Available online at
ScienceDirect
www.sciencedirect.com
Elsevier Masson France
EM|consulte
www.em-consulte.com/en
Diabetes & Metabolism 41 (2015) 437–445

Review

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

L. Bahler [a,*], R.J. Molenaars [a], H.J. Verberne [b], F. Holleman [a]

[a] *Academic Medical Center, Department of internal medicine, Amsterdam, The Netherlands*
[b] *Academic Medical Center, Department of nuclear medicine, Amsterdam, The Netherlands*

Received 10 June 2015; received in revised form 21 August 2015; accepted 28 August 2015
Available online 26 September 2015

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 ^{18}F-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.

Keywords: Adrenergic receptor; Brown adipose tissue; Human; Parasympathetic nervous system; Sympathetic nervous system

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

* Corresponding author. Meibergdreef 9, Room F4-257, PO Box 22660, 1100 DD, Amsterdam, The Netherlands. Tel.: +3120 56 65 981.
E-mail address: l.bahler@amc.uva.nl (L. Bahler).

http://dx.doi.org/10.1016/j.diabet.2015.08.005
1262-3636/

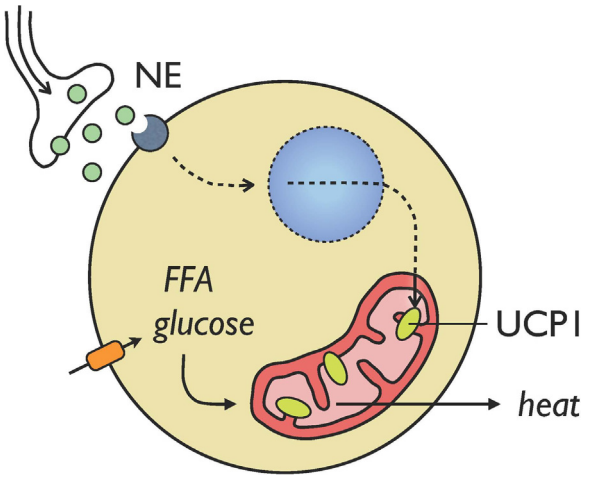

Fig. 1. The brown adipose tissue (BAT) cell. Stimulation of the adrenergic receptor by the neurotransmitter norepinephrine induces expression of UCP1 in BAT mitochondria. As a result, uncoupling of aerobic respiration of free fatty acids (FFAs) and glucose leads to the production of heat.

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 adenotriphosphate (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.

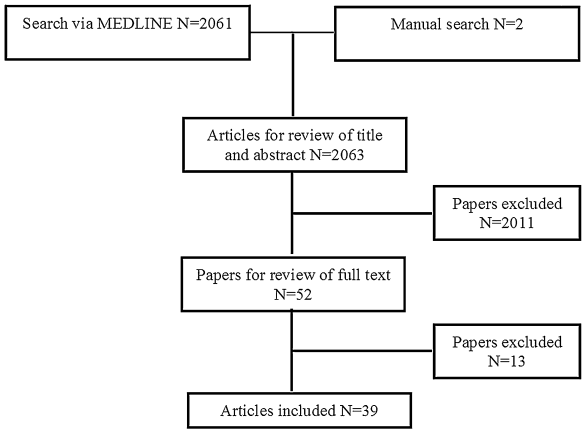

Fig. 2. Flow chart of our literature search. Excluded were animal studies, studies not considering the role of the autonomic nervous system in human BAT and reviews.

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]; Fukuchi 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 ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography–computed tomography (PET–CT), to show the