Role of the autonomic nervous system in activation of human brown adipose tissue: A review of the literature

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Abstract

Brown adipose tissue (BAT) is able to convert calories into heat rather than storing them. Therefore, activated BAT could be a potential target in the battle against obesity and type 2 diabetes. This review focuses on the role of the autonomic nervous system in the activation of human BAT. Although the number of studies focusing on BAT in humans is limited, involvement of the sympathetic nervous system (SNS) in BAT activation is evident. Metabolic BAT activity can be visualized with 18F-fluorodeoxyglucose, whereas sympathetic activation of BAT can be visualized with nuclear-medicine techniques using different radiopharmaceuticals. Also, interruption of the sympathetic nerves leading to BAT activation diminishes sympathetic stimulation, resulting in reduced metabolic BAT activity. Furthermore, both β- and α-adrenoceptors might be important in the stimulation process of BAT, as pretreatment with propranolol or α-adrenoceptor blockade also diminishes BAT activity. In contrast, high catecholamine levels are known to activate and recruit BAT. There are several interventional studies in which BAT was successfully inhibited, whereas only one interventional study aiming to activate BAT resulted in the intended outcome. Most studies have focused on the SNS for activating BAT, although the parasympathetic nervous system might also be a target of interest. To better define the possible role of BAT in strategies to combat the obesity epidemic, it seems likely that future studies focusing on both histology and imaging are essential for identifying the factors and receptors critical for activation of human BAT.

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1. Introduction

Brown adipose tissue (BAT) has the capacity to turn free fatty acids (FFAs) and glucose into heat. While BAT was thought to be present only in children, in 2009, it became clear that adults also have functional BAT following cold exposures [1–3]. Intriguingly, BAT was more often observed in lean than in obese individuals [1,4]. These findings sparked interest in BAT activation as a potential treatment target for type 2 diabetes (T2D), one of the world’s leading health problems in terms of both increased all-cause mortality as well as health costs [5–9]. Although interest in BAT has exponentially increased, there are still many uncertainties. It is not known, for example, whether the relatively small amount of BAT in humans is enough to correct body mass index (BMI) scores or metabolic imbalances. Furthermore, the exact workings and control mechanisms of BAT are yet to be unravelled.

Obesity reflects an imbalance between energy consumption and energy expenditure. Strategies to combat obesity focus on correcting this imbalance by decreasing energy intakes with dietary strategies and bariatric surgery, and increasing energy expenditures through physical-exercise programmes. However, energy expenditure is the sum of physical activity, diet-induced thermogenesis and resting energy expenditure, and cold-stimulated heat production by BAT increases resting energy expenditure [10,11]. Thus, BAT may be an interesting option in the treatment of obesity and obesity-associated T2D.

BAT is able to convert excess calories into heat, whereas white adipose tissue (WAT) stores these excess calories. Brown

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adipocytes contain multiple lipid droplets in comparison to the large lipid droplets found in white adipocytes, and brown adipocytes also contain far more mitochondria, causing the typical brown color of BAT [12]. In addition, the mitochondria in brown adipocytes contain a unique mitochondrial inner membrane protein: uncoupling protein 1 (UCP1). UCP1 enables brown adipocytes to uncouple the respiratory chain, which means that BAT mitochondria are able to rapidly turn FFAs and glucose into heat instead of generating adenosine triphosphate (ATP; Fig. 1) [12,13]. In addition, BAT differs from WAT by having a greater degree of vascularization and a more pronounced sympathetic innervation [12,14,15]. The latter has raised the hypothesis that the sympathetic nervous system (SNS) plays a major role in the activation of BAT.

Indeed, the SNS appears to be involved in cold-activated BAT. Animal studies show that cold sensation in the skin, by cooling cutaneous thermal sensory receptors and lowering core body temperature, initiates peripheral vasoconstriction, resulting in the release of the sympathetic neurotransmitter norepinephrine in BAT to maintain normal body temperature [16,17]. However, data derived from rodent research on the stimulating factors of BAT are not easily translated to humans, and it remains to be determined whether the same pathways are involved in human adults [18–20].

So far, only a few studies have shown that recruitment of BAT in human adults is possible by either bariatric surgery in obese subjects or repetitive cold exposure in lean subjects [10,21–23]. However, most people will not tolerate cold exposure for the majority of the day. Therefore, alternative activators of BAT have to be investigated.

The present review discusses human BAT studies focused on factors that might influence the autonomic nervous system control of BAT in adult humans. A broader aim of this review is to identify gaps in our knowledge, thereby providing directions for future research.

Fig. 2. Flow chart of our literature search. Excluded were animal studies, studies not considering the role of the autonomic nervous system in human BAT and reviews.

2. Materials and methods

For our literature search on the autonomic nervous system and BAT in humans, MEDLINE was searched for studies on BAT published up to 16 March 2015, using the following text terms and medical subheadings: [(Brown Adipose Tissue [mesh] OR Brown Adipose Tissue [tiab] OR Brown Fat [tiab] OR Hibernating Gland [tiab]) NOT (animals [MeSH] NOT humans [MeSH]) OR (rat [ti] OR rats [ti] OR mouse [ti] OR mice [ti]).] A broad definition of entry terms was used to avoid missing potentially relevant articles. The papers thus obtained were scanned by two authors (L.B. and R.J.M.) for relevance, based on titles and abstracts, and all studies providing insight into the role of the nervous system in human BAT were included. Finally, the reference lists of the obtained papers were manually examined for relevant studies.

The MEDLINE search resulted in 2061 articles, and two further articles were found by reference screening; in total, 39 articles were suitable for the present review. Of these 39 publications, six were related to two different topics: Gelfand, 2004 [24]; Fukushima et al., 2004 [25]; Ochoa-Figueroa et al., 2012 [26]; Hadi et al., 2007 [27]; Cheng et al., 2012 [28]; and Søndergaard et al., 2015 [29] (Fig. 2). Eleven articles considered BAT visualization and the SNS, while eight articles described BAT inhibition, two described interruption of the sympathetic nerves leading to BAT activation and six interventional studies tried to decrease BAT activity. Also, 26 articles considered BAT activation: 20 described patients with high catecholamine levels causing BAT activity; and six were interventional studies aiming to activate BAT.

3. Imaging studies highlighting the importance of the SNS in BAT activation

Several imaging studies provided evidence of the importance of sympathetic stimulation in the activation process of BAT. Most prospective BAT studies were performed, using 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography–computed tomography (PET–CT), to show the
glucose metabolic activity of BAT. However, several tracers are now available with the ability to visualize sympathetic BAT activity.

The radiolabelled norepinephrine analogue $^{123}$I-meta-iodobenzylguanidine ($^{123}$I-mIBG) can be used to visualize and quantify sympathetic stimulation, using single-photon emission CT (SPECT). $^{123}$I-mIBG SPECT is often used in the diagnosis of children with neuroblastoma. Frequently, bilateral symmetrical uptake of $^{123}$I-mIBG in the upper thorax has been found and, by 1994, the uptake of $^{123}$I-mIBG at these specific sites was already being reported as physiological in these children. However, it took until 2002 for the origin of this physiological uptake to be identified as BAT [30–32].

Since then, several imaging studies using $^{123}$I-mIBG have suggested the importance of sympathetic innervation for BAT [24–26,31]. In a retrospective study of paediatric patients with neuroendocrine tumors, the accumulation of $^{123}$I-mIBG at BAT-specific sites was observed with $^{123}$I-mIBG SPECT [31]. This accumulation was observed more frequently in winter than in summer, leading to the hypothesis that BAT might be involved. In particular, the CT part of SPECT has allowed the colocalization of functional and anatomical images, thereby offering better differentiation of adipose tissue and tumor localization.

Two prospective studies compared $^{18}$F-FDG and $^{123}$I-mIBG uptakes in BAT in subjects under mild cold conditions [33,34]. In all subjects showing $^{123}$I-mIBG uptake in BAT, $^{18}$F-FDG uptake was also observed at the same anatomical locations, confirming the uptake of $^{123}$I-mIBG in BAT. Furthermore, a positive correlation was found between $^{18}$F-FDG uptakes and semi-quantitative uptakes of $^{123}$I-mIBG 24 h after administration ($r=0.64, P=0.04$) [33].

$^{18}$F-Fluorodopamine ($^{18}$F-FDA) is also used as a PET radiopharmaceutical to image sympathetic innervation [35]. In one retrospective study, $^{18}$F-FDA and $^{18}$F-FDG PET–CT scans of 96 patients with phaeochromocytoma were evaluated to determine the presence of BAT. If present, $^{123}$I-mIBG SPECT scans were also evaluated for the presence of BAT. BAT was found in 18% of the $^{18}$F-FDA PET scans, 19% of the $^{18}$F-FDG PET–CTs and 18% of the $^{123}$I-mIBG SPECT scans. Even though the uptake of $^{18}$F-FDA, $^{18}$F-FDG and $^{123}$I-mIBG in BAT was not always concordant, it was clear that $^{18}$F-FDA can localize BAT [27].

Pain is known to activate the SNS, and studies looking at analgesics (such as diazepam and opioids) suggest an inhibiting role in BAT, although the results have not always been consistent [36–39].

4. BAT inhibition

4.1. Interruption of sympathetic nerves

The actual causal relationship between sympathetic BAT innervation and BAT activity in humans has been nicely described in patients whose sympathetic nerves have been interrupted.

One case report describes a child with neuroblastoma in the right upper chest in the paraspinal region. Surgical removal of the neuroblastoma caused an interruption of the right upper thoracic and cervical sympathetic nerves, resulting in right-sided Horner’s syndrome. After the operation, $^{123}$I-mIBG uptakes in BAT were detected in the clinical findings of Horner’s, but only on the ipsilateral side, in the left upper thoracic region. This asymmetrical $^{123}$I-mIBG BAT uptake, with no uptake on the operated side, is most likely explained by surgical interruption of the sympathetic nerves [24].

 Destruction of the sympathetic nerves supplying BAT also interrupts the metabolic activity of BAT. This is clearly described in a small case series of two patients with Horner’s syndrome and one patient who had undergone surgical sympathectomy. All patients showed unilateral uptake of $^{18}$F-FDG in BAT on PET–CT on the unaffected side, but not on the side of interruption of the cervical/thoracic sympathetic chain [40].

This means that interruption of the sympathetic innervation of BAT results in diminished sympathetic stimulation of BAT and, thus, reduced metabolic BAT activity.

4.2. Interventional studies

While these observational studies provide some insight into the working mechanism(s) of BAT activation, such findings are not always easy to translate to interventional studies. Several interventional studies have aimed at inhibiting BAT activity, with the primary goal of reducing false-positive outcomes in patients undergoing $^{18}$F-FDG PET for clinical reasons, and most of these interventional studies in humans have been performed with the non-selective β-antagonist propranolol (primarily blocking β1- and β2-adrenoceptors). However, there is also evidence for the influence of α1 receptors in the activation of BAT [41].

In 2005, a case report described, for the first time, that 80 mg of propranolol successfully suppressed the uptake of $^{18}$F-FDG in BAT in a 51-year-old man diagnosed with renal carcinoma [42]. His diagnostic scan showed extensive $^{18}$F-FDG uptake in BAT, but BAT activity disappeared on a second scan taken 21 days later under the same circumstances, but following pretreatment with 80 mg of propranolol (single dose, orally) to examine whether this pretreatment could reduce BAT $^{18}$F-FDG uptake in patients with BAT activity under thermoneutral conditions [43]. In this case, all patients (two men, nine women) showed a clear reduction of BAT activity after the administration of propranolol.

Another study was performed in a larger sample (26 men, 14 women) of patients who had shown BAT activity on their scans, this time using a lower dose of propranolol (40 mg, single dose, orally) [44]. Of the 40 patients, 36 (90%) showed the complete disappearance of $^{18}$F-FDG uptake in BAT after propranolol administration. In addition, in a third study of 26 patients with BAT activity on scans, a clear reduction of $^{18}$F-FDG uptake was evident after an even lower dose of propranolol (20 mg, single dose, orally) [45]. Interestingly, β-adrenergic receptor blockade was even able to block $^{18}$F-FDG uptakes in BAT in a patient with phaeochromocytoma, known to be associated with massively increased metabolic BAT activity [28].

From these data, it is clear that β-adrenergic receptor blockade blocks $^{18}$F-FDG uptakes in BAT. However, the role of α-receptors and α-blockade is less clear. There is only one
case report which describes pretreatment with α-blockade in a patient with a catecholamine-secreting paraganglioma [29]. On 18F-FDG PET–CT at diagnosis, there was massively increased metabolic BAT activity. Treatment with α-blockade markedly suppressed 18F-FDG uptakes in BAT, and 18F-FDG uptakes were further normalized after surgical removal of the tumor.

The role of central sympatholytic drugs has never been investigated in humans; nonetheless, clonidine has been shown to inhibit catecholamine-mediated thermogenesis. Whether this effect is caused by inhibition of BAT activity is not yet known [46].

In summary, both α- and β-adrenergic receptors appear to be involved in the activation of BAT, whereas the role of central sympatholytic drugs has yet to be investigated.

5. BAT activation

5.1. BAT activation through high catecholamine levels

Both α- and β-adrenergic agents are of potential interest in the search for activators of BAT. Indeed, extremely high BAT activity is often seen in patients with phaeochromocytoma, who are known to have elevated levels of catecholamines. The cause of such high catecholamine levels and BAT activity has been demonstrated in several ways. One case series described the positive relationship between plasma catecholamine levels and BAT activity in 14 patients with phaeochromocytoma and 14 healthy subjects [47]. Plasma catecholamine levels were determined by plasma total metanephrines (TMNs). Phaeochromocytoma patients were divided into two groups according to TMN levels: eight had high TMN levels and six had normal TMN levels. All subjects underwent 18F-FDG PET–CT under thermoneutral conditions. Only patients with high TMN levels showed BAT activity on 18F-FDG PET–CT imaging, and this activity was positively correlated with TMN levels (r = 0.83, P < 0.0001). Both the phaeochromocytoma patients with normal TMN levels and the healthy controls showed no BAT activity.

The presence of BAT has also been confirmed in one case series and one case report, both of which took perinephric adipose tissue samples from patients with phaeochromocytoma and those with adrenocortical adenoma [48,49]. Also, causality has been even more strongly indicated by several case reports of patients with phaeochromocytoma before and after surgery. Before surgery, intense bilateral and symmetrical 18F-FDG uptakes in BAT regions were observed, whereas these uptakes disappeared after tumor excision [50–52].

Although increased BAT activity appears to result from increased catecholamine levels, the SNS is at least partly involved. The involvement of the SNS in BAT activation through excess levels of catecholamines is clearly seen in several studies describing increased uptakes of both 18F-FDA and 123I-mIBG in BAT in patients with phaeochromocytoma [25–27]. Strikingly, the presence of phaeochromocytoma appears to induce metabolic BAT activity at the usual sites (for example, the shoulder–neck region, along the greater vasculature), as well as at less typical places (such as perinephric adipose tissue) and even at atypical places (omentum fat) [28,29,53–61]. Thus, not only do excessive levels of catecholamines induce (excessive) BAT activity, but they may also induce recruitment of BAT even at atypical sites. Furthermore, the increased uptake of 6-18F-FDA, 18F-FDG and 123I-mIBG indicate that activation of BAT results, at least in part, through activation of the SNS.

5.2. Interventional studies using sympathomimetics

Given the promising effects of catecholamines on BAT recruitment described above, four prospective studies have been performed to study the effects of sympathomimetics on BAT activation in humans.

In the first study, the effect of the non-selective sympathomimetic ephedrine at 1 mg/kg (single dose, intramuscular) in 10 healthy volunteers was compared with a placebo (saline) injection and exposure to cold. At 2 h after the intervention, BAT activity was visualized with 18F-FDG PET–CT scans. The intramuscular injection of ephedrine resulted in marked adrenergic signs, including increases in blood pressure, heart rate, basic metabolic rate and metabolites in the blood, but no increase in BAT activity. In contrast, cold exposure caused a substantial increase in BAT activity in all volunteers, as well as increases in energy expenditure, blood pressure and higher plasma norepinephrine. However, the overall systemic activation of the SNS was less pronounced than with ephedrine, as nearly all other metabolites remained unchanged together with a decrease in heart rate [62].

In the second study, the effect of ephedrine (2.5 mg/kg, single dose, orally) or a placebo (lactose) on BAT activity was evaluated in nine lean and nine obese men [63]. In both lean and obese participants, oral administration of ephedrine caused an increase in systemic sympathetic activation (blood pressure, heart rate, energy expenditure, plasma glucose and plasma norepinephrine). However, while BAT activity was increased in seven of the nine lean subjects – observed as an increase in 18F-FDG maximum standardized uptake (SUVmax) by 145 ± 48% – it did not increase BAT activity in obese subjects.

In the third study, the effects of a systemic infusion of the non-selective β-adrenergic agonist isoprorenaline were investigated in 10 lean men [64]. The subjects were first exposed to cold to define BAT activity, using 18F-FDG PET–CT, after which isoprorenaline (at incremental doses of 6, 12 and 24 mg/kg fat-free mass−1·min−1) was intravenously administered under thermoneutrality. Cold exposure led to a substantial increase in BAT activity on 18F-FDG PET–CT in all subjects. Moreover, cold exposure increased energy expenditure, blood pressure, core body temperature and several metabolites in the blood (plasma norepinephrine, plasma FFAs, glycerol, triglycerides and glucose), while decreasing respiratory quotient, heart rate, and distal skin temperature and perfusion. In contrast, only one of the 10 subjects showed BAT activity after isoprorenaline infusion, despite increased sympathetic stimulation in all patients.

In the fourth study, the effects of ephedrine were again investigated in 12 subjects who received ephedrine (1.5 mg/kg) and 11 subjects who received a placebo for 28 days in a double-blind, randomized, placebo-controlled trial. BAT activity was
measured after 28 days following a single 2.5 mg/kg dose of ephedrine. Those in the ephedrine group lost significant amounts of total body fat and visceral fat compared with the placebo group. However, BAT activity was significantly reduced [65].

Thus, the promising effects of sympathomimetics suggested by observational studies were not readily reproduced in prospective interventional studies: only one of the four studies showed an increase in BAT activity. However, cut-off values for BAT activity differed across the studies, with values for active BAT ranging from an SUV ≥ 2.0 g/mL [62] to ≥ 1.0 g/mL [63], making comparisons of the studies difficult. The BAT activity found after ephedrine administration may have resulted from the use of either a higher ephedrine dose or a lower SUV cut-off value. In addition, all subjects experienced side-effects with ephedrine. In any case, the increase in BAT activity after ephedrine administration was much smaller than the increase observed after cold exposure [63] and, in the last study, ephedrine even appeared to reduce BAT activity [65].

Thus, neither ephedrine nor isoprenaline appear to be activators of first choice for the activation and recruitment of BAT in humans.

5.3. Interventional study using β3-adrenergic receptor agonists

Only one study has investigated the role of β3-adrenergic receptor agonists in humans. This study evaluated the effect of 200 mg of oral mirabegron, a β3-adrenergic receptor agonist approved for treatment of an overactive bladder, on BAT activity compared with a placebo. BAT activity was measured using 18F-FDG PET–CT at a room temperature of 23 °C (73 °F). All 12 study subjects showed significant increases in BAT activity [66].

5.4. Role of the parasympathetic nervous system

Not much is known of the role of the parasympathetic nervous system (PNS) in the activation process of BAT. However, the PNS appears to play an important role during hibernation [67,68]. Therefore, it seems likely that the PNS has at least some involvement in the activation of BAT. Indeed, one study has shown cholinergic nerves supplying mediastinal BAT in rodents [69].

Vagal nerve stimulation (VNS) is known to induce weight loss in humans. One study evaluating the effect of VNS on energy expenditure and BAT activity included 15 patients receiving stable VNS therapy for refractory epilepsy. In 10 of the patients, BAT activity and energy expenditure were investigated during active and inactive VNS; in the remaining five patients, these BAT expenditures were investigated during active VNS under conditions of cold exposure and at room temperature. Energy expenditure decreased significantly when VNS was inactivated.

While no significant difference in BAT activity was found between active and inactive VNS therapy, the change in energy expenditure after inactivation of VNS was significantly related to changes in BAT activity [70]. Nevertheless, it should be noted that the patients in this study were relatively old for the detection of active BAT, as BAT activity is known to diminish with increasing age [2]. Although this study seems to show no real role for the PNS in the activation of BAT, it would be premature to reject the idea completely.

6. Conclusion: clinical impact and future considerations

Our present review of the literature on human BAT activation clearly indicates the involvement of sympathetic stimuli through a number of findings (Tables 1 and 2). First, the uptake of the sympathetic tracers 123I-mIBG and 6-18F-FDA in BAT [27,31,33] and, second, interruption of the sympathetic nerves innervating BAT diminishes its metabolic activity [24,40]. Third, β- and α-adrenergic receptor blockade are highly successful pre-treatment strategies for reducing BAT activity [28,29,42–45]. In contrast, only one study aiming to activate BAT using sympathomimetics was successful, and used the β3-adrenergic receptor agonist mirabegron [62–66]. Surprisingly, while β3-adrenergic receptors are present on human BAT cells [3], and are considered to be responsible for thermogenesis in rodents, only high doses of propranolol inhibited the β3-adrenergic receptor [71].

This raises the question of whether the effect of propranolol in humans is caused by blocking β1- and β2-adrenergic receptors or by blocking β3-adrenergic receptors, too. Histological analysis of human BAT might help to determine the presence and importance of other β- (and α-) adrenergic receptor subtypes in BAT, but such analyses are difficult to perform due to the close proximity of the main arteries and central nervous system. Nevertheless, delineating the contributions of individual α and β receptors to human obesity and its treatment should be a focus of future research. Virtanen et al. [3] calculated that, on the basis of one subject who had 63 g of activated BAT, this could burn the caloric equivalent of approximately 4.1 kg of adipose tissue over the course of a year. Thus, successfully activated BAT could contribute substantially to weight-loss strategies.

During the past few years, considerable knowledge has been gained on the physiology of BAT, albeit mostly from animal research. Although rodent and human data are frequently used interchangeably, this has to be done with caution because of known differences in BAT between species [18–20]. First, the location and volume of BAT differs between rodents and humans [72]. Second, human BAT in adults may not consist of “true” brown adipocytes, but may rather result from the “browning” of BAT: the process by which white adipocytes increase their mitochonrdia, leading to increased expression of UCP1 (beige adipose tissue) [73,74]. There is also evidence that beige fat might originate from stem cells other than those of WAT [48]. If beige adipocytes originate from a cell lineage different from “true” brown adipocytes, they may also have different physiological properties and, therefore, the control of BAT in rodents and humans could differ substantially. In fact, ephedrine has been found to stimulate BAT in animals, whereas contrary effects have been found in human studies [62–64,75]. Thus, it is essential to extend BAT research in humans.

It is also important to note that the effects of drugs modulating autonomic nervous system activity may differ between individuals according to their basal sympathetic and parasympathetic
activity [76]. Also, basal sympathetic and parasympathetic activity changes with increasing BMI and age. For instance, vagal (cardiovascular) activity is depressed in a large proportion of non-diabetic obese people, while central sympathetic overactivity is present in the obese [77]. In addition, both older and obese subjects have diminished BAT activity [1,2,78,79]. What reconciles these data is some evidence suggesting a diminished sensitivity of BAT to SNS stimulation in older men, whereas there was no difference in BAT activity between obese and lean men [80].

As the SNS plays a pivotal role in the activation of human BAT, it is remarkable that 18F-FDG PET–CT has become the main method for visualizing active BAT, as 18F-FDG is just a reflection of glucose metabolism. Because BAT uses FFAs as its main substrate, the absence of BAT activity cannot be inferred from a lack of 18F-FDG uptake, thereby limiting the interpretation of negative 18F-FDG findings. As it is estimated that approximately 10% of the substrate used by BAT is glucose [81], the use of fatty-acid tracers would appear to be a more logical step; in fact, the fatty-acid tracer 18F-fluoro-6-thia-hexadecanoic acid was successful in identifying active BAT in humans [82]. However, internally stored fats cannot be measured, thereby causing a gap in the actual substrate consumption of BAT. Nevertheless, as the SNS is such an important factor in the activation of BAT, both 123I-mIBG SPECT and 6-18F-FDA PET could serve as alternative visualization techniques. While such techniques cannot evaluate metabolic BAT activity, they are still of value for identifying factors that might stimulate BAT via the SNS.

While the main focus has been on the SNS in the activation of human BAT, the role of the PNS has generally been overlooked in both rodent and human studies. Organs are generally innervated by both the SNS and PNS and yet, until now, the one available PNS study showed no activating effect of VNS stimulation on BAT. However, the subjects in this study were relatively old (45 years) for the detection of active BAT [70]. There is also considerable controversy over the question of whether BAT and WAT are innervated by the PNS, with various studies suggesting either null, regional or global PNS supplies to these tissues [69,83–85]. Clearly, the role of the PNS in BAT is still a matter of debate and should be investigated in future studies.

Such future studies could also use various tracers for imaging the PNS [86]. 11C-methyl-quinuclidinyl-benzylate is a metabolically stable muscarinic (M2) receptor antagonist, and studies in humans have shown its high affinity for cholinergic receptors, at least in the heart. Also, 2-deoxy-2-18F-fluoro-d-glucose-A85380 is an antagonistic nicotinic acetylcholine receptor that binds with high affinity to β2 nicotinic-receptor subunits.

<table>
<thead>
<tr>
<th>Method &amp; target</th>
<th>What is visualized</th>
</tr>
</thead>
<tbody>
<tr>
<td>18F-FDG PET–CT</td>
<td>Glucose analogue targets glucose transporters &amp; hexokinases; phosphorylation prevents tracer release from cells</td>
</tr>
<tr>
<td>6-18F-FDA PET–CT [27]</td>
<td>Sympathetic neuron transporters &amp; dopamine β-hydroxylase; 6-18F-FDA is converted to 18F-FNE &amp; stored in presynaptic vesicles in sympathetic nerve endings</td>
</tr>
<tr>
<td>123I-mIBG SPECT (CT) [24,26,27,30,31,33,34]</td>
<td>Noradrenaline analogue with presynaptic reuptake via noradrenaline transporters; 123I-mIBG is taken up by neuroendocrine cells &amp; stored in presynaptic neurosecretory granules</td>
</tr>
</tbody>
</table>

18F-FDG PET–CT: 18F-fluorodeoxyglucose positron emission tomography–computed tomography; 6-18F-FDA: 6-18F-fluorodopamine; 18F-FNE: 18F-fluoronorepinephrine; 123I-mIBG SPECT: 123I-meta-iodobenzylguanidine single-photon emission CT

Table 2
Pharmacological drugs used in human brown adipose tissue (BAT) studies [references].

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Affects α receptors</th>
<th>Affects β receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activating</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ephedrine [62,63]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Isoprenaline [64]</td>
<td>No</td>
<td>Yes (particularly β1 &amp; β2)</td>
</tr>
<tr>
<td>Mirabegron [66]</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Inhibiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propranolol [28,42–45]</td>
<td>Non-selective β-adrenergic antagonist</td>
<td>No</td>
</tr>
<tr>
<td>Alpha-blocker (type unknown) [29]</td>
<td>Non-selective α-adrenergic antagonist</td>
<td>Yes</td>
</tr>
</tbody>
</table>
However, the presence of BAT has not been described while using these imaging tracers. Thus, the SNS appears to play an important role in the activation of human BAT, while the role of the PNS remains to be elucidated. Future research using both histological analyses as well as imaging studies is now needed to establish which factors are essential to the activation process of human BAT.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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