAL MRI and 18F-FBnTP with PET/CT in humans will be of importance in the study of human BAT physiology in the years to come.

Conclusions

Targeting BAT for obesity therapy is still at a preliminary stage. As early as 1982, Rothwell and Stock urged that we need to exercise “caution in extrapolating indirect histological and thermographic evidence to a major role for BAT in human energy metabolism.”

Despite significant advances in BAT research, multiple questions remain: What is the exact amount of BAT in humans? What is its exact role in the energy balance? Do the correlations between BAT mass and BMI indicate a role for BAT in the regulation of body weight? The advances in imaging techniques and cold activation of BAT before PET/CT scans indicate that BAT prevalence is likely to be high. Therefore, other important questions to be answered: Do most people keep a “hibernating” BAT that needs to be activated to regulate body weight by increased thermogenesis and thus buffer excess energy intake? What physiological counterregulations would be engaged if BAT could be transformed into an energy store...
burner? Will humans exhibit increased appetite such as that encountered with exercise training? Will the main drivers for thermogenesis, namely the sympathetic and thyroid axes, be turned off? All these questions must be answered before BAT thermogenesis can be used efficiently and safely as an anti-obesity strategy.

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None.

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