

Brown adipose tissue: clinical impact of a re-discovered thermogenic organ

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1. ABSTRACT

Brown adipose tissue (BAT) is physiologically present and active in adult humans. The stimulation of BAT in man can potentially increase total daily energy expenditure and is seen as a possible target to treat obesity. Altered BAT activity is also related to other diseases and therefore the therapeutic potential of BAT could reach beyond obesity. This is supported by both *in vitro* and *in vivo* reports from animal studies, describing the possible role of BAT in both physiology and pathophysiology. In addition, since the discovery of functional BAT several clinically relevant studies have been conducted in adult man. Clinical observations report BAT activity under multiple conditions, suggesting BAT could be important in the onset and/or treatment of diseases related to the metabolic syndrome, thyroid disorders, cancer and immune system dysfunction. This review highlights those diseases or syndromes in which BAT may play a role in relation to prevention, diagnosis or therapy, by translating basic research into clinical relevance.

2. INTRODUCTION

Recently, active brown adipose tissue (BAT) was discovered in healthy adults (1-3). In rodents, BAT is known for its high heat production capacity that can significantly increase total energy expenditure (4). Since the discovery of functional BAT in man, increasing energy expenditure by the stimulation of BAT is seen as a new anti-obesity target (5, 6). Interestingly, in man BAT activity is low or absent in obese subjects. Possibly, increasing energy expenditure by stimulation of BAT could be important in weight maintenance or could create a negative energy balance leading to weight loss.

Studies in both man and animals also show active BAT under several clinical conditions. These studies suggest involvement of BAT in conditions that are associated with the metabolic syndrome (obesity, type 2 diabetes, dyslipidemia, fatty liver disease), endocrine disorders (pheochromocytoma, thyroid gland dysfunction), neoplasms (cancer cachexia, hibernoma), general

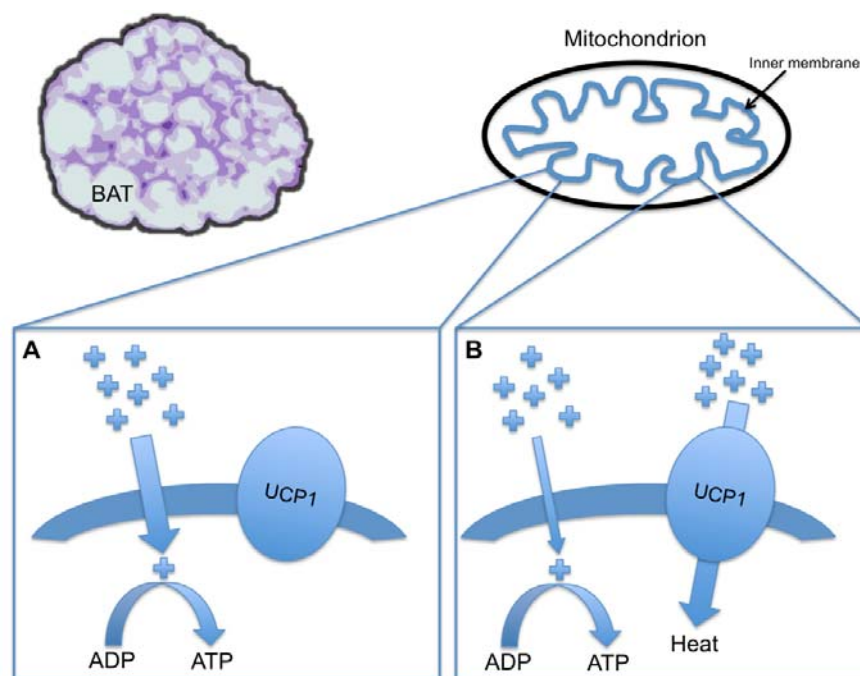


Figure 1. Uncoupling protein 1 (UCP1) mediates mitochondrial uncoupling in brown adipose tissue (BAT). Schematic overview of BAT (top left), BAT mitochondrion (top right) and inner mitochondrial membrane (A and B). The proton gradient across the inner mitochondrial membrane can be used to generate ATP (coupled respiration, depicted in A). When BAT is stimulated to become active, UCP1 facilitates uncoupling of ATP-generation to induce thermogenesis (uncoupled respiration, depicted in B).

inflammation and the immune response. Here, we will discuss the relevance of BAT in relation to these conditions, and its possible therapeutic impact.

3. PHYSIOLOGY OF BAT

Classically, BAT is associated with cold exposure. To prevent hypothermia, increasing insulation (clothing) and change of environment are effective behavioral strategies. However, if this is not possible or insufficient, generating body heat is necessary to prevent hypothermia. Shivering in skeletal muscle is very effective to increase heat production, but this cannot be sustained for longer periods of time (7). Interestingly, when a subject is exposed to cold, heat production already increases prior to the onset of shivering (8). This process is defined as nonshivering thermogenesis (NST). In rodents BAT is the main site for NST (4). In man, there are indications that both BAT and skeletal muscle are involved (9).

3.1. Mitochondrial uncoupling induces thermogenesis in BAT

NST in the brown adipocyte is facilitated by ‘uncoupling’ of the mitochondrial respiration from adenosine-tri-phosphate (ATP) production. The mitochondrial respiration chain generates a proton gradient across the inner mitochondrial membrane to produce ATP. However, during BAT stimulation the cross-membrane proton gradient is used to produce heat instead of ATP. An essential protein for this process, that also typifies BAT, is the uncoupling protein 1 (UCP1, Figure 1) (4). In order to

facilitate uncoupling by UCP1 in the brown adipocyte, free fatty acids (FFAs) are necessary (4). The exact contribution of FFAs to UCP1 activation is still unknown, but most likely they facilitate a membrane entrance for protons to generate thermogenesis (4). Besides FFAs, BAT also uses glucose during thermogenesis (4). The purpose of glucose-uptake in active BAT is largely unknown. Possibly, glucose is necessary to maintain the citric cycle, ATP production and the proton gradient (4). Alternatively, glucose is converted to FFAs (4). The function of glucose uptake in BAT would then be to increase the amount of FFAs, necessary for mitochondrial uncoupling.

3.2. Involvement of sympathetic nervous system in BAT activation

The sympathetic nervous system (SNS) stimulates BAT to produce heat during NST. Sympathetic innervation is essential for BAT to become active, as disruption of the sympathetic fibers to BAT completely ceased BAT activity (10). In man, most likely responses from warm- and cold sensitive neurons regulate the activation of thermogenesis (11). In the hypothalamus and medulla input from these neurons is mediated into sympathetic stimuli that control BAT thermogenesis by the release of norepinephrine on the adrenergic receptors of BAT cells (11). In rodents, BAT activity is associated with both adrenergic α - and β -receptor subtypes. Although the α_{1A} -receptor is abundant in BAT, stimulation could only account for maximally 10% of total BAT thermogenesis in rodents (4). The α_2 -receptor is even suggested to inhibit thermogenesis. The β_3 -receptor seems to be the most

significant mediator of thermogenesis, as suggested from studies that have compared BAT stimulation with β_3 -agonists versus norepinephrine (4). Most likely β_3 -activation, and to a much lower extent α_{1A} -activation, mutually mediate norepinephrine-induced thermogenesis in mammals. Although present in BAT, the β_1 -receptor is only suggested to influence BAT activity when β_3 -receptor signaling is dysfunctional (e.g. β_3 -receptor-ablation) (4).

3.3. Thyroid hormone induces BAT activation

In addition to sympathetic stimulation of BAT, thyroid hormone plays a significant role in BAT thermogenesis. The thyroid gland mainly secretes the inactive pro-hormone thyroxine (T4), which needs to be deiodinised (lose an iodine atom) by deiodinases to triiodothyronine (T3) to become active. In rodents, T3 can stimulate BAT (12). After conversion of T4 to T3 by the BAT-specific type-II-iodothyronine-5-deiodinase (D2), thyroid hormone enhances BAT thermogenesis (12, 13). In addition, thyroid hormone supplementation in the brain increased BAT activity and induced weight loss in rodents (13). This activation of BAT could then be reversed by the β_3 -adrenergic receptor antagonist SR59230A, indicating this central thyroid activation was mediated via the SNS (13). These results indicate interplay at the central nervous system level between the endocrine (thyroid axis) and sympathetic regulation of BAT.

3.4. Presence of BAT in man

In humans, BAT is present in significant amounts during childhood. Compared to adults, newborns have several disadvantages regarding their maintenance of body temperature. The higher body surface-to-volume ratio may cause a more rapid heat loss. Due to low amount of muscle, the ability to induce thermogenesis by shivering is limited. Therefore NST is important in newborns (4). During infancy growth changes the relative surface area and the amount of BAT gradually decreases. In adulthood BAT has been reported in autopsies (14), but it was always believed to be dysfunctional (15). Strikingly, BAT has recently shown to be present in significant amounts in adults and becomes functionally active upon cold exposure (1, 2). 2-deoxy-2- ^{18}F -fluoro-D-glucose (^{18}F -FDG), a radioactive labeled glucose tracer, is used in nuclear imaging (positron-emission-tomography-and-computed-tomography (PET-CT)) to depict glucose uptake for tumor diagnosis. Frequently non-malignant uptake in adipose tissue was seen, which later appeared to be related to mild cold conditions during the tracer administration. Prospective, controlled mild cold exposure consistently showed this activity in supraclavicular, cervical and paravertebral adipose tissue regions. Tissue biopsies from PET-active supraclavicular adipose tissue regions confirmed BAT presence (1, 2).

Retrospective ^{18}F -FDG PET-CT series in infants show high amounts of BAT that even increase during adolescence (16). In adolescence, muscle mass also still increases under influence of metabolic and hormonal factors (16). Seale *et al.* showed that skeletal muscle and BAT share a similar developmental origin (17) and therefore it is suggested the factors that induce muscle

growth during adolescence could similarly influence BAT (16). After the volume of BAT peaks up to amounts of 1200 cm^3 in the second decade of life (16), ^{18}F -FDG PET-CT studies (3) and histological analyses (18) indicate the amount of BAT decreases with age. BAT expresses sex hormone receptors and the age-related involution of BAT could be influenced by the lowering levels of sex hormones (19). If low BAT is related to disease, the age-related BAT loss could be important in the onset of the metabolic syndrome and other pathologic conditions.

4. BAT IN DISEASE

4.1. Metabolic syndrome

4.1.1. Obesity

In mice, absence of active BAT through ablation of UCP1 causes a weight gain of >50% within 30 days after birth (20). In man, dedicated studies show a strong negative correlation with BAT activity and body fat percentage and body mass index (1, 3, 21). Retrospective analyses of patient ^{18}F -FDG PET-CT-scans reveal comparable relations (22-25). Possibly, due to the insulation by subcutaneous adipose tissue in obese subjects there is less need to activate BAT in daily living situations. Subjects without BAT activity show significantly lower NST (21, 26), suggesting BAT is involved in the human energy balance. A classic overfeeding study in man showed large differences in weight gain on a high-calorie diet (27). If low or absent BAT activity would be responsible for the differences in weight gain after overfeeding, increasing BAT activity could possibly prevent or treat obesity. An explanation for the individual variation in BAT could be associated with polymorphisms in the UCP1-gene. Resting energy expenditure, sympathetic nervous system activity and the thermal effect of a meal show a relation with the UCP1 G/G genotype (28). Moreover, if the UCP1 G/G genotype is accompanied by a Trp64Arg polymorphism of the β_3 -receptor gene this is associated with a lower basal metabolic rate, lower sympathetic nervous system activity and a higher amount of visceral adipose tissue (29, 30). However, there are no studies that have directly related BAT activity and UCP1-polymorphisms yet.

In summary, active BAT is low or absent in obesity. Body composition (body fat percentage) and environmental factors (lifestyle) may cause variations in amount and activity of BAT. Increasing BAT activity could be a new target to both prevent and treat overweight.

4.1.2. Type 2 diabetes

The significant uptake of glucose in active BAT is shown by ^{18}F -FDG PET-CT. Stimulating glucose uptake in BAT can be beneficial *in situations* of impaired glucose clearance, as in type 2 diabetes. Indeed, retrospective cohort studies suggest an association with high blood glucose levels and absence of active BAT on ^{18}F -FDG PET-CT (24, 31, 32). Interesting is the case of a patient with a resected thyroid gland because of thyroid cancer and an extreme insulin resistance due to an insulin receptor mutation (33). The therapeutic treatment of this patient with high doses of thyroid hormone was accompanied with an increase of active BAT. The supplementation with thyroid hormone also resolved the patient's hyperglycaemia,

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hinting towards an association between BAT activity and glucose homeostasis.

To estimate the glucose clearing capacity of BAT in man, the uptake of glucose in cold-stimulated BAT can be used. Calculations made from dynamic ^{18}F -FDG PET-CT scans during cold exposure show a mean glucose clearance in BAT of $9.1 \pm 5.1 \mu\text{mol}/100 \text{ g}/\text{minute}$ ($n=27$) (34) to $22.67 \pm 18.28 \mu\text{mol}/100 \text{ g}/\text{minute}$ ($n=5$) (unpublished results). To assess the possible contribution of cold stimulated BAT on whole body glucose clearance, glucose uptake in BAT (0.7 mM glucose for 100 g BAT per hour, based on reports above) can be compared to the glucose infusion rate in a hyperinsulinemic-euglycemic clamp test (166 mM glucose per hour) (35). In this comparison, BAT accounts for 0.4% of the body's maximal glucose uptake.

In summary, active BAT takes up glucose and BAT in man can be important in glucose clearance. Therefore, BAT is a new potential target tissue for the treatment of type 2 diabetes.

4.1.3. Dyslipidemia

FFAs are essential for BAT thermogenesis (see Physiology of BAT). They are delivered to BAT by plasma circulating triglyceride-rich lipoproteins (TRLs) and cold-activated BAT in mice cleared a large amount of TRLs from the blood after a meal (36). On a cellular level, BAT-released lipoprotein lipase (LPL) converted the TRLs to free fatty acids (FFA), then used for thermogenesis (36). In conclusion, after BAT activation by cold exposure experimentally induced hyperlipidemia could be corrected. Although the condition of cold exposure was extreme (4°C), the reported high clearance of plasma triglycerides ($>50\%$) provides hope for the treatment of dyslipidemia in man. In man, current treatment for dyslipidemia with statins generates a 40-60% reduction in plasma low density lipoprotein (LDL) cholesterol, a direct lipolysis product of TRLs (37). Increasing BAT activity theoretically requests more lipolysis and could positively affect dyslipidemia.

4.1.4. Hepatosteatosis

Obesity, type 2 diabetes and dyslipidemia are all associated with an increased accumulation of fat in the liver, defined as hepatosteatosis (or non-alcoholic fatty liver disease (NAFLD)). Hepatosteatosis is associated with a decrease in liver functionality and a high risk of developing steatohepatitis and liver cirrhosis (38). A retrospective analysis of ^{18}F -FDG PET-CT-scans suggests an inverse relation between BAT activity and hepatosteatosis (39). Subjects without BAT activity had a significantly higher risk of hepatosteatosis and BAT activity was inversely correlated with the level of liver steatosis and body mass index (BMI). In addition to the association with energy balance, genetic polymorphisms of UCP1 are also associated with hepatosteatosis (40).

In conclusion, hepatosteatosis is associated with low BAT activity and prospective studies are needed to define the role of low BAT in the development of hepatosteatosis.

4.2. Thyroid disease

Patients with thyrotoxicosis (high levels of plasma T4 and T3 due to a toxic goiter) have an increase in resting energy expenditure (REE) up to 30% that returns to normal values after treatment with thiamazole (41). Upon T3-suppletion (resulting in T3 values twice as high compared to normal) in healthy subjects basal metabolic rate (BMR) increased (42). During hypothyroidism (low plasma levels of thyroid hormone) REE decreases 20-25% (43). Even the induction of subclinical variations in thyroid function by suppletion of thyroid hormone already caused changes in REE of 5-10% (43). This indicates thyroid function is relevant for at least REE in man, but the contribution to thermogenesis and BAT has not been clearly defined yet. Support for thyroid-induced BAT activity in man is given by the above-mentioned case report of a patient with a resected thyroid gland because of thyroid cancer (33). Treatment with thyroid hormone was accompanied with active BAT on ^{18}F -FDG PET-CT, without cold exposure.

Similar to the influence of thyroid hormone on REE, variations in thyroid function within normal ranges could also impair or stimulate BAT activity. Therefore, dedicated studies on thyroid function and BAT in man are necessary.

4.3. Pheochromocytoma

The pheochromocytoma is a tumor of chromaffin-cells. In man, chromaffin cells are present in the medulla of the adrenal gland and secrete the catecholamines norepinephrine and epinephrine. During cold exposure, BAT is activated by sympathetic stimuli from the brain that release norepinephrine to stimulate the adrenergic receptors on BAT cells (11). Catecholamines released in the blood plasma induce adrenergic responses similar to activation of the sympathetic nervous system. In rodents, suppletion of norepinephrine is known to be able to increase the activity of BAT up to a fourfold (4). In patients with pheochromocytoma, retrospective ^{18}F -FDG PET-CT studies often show high BAT activity even under thermoneutral conditions (44, 45). Interestingly, the high levels of circulating plasma catecholamines in pheochromocytoma were significantly related to the level of BAT activity (25). This suggests that the principle of catecholamine-activated BAT (by suppletion of norepinephrine into the circulation) as observed in rodents also applies to man.

4.4. Cancer cachexia

During cancer cachexia high BAT activity is reported. In autopsy studies in man high BAT presence in cachectic cancer patients was already described years ago (46). Active BAT is also often reported in ^{18}F -FDG PET-CT-imaging of oncologic patients (47). It is hypothesized that the high production of cytokines in cancer stimulates thermogenesis in BAT, both via the hypothalamus and directly on BAT cells. This is supported by studies in mice that show tumor implantation or stimulation with carcinogenic factors increases BAT activity (48).

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Experimental denervation of BAT and β_3 -receptor antagonism reduces the effect of a cytokine-induced increase in energy expenditure (49). Therefore, the tumor-induced high BAT activity is held responsible for the increased thermogenesis that causes body mass loss up to anorectic levels in cancer cachexia.

4.5. Hibernoma

In addition to the high BAT activity in physiological depots in patients with malignant tumors, BAT can be present within a tumor itself (50). The rare hibernoma, a benign lipomatous tumor of brown adipocytes, was visible on ^{18}F -FDG PET-CT-imaging (23). Although the hibernoma shows activity on ^{18}F -FDG PET-CT, its activity apparently seems not high enough to significantly induce weight loss (23). In spite of the fact large amounts of BAT are present in the hibernoma, it is not activated in daily life.

4.6. Immune response

In rodents BAT thermogenesis increases during fever (51). In the inflammatory state BAT serves as the main heat-producing tissue in rodents (51). After the injection of lipopolysaccharide (LPS), an endotoxin present in bacteria, BAT is triggered to increase thermogenesis which causes fever (51). The increase in BAT activity also occurs in response to sympathetic stimuli from the hypothalamus, which itself is stimulated by pyrogenic cytokines (11). Besides the sympathetic stimulus from the brain, macrophages in the blood of mice are able to release catecholamines that activate BAT (52). Interestingly, during fever BAT starts producing its own endogenous pyrogens (51). BAT is reported to produce interleukin-6 (IL-6), a pro-inflammatory cytokine normally secreted by cells of the immune system, e.g. macrophages. IL-6 is not only present during fever, but is also important during inflammation and infection and is seen in other immune reactions (53). In fever, IL-6 initiates the pyrogenic mediator prostaglandin E₂ (PGE₂) which in the hypothalamus increases the temperature setpoint (11). In this perspective BAT thus could be capable of both controlling the level of fever and increasing heat production. This is interesting, because it makes BAT not only a tissue that responds when stimulated, but also a controller of thermogenesis itself. Cyclooxygenase 2 (COX-2), an important controller of PGE₂ production, recruits BRITE (brown-in-white) cells in white adipose tissue (WAT) of mice (54). These cells are non-thermogenic preadipocytes present in WAT that differ from white adipocytes because they can become thermogenic to similar levels as BAT (55). Others factors for BRITE recruitment are a currently further explored treatment target (see Stimulation of BAT). Since IL-6, COX-2 and PGE₂ are important in inflammation, increasing the amount of BAT or BRITE could be an interesting target to enhance the immune response during immunodeficiency.

Besides cold induced thermogenesis, BAT may be involved in immune competence of neonates (56). Sudden infant death syndrome (SIDS) is associated with a depletion of BAT, as observed afterwards during autopsy (56). It is suggested this BAT depletion could follow from maternal conditions during pregnancy. Indeed, animal studies show that maternal cold exposure increased BAT activity in newborn

lambs and lactation conditions were important for BAT development in mice (57, 58).

Results from autopsies (14), ^{18}F -FDG PET-CT-imaging studies (3) and histological analyses (18) indicate the amount of BAT decreases with age. If BAT is important in the immune response, a lower amount of BAT in the elderly could possibly account to more disease susceptibility.

In conclusion, BAT can be important for our immune system. However, more prospective studies on BAT activity or recruitment during fever or immune activation are needed.

5. STIMULATING BAT

5.1. Cold exposure

Functional BAT in man was discovered by exposing subjects to mild cold (1, 2). Under thermoneutral conditions, healthy subjects did not show active BAT (1). Indeed, active BAT is related to thermogenesis under mild cold exposure (21, 26, 59). During cold acclimatization (days to weeks) nonshivering thermogenesis (NST) increases (60). In mice, the increased NST after cold acclimatization originates from increased BAT activity (4). Cold acclimatization also causes recruitment of BAT in rodents and primates (4).

In man, high volumes of BAT were observed in autopsy studies on Finnish outdoor workers, who were acclimatized to cold (61). Hence, cold acclimatization could be an interesting treatment modality to increase energy expenditure by activating NST in BAT (7).

5.2. Insulin stimulation

In mice, injection of insulin in the hypothalamus increases thermogenesis by activating BAT (62). In man, insulin infusion increased glucose uptake in BAT five-fold compared to baseline, from 0.9 to 4.7 $\mu\text{mol}/100\text{ g}/\text{minute}$ (34). This insulin stimulated glucose uptake in BAT amounted to half of the cold stimulated BAT activity. In contrast to glucose uptake during cold exposure, insulin-stimulated glucose uptake in BAT is suggested to be more active under non-thermogenic conditions (no cold exposure) (4). Under such conditions glucose would mainly be taken up in BAT to be converted into FFAs, that later can be used for mitochondrial uncoupling during BAT activation (4).

In summary, BAT can be stimulated by insulin to take up glucose under thermoneutral conditions. Possibly, insulin-stimulated BAT could decrease blood glucose levels and serve as a therapeutic target for type 2 diabetes.

5.3. Sympathetic stimulation

Sympathetic β -receptor agonists increase SNS activity, which could possibly stimulate BAT thermogenesis. Interestingly, cold-induced BAT activity in man can be fully blocked by the β -antagonist propranolol (63). Propranolol is highly specific for β_1 - and β_2 -receptors and rodent studies indicate BAT mainly contains β_3 -receptors (4). This suggests BAT activity in man is

Table 1. Diseases associated with brown adipose tissue (BAT) activity and possible implications for therapy

Disease	Effect on BAT ¹	Evidence	Potential implication
Obesity	Decrease of BAT activity with increased BMI and body fat %	Retrospective (human) (22-25, 31, 32) Prospective (human) (1, 3, 21)	Increase BAT activity to prevent and/or treat obesity
Type 2 diabetes	Association with high blood glucose and absence of BAT activity	Retrospective (human) (24, 31, 32) Prospective evidence of insulin-mediated BAT activity (34)	Increase BAT activity to decrease hyperglycemia
Dyslipidemia	BAT activation decreases hyperlipidemia	Mice (36)	Increase BAT activity to improve hyperlipidemia
Hepatosteatosis	Association with absence of BAT activity and hepatosteatosis	Retrospective (human) (39)	Absence of BAT activity could be a risk to develop hepatosteatosis
Hyperthyroidism	Increase in BAT activity during hyperthyroidism	Rats (13)	Target thyroid function to correct impaired BAT activity
Hypothyroidism	Absence of BAT activity during hypothyroidism	Case-report after thyroid resection (human) (33)	
Pheochromocytoma	Association with active BAT and high plasma catecholamine levels	Pheochromocytoma patients (44, 45)	Stimulation of sympathetic nervous system to induce BAT activity
Cancer cachexia	Active BAT during cancer cachexia	Tumor-bearing mice (48) Autopsy (human) (46) Cancer cachexia (human) (47)	Cancer-induced BAT activity increases cachexia
Hibernoma	High amount of active BAT in hibernoma	Human (23, 50)	Activated BAT in hibernoma affects energy balance
Immune-activation	Immune response influences BAT activity	Cell studies (52) Mice (54)	BAT activity is relevant in immune activation

Abbreviations: ¹Brown adipose tissue

mediated differently from rodents. The β -agonist ephedrine was used to stimulate BAT and increase energy expenditure many years ago, but activation of BAT was not reported possibly due to the limited methods then available (15). Since ephedrine mainly stimulates β_1 - and β_2 -receptors and propranolol shows blockage of these receptors inhibits BAT, ephedrine (or other β -receptor agonists) could be effective in activating BAT in man after all. Controversially, propranolol suppletion did not reduce cold-induced NST in man (64). Since NST in man upon cold exposure is associated with BAT, this again supports the β_3 -receptor specificity of BAT seen in rodents. These contrasting results could possibly become more clear after an intervention study with β_3 -receptor specific agonists (5).

5.4. BAT stimulation via the gut

In rodents, the feeding of bile acids increases fat combustion in BAT (65). This signal is mediated via the G protein-coupled bile acid-receptor TGR5 (TGR5), present on BAT (66). TGR5-agonists increase energy expenditure, decrease non-alcoholic fatty liver disease (NAFLD) and improve glucose tolerance in rodents (65). Interestingly, this process is dependent of the thyroid hormone converter D2 (for thyroid function and BAT, see BAT physiology) (67). If D2 is disrupted in mice, bile acids do not increase BAT activity anymore, indicating the importance of thyroid-induced thermogenesis in bile acid-stimulated BAT activity (67).

Gut hormones are involved in food intake regulation via the brain (68). Rodent studies indicate the central responses involved in ingestion are most likely located in the paraventricular hypothalamus, which is also known to induce the sympathetic nervous system (SNS) and thyroid axis (68). Increased SNS activity stimulates BAT activity, and therefore the response that mediates a decrease in food intake could stimulate energy expenditure in BAT. In man, this is illustrated by the observation that after suppletion of the appetite hormone oxyntomodulin energy expenditure was also stimulated (69).

In summary, the suppletion of bile acids and gut hormones could induce an increase in BAT activity via the gut (70).

5.5. Transforming WAT to BAT

All options described above consider the stimulation of BAT present at birth, often referred to as 'native' BAT depots. BAT in these depots was shown the share a developmental origin that is very similar to skeletal muscle (17). The presence or absence of the signaling molecule PRDM16 stimulates dermomyotomal precursors to end up as a skeletal muscle cell (absence of PRDM16) or as a brown adipocyte (PRDM16+) (17). WAT seems to derive from a different developmental origin without the thermogenic capacity of BAT (71). However, within WAT depots a subpopulation of cells is indeed capable of developing into thermogenic 'beige' or BRITE (brown-in-white) cells (55, 71). These cells possess UCP1 and are thus capable of thermogenesis. Chaffee *et al.* already reported 'darker yellow adipose tissue' in rhesus monkeys after 12-24 months cold-acclimatization at 5°C in comparison to controls housed at 35°C (4). Several studies have now reported the development of BRITE cells upon diverse stimuli under cell culture conditions and in rodents (55, 72, 73). Here, three studies are of special clinical interest because of the use of human samples (73-75). Irisin, a novel hormone that induced 'browning' and UCP1-expression in subcutaneous adipose tissue from mice, was shown to increase in human plasma after 10 weeks of exercise (75). However, this study did not study the effects of irisin on human adipocytes and therefore further human studies are needed. Lee *et al.* show *in vitro* development of thermogenic adipocytes that derive from preadipocytes isolated from supraclavicular adipose tissue biopsies in both FDG-PET-CT-positive (n=2) and FDG-PET-CT-negative (n=4) subjects (74). The stimulants used in this study were both β -agonists and proliferator-activated receptor gamma (PPAR-gamma), an agent present in several antidiabetic agents (rosiglitazone, pioglitazone). In

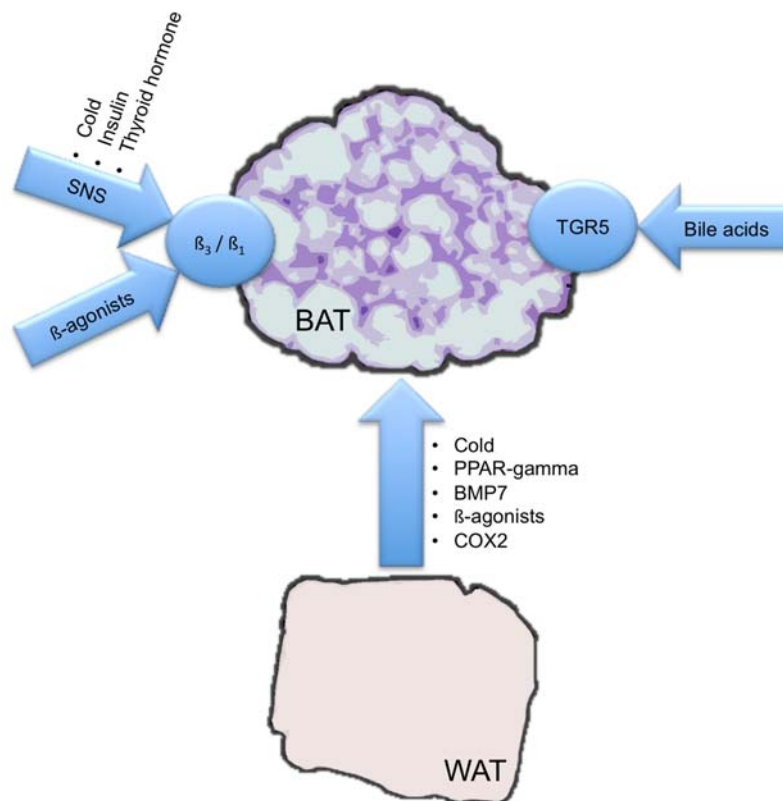


Figure 2. Potential therapeutic targets to stimulate BAT based on clinical observations. Schematic representation of brown adipose tissue (BAT) with beta-receptors (β_3 , β_1) and the bile-acid receptor TGR5. SNS indicates sympathetic nervous system, PPAR-gamma indicates peroxisome proliferator-activated receptor gamma, BMP7 indicates bone morphogenic protein 7, COX2 indicates cyclo-oxygenase-2, WAT indicates white adipose tissue.

another study, Schulz *et al.* treated preadipocytes isolated from human subcutaneous WAT with a mix of several agonists and showed the induction of UCP1 presence as a marker of BAT (73). Although no evidence exists of BRITE recruitment *in vivo* in man, the cell studies suggest that transformation of non-thermogenic to thermogenic fat cells is possible in man.

6. PERSPECTIVE

Increasing evidence appears on the important role of BAT in adult physiology in both health and disease. Several recent studies illustrate possible therapeutic potentials of BAT (Table 1, Figure 2). This overview shows that in addition to nonshivering thermogenesis, BAT could be important in the metabolic syndrome (obesity, type 2 diabetes, dyslipidemia, hepatosteatosis), neoplasms (cancer cachexia, hibernoma) and the immune system. However, to define the clinical impact of BAT on disease more basic and clinical controlled studies are needed. Recent studies clearly show metabolic activity of BAT in adult humans, although there are indications of decreasing BAT activity with ageing. Therefore, the factors that account for this decrease should be targets for future investigations. Since it is considered unethical to use PET-CT-techniques to prospectively determine BAT activity in healthy infants and for repeated measurements in healthy

adults, less invasive techniques need to be developed (like magnetic resonance imaging (MRI)). On the other hand it is feasible to perform clinical studies on BAT activity and recruitment during existing therapies. Thyroid hormone suppletion, insulin therapy, weight loss treatment and sympathetic stimulation can provide much insight in the dynamics of BAT and possible clinical targets.

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Abbreviations: ^{18}F -FDG: 2-deoxy-2- ^{18}F -fluoro-D-glucose, ATP: Adenosine triphosphate, NST: Non-shivering thermogenesis, BAT: Brown adipose tissue, BMI: Body mass index, BMP7: Bone morphogenic protein 7, BMR: Basal metabolic rate, BRITE: Brown-in-white, COX-2: Cyclo-oxygenase 2, D2: Type-II-iodothyronine-5-deiodinase, FFAs: Free fatty acids, IL-6: Interleukin 6, LPL: Lipoprotein lipase, NAFLD: Non-alcoholic fatty liver disease, PET-CT: Positron-emission-tomography-and-computed-tomography, PGE2: Prostaglandin E2, PPAR- γ : Peroxisome proliferator-activated receptor gamma, PRDM16: PR domain containing 16, REE: Resting energy expenditure, SIDS: Sudden infant death syndrome, SNS: Sympathetic nervous system, T3: Triiodothyronine, T4: Thyroxine, TGR5: G protein-coupled receptor, TRLs: Triglyceride rich lipoproteins, UCP-1: Uncoupling protein 1, WAT: White adipose tissue

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