Obesity develops when energy intake exceeds energy expenditure. Now used increasingly for diagnostic purposes, fluorodeoxyglucose positron emission tomography (FDG-PET) has revealed that active brown adipose tissue (BAT) exists in normal adult humans. The thermogenic capacity of brown adipocytes enables BAT to effectively increase substrate oxidation, and it has been estimated that in humans as little as 40 to 50 g of BAT, if maximally stimulated, can account for up to 20% of daily energy expenditure. Several studies have demonstrated an inverse relationship between BAT activity and body fat content, and together these data suggest that BAT is a regulatory site of thermogenesis and body fat metabolism in humans. This has made BAT an attractive target for the development of new therapeutic approaches for the treatment of obesity and its associated metabolic complications. However, we must first understand how BAT activity and mass are regulated in humans if we are to fully assess the therapeutic potential of BAT; important questions remain. This review highlights our current understanding.

Brown, beige, and brite cells

Brown adipocytes have traditionally been defined as lipid-containing cells with multivacuolar appearance and a high content of mitochondria expressing uncoupling protein 1 (UCP1). BAT contains large amounts of brown adipocytes and is highly vascularized and innervated. The study of BAT has recently revealed
that in addition to brown adipocytes in BAT, distinct types of thermogenic fat cells can be found in white adipose tissue depots. These cells have been termed “beige” or “brite” adipocytes, and although they share thermogenic properties with classical brown adipocytes, they do not originate from the same progenitor cell. Lineage-tracing studies show beige cells originate from myogenic factor 5 (Myf5)-negative progenitor cells, much like white adipocytes, whereas classical brown adipocytes derive from Myf5-positive progenitor cells, similarly to skeletal myocytes. In rodents, beige adipocytes are not confined to classical BAT locations—such as interscapular, cervical, and periaortic areas—but can be found scattered in white adipose tissue and between muscle bundles in skeletal muscle. Specific cell-surface markers can be used to identify the different UCP1-expressing types of adipocytes, and using such markers, it has been shown that most brown adipocytes in human BAT are Myf5-negative–beige adipocytes. Interestingly, overfeeding in mice triggers diet-induced thermogenesis, and this physiological mechanism permits excessive calorific intake to be dissipated as heat, allowing animals to eat without gaining weight. UCP1-knockout mice lack this mechanism, and they are prone to diet-induced obesity. Specific strains of mice, such as SvEv, are resistant to diet-induced obesity—whereas other strains, such as C57B6, are prone to obesity—and this resistance is associated with a greater number of UCP1-positive beige adipocytes in the SvEv strain than in C57B6. Higher numbers of beige adipocytes in SvEv mice than in C57B6 mice are especially found intermixed with white adipose tissue adjacent to the thigh muscle. The differences in beige adipocyte numbers between SvEv and C57B6 strains appear to be genetically determined. In humans, BAT activity is negatively correlated with body mass index, body fat content, and visceral fat, and the amount of BAT that can be detected by FDG-PET decreases with age. However, when interventions that activate BAT are repeated for a prolonged period, BAT activity can be detected even in previously BAT-negative subjects. This demonstrates that BAT can be recruited in humans.

Nonpharmacological regulation of BAT

Temperature

Nonpharmacological activation of BAT in humans can be achieved by reducing temperature. Acute (1-2 hours) mild cold exposure (18°C-19°C) is sufficient to activate BAT in humans. In fact, it is often necessary to scan patients at thermoneutrality when performing [18F]FDG-PET imaging in order to reduce distracting signals from areas with BAT. Studies of prolonged cold exposure for a period between 10 days and 4 months have shown significant increases in BAT mass and activity. The increases in BAT mass and activity are predominantly within classical locations, such as cervical and supraclavicular areas. None of these studies reported any significant reduction in total body weight. However, a study with a 6-week intervention period found a significant 5% reduction in body fat mass. Evaluation of body composition in another study after 4 months of repeated cold exposures did not find a similar effect, but this study only included 5 subjects. Simply lowering ambient temperature or introducing a variable indoor environment with frequent cold exposures may therefore be practical, easy, and effective antiobesity regimens. However, care should be taken to prevent an increase in energy intake, because an increased desire to eat has been observed after cold acclimation. Large scale studies are warranted to test whether cold exposure is indeed an efficient strategy to treat obesity in humans.

Exercise

Regular physical exercise prevents many of the metabolic complications associated with obesity, and exercise interventions can be effective in achieving weight loss in obesity. Physical exercise is itself thermogenic, and regular physical activity can decrease the need for thermogenic activity in BAT. Indeed, most animal studies investigating the effect of exercise on BAT activity in classical depots, such as the interscapular area, have shown reduced activity. Nevertheless, some reports indicate that physical ex-
Exercise may have a positive effect on ectopic UCP1 expression, and this may be under hormonal regulation. Irisin, a circulating protein that is released by cleavage from its precursor protein, fibronectin type III domain-containing 5, has been described to promote the appearance or recruitment of beige cells in white adipose depots.\textsuperscript{17} It is speculated that increased irisin expression with exercise and the recruitment of BAT have evolved as a consequence of muscle contraction during shivering.\textsuperscript{17} However, the existence of this protein in humans and its role there is still a matter of debate.\textsuperscript{18}

**Diet**

BAT has also been found to be activated by food ingredients, like capsaicin.\textsuperscript{12} Capsaicin—an active component of chili peppers—and intake of red peppers can increase energy expenditure.\textsuperscript{19} Changing diet to include more “hot foods” may therefore be a simple way to activate thermogenesis in BAT. The underlying mechanism has been suggested to involve capsaicin-induced activation of transient receptor potential (TRP) channels.\textsuperscript{20} TRP channels can be activated by cold stimuli\textsuperscript{20} and may transmit activation of BAT by cold exposure. However, propranolol can block the increase in energy expenditure induced by intake of red pepper, indicating that adrenergic stimulation may also be involved in capsaicin-induced thermogenesis.\textsuperscript{21}

**Pharmacological regulation of BAT**

**Adrenergic stimulation**

Among the pharmacological factors that influence the brown adipocyte is norepinephrine, which is both the most important and also the most well-studied. BAT can be pharmacologically activated by β\textsubscript{3}-adrenergic-receptor–agonist treatment.\textsuperscript{22} However, despite the use of somewhat specific β\textsubscript{3}-agonists, other adrenergic receptors may also be involved.\textsuperscript{7} In rodents, norepinephrine stimulation of brown preadipocytes and mature adipocytes leads to recruitment in BAT.\textsuperscript{23} This mechanism may translate to humans; increases in BAT mass and activity have been observed in patients with pheochromocytoma and paraganglioma.\textsuperscript{24,25} Such patients are subjected to chronic catecholamine stimulation and severe adrenergic stress, as seen in severely burned patients, and also develop ectopic BAT within their white adipose tissue depots. The degree to which BAT can be recruited in humans is clearly relevant for obesity therapies. This can perhaps best be illustrated by a recent case report from our hospital. In a male patient, a catecholamine-secreting paraganglioma was diagnosed and was associated with massive induction of BAT mass in the visceral adipose tissue.\textsuperscript{25} The presence of UCP1 expression was clearly detected in tissue biopsies and the metabolic activity of his BAT was documented by FDG-PET (Figure 1). This patient had a resting energy expenditure at presentation of 15 188 kJ, which is more than double the expected value. We observed a massive decrease in BAT activity measured by FDG-PET after initiation of treatment with the α-adrenergic-receptor–blocker phenotybenzamine.\textsuperscript{25} In rodents, the presence of α-adrenergic receptors in BAT have been documented, and stimulation of these receptors can activate BAT.\textsuperscript{26} More investigation of the effects of

![Fig. 1](image-url) A patient with catecholamine-secreting paraganglioma demonstrates the degree to which brown adipose tissue (BAT) mass can be induced in humans. Maximum intensity projection [\textsuperscript{18}F]FDG-PET images of the patient (A) at diagnosis, (B) during α-blockade, and (C) 3 months after surgery. (D) Visceral adipose tissue from the omentum, stained using anti-uncoupling protein 1 (UCP1) antibody. The tissue displays capillary-rich areas with large amounts of cells staining positive for UCP1 and having a classic multilocular appearance that resembles brown adipocytes. (E) Subcutaneous tissue (from the same patient) stained for UCP1, showing no infiltration by UCP1-positive cells in the subcutaneous adipose tissue.
α-adrenergic stimulation of BAT activity in humans, therefore, is attractive. This is further supported by failed attempts to induce BAT activity by sympathomimetics in humans.\textsuperscript{27}

**Thyroid-hormone treatment**

Treatment with thyroid hormones has been shown to induce UCP1 expression in brown adipocytes in animals.\textsuperscript{7} The underlying mechanism is suggested to be the binding to thyroid hormone–responsive elements in the UCP1 promoter. However, it is not clear whether the effects of thyroid hormones observed in animals translate into humans. Treatment with thyroid hormone reduces weight in patients with hypothyroidism, but there is no consistent evidence that thyroid-hormone treatment induces weight loss in obese euthyroid individuals.\textsuperscript{7} In addition, a recent study of BAT activity in hyperthyroid patients using \textsuperscript{18}F-FDG uptake under hyperthyroid and euthyroid conditions showed no positive effect of thyroid hormone on BAT activity.\textsuperscript{28} Activating BAT through thyroid-hormone treatment is, therefore, not appealing at present. However, development of novel agonists of thyroid hormone–responsive elements in the UCP1 promoter could be a future treatment strategy.

**Other strategies**

Another promising strategy to treat obesity by targeting BAT is simply to implant BAT into obese subjects. Transplantation of BAT into mice improves glucose tolerance and causes weight loss in these mice.\textsuperscript{29,30} The transplantation of BAT also ameliorated the harmful effects of a high-fat diet.\textsuperscript{29,30} The beneficial effects on whole-body metabolism are blunted when BAT is transplanted from interleukin 6–knockout mice.\textsuperscript{30} This finding indicates that some of the beneficial effects of increased BAT mass can be, at least in part, hormonally mediated and that BAT may have endocrine functions. It is well-established that white adipose tissue secretes bioactive peptides, termed “adipokines,” which act locally and distally in an autocrine, paracrine, and endocrine manner. These adipokines regulate multiple functions, such as appetite, energy balance, and insulin sensitivity. Thus, the degree to which BAT secretes adipokines is an interesting topic for future research and may have promising perspectives for new obesity therapies.

**Conclusion**

Our growing understanding of the factors that regulate BAT activity and recruitment continues to support the perspective of targeting BAT in obesity treatment. Humans are capable of recruiting large amounts of ectopic BAT, which can significantly increase energy expenditure. Strategies to activate BAT involve both pharmacological and nonpharmacological interventions (Figure 2). However, if the increased energy expenditure is met by a matching increase in energy intake, the intervention against obesity will be futile.\textsuperscript{15} This is exemplified by our case report showing massive infiltration of BAT in a patient with paraganglioma.\textsuperscript{25} This patient was able to maintain a normal body weight despite a massive increase in resting energy expenditure, and he presented with a body mass index of 25.6 kg/m\textsuperscript{2}. After removal of the tumor, his resting energy expenditure normalized; however, 3 months later his body weight increased from 82.6 to 90.8 kg and his body fat, from 27.1% to 30.9%.\textsuperscript{25} Therefore, strategies to activate and/or recruit BAT in humans cannot necessarily stand alone, but are more likely to be effective if they are combined with interventions that reduce energy intake.

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