Biochimica et Biophysica Acta xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbalip

Brown adipose tissue functions in humans ☆

Kirsi A. Virtanen [a,*], Wouter D. van Marken Lichtenbelt [b], Pirjo Nuutila [a,c]

[a] Turku PET Centre, Turku University Hospital and University of Turku, Turku, Finland
[b] Department of Human Biology, Maastricht University Medical Centre + (MUMC +), Maastricht, Netherlands
[c] Department of Medicine, Turku University Hospital, Turku, Finland

ARTICLE INFO

Article history:
Received 27 September 2012
Received in revised form 17 December 2012
Accepted 18 December 2012
Available online xxxx

Keywords:
Brown adipose tissue
PET
Cold
Insulin
Human

ABSTRACT

Human adults have functionally active BAT. The metabolic function can be reliably measured in vivo using modern imaging modalities (namely PET/CT). Cold seems to be one of the most potent stimulators of BAT metabolic activity but other stimulators (for example insulin) are actively studied. Obesity is related to lower metabolic activity of BAT but it may be reversed after successful weight reduction such as after bariatric surgery. This article is part of a Special Issue entitled Brown and White Fat: From Signaling to Disease.

1. Introduction

Humans, including adults have functional brown adipose tissue (BAT) [1–4]. Its importance for heat production is regarded as more important in newborns with minimal or uncontrolled muscle work and in early childhood than in adulthood. However, heat production may also be essential in adults, and other functions such as lipid clearance from blood stream as indicated by animal studies [5,6] may be relevant for humans as well.

Classical brown adipocytes arise from the myoblastic Myf-5 cellular lineage, not from preadipocytes as was previously thought [7]. Just recently it was shown that in addition to classical brown adipocytes, typical BAT sites – such as supraclavicular fat depot – also include beige/brite adipocytes which are recruitable for thermogenesis from white adipocytes [8]. This recruitment may also be stimulated by exercise and consequently skeletal muscle is secreting a hormone named irisin which promotes UCP1 expression in white adipocytes [9]. Thus BAT compartments arise partly from the same stem cell origin but may also be functional in close collaboration with skeletal muscle.

Different cell types partly explain that the amount of BAT in humans may be flexible — newborns may have 40–200 g of BAT in their body, and the mass measured from the recent human studies [10–13] suggests up to 100–200 g of BAT in adults. The anatomical sites of classical BAT from childhood to adulthood seem to remain quite similar. However, BAT is very dynamic adipose tissue type: 1) it includes several types of adipocytes: at least classical brown cells, brite/beige cells and white adipocytes [14], and 2) the amount of BAT may first decrease during childhood and then again increase during puberty [15].

From the functional point of view BAT is potentially important for thermogenesis. The importance of BAT function for glucose and lipid metabolism at tissue and whole body level is under intense investigation. Here we will present the latest studies on these topics and the techniques involved. The focus will be on studies in humans.

2. Discovery of BAT in adult humans using molecular imaging, PET — the technique for metabolic studies of BAT

Molecular imaging using ^{18}FDG-PET has been widely used for clinical diagnostics during the last decades. Positron emission tomography (PET) is a quantitative in vivo functional imaging method that can generate information on human physiology and pathophysiology at a molecular level currently unobtainable with other methods. PET is based on the use of short-lived positron emitting radioisotopes. PET imaging is based on the detection of paired photons created after an annihilation reaction of the tracer. Physiological and pharmacological phenomena and biological parameters can be estimated in vivo by mathematical modeling of the tissue and blood time-activity curves obtained.

Hybrid PET/computed tomography (CT) scanners became available in the beginning of this century. These devices were the first reliable means to show precisely both the localization and function at the same time and boded the existence of BAT in adult humans [1].

Anatomic information from computerized tomography (CT) and magnetic resonance imaging (MRI) add to the functional information obtained with PET and the three 3-D imaging modalities can be seen

☆ This article is part of a Special Issue entitled Brown and White Fat: From Signaling to Disease.

* Corresponding author.
E-mail address: kirsi.virtanen@utu.fi (K.A. Virtanen).

1388-1981/$ – see front matter © 2012 Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.bbalip.2012.12.011

as complementary to each other. The image correlation can be facilitated by sophisticated software allowing co-registration of CT or MRI images with PET. Currently, PET scanners combined with CT have shown to be superior in diagnostics and within short time become widely available.

Before the strong and definitive evidence of the existence of BAT in adult humans [2–4], tracer accumulation in supraclavicular region during diagnostic clinical ^{18}FDG-PET studies was problematic for clinicians. The association between the prevalence of supraclavicular ^{18}FDG accumulation and the cold outdoor temperature were reported [4,16]. Since 2009, numerous laboratories and diagnostic units have eagerly studied BAT using ^{18}FDG-PET. Unfortunately, the results have not always been conclusive and the analyzing methods have varied remarkably. The main reason for this is that imaging studies have often been conducted with protocols which are valid for diagnostics giving semiquantitative information on glucose metabolic rate (e.g. standard uptake value, SUV) in tumors and metastasis. Although the graphical method has been validly used for the assessment of ^{18}FDG-PET data, many groups have estimated BAT activities using SUVs and static late scanning. Dynamic data acquisition enables lower radiation dose and better accuracy. Mathematical modeling becomes even more important when the effects of hormones and nutrients on brown fat activity are studied. In these situations muscle glucose uptake is stimulated up to six-fold and covers more than half of the whole body glucose utilization. In line with this, ^{18}FDG biodistribution is changed and availability from the plasma decreased resulting in lower accumulation of radioactivity in BAT without indicating that BAT metabolic activity as such is changed. In fact, only dynamic data analysis with input information gives reliable values of BAT activity for comparisons between groups or subjects in interventions.

The acquisition of data using dynamic imaging and the application of quantitative graphical analysis become even more important when tracers other than ^{18}FDG are used for the study of BAT metabolism. In humans fatty acid uptake has been measured with synthetic long chain fatty acid PET tracer 18-fluoro-thia-heptadecanoid-acid, ^{18}FTHA in the heart and muscle [17,18] and adipose tissue [19]. Recently the use of ^{18}FTHA in humans was also introduced for BAT [12]. Tracer metabolites appear in blood approximately 20 min after injection which need to be measured in order to quantitate proper input function and fatty acid uptake in the tissue.

Oxygen consumption may be determined directly in BAT using $^{15}O_2$-PET [20]. This tracer is given by inhalation and due to very short half-life (2 min) requires on-site blood radioactivity measurement or the use of image derived input function for the modeling. Measurement of perfusion with ^{15}O–H_2O-PET in BAT was recently introduced [10] and has now been used also by another study group [20]. ^{15}O–H_2O is given intravenously and similar to $^{15}O_2$ requires on-site detection of radioactivity in blood. In addition to a measure of perfusion or blood flow of the tissue, ^{15}O–H_2O-PET may be used as an indirect measure of oxygen consumption of the tissue [20] — as may be done also with ^{11}C-acetate-PET [12].

3. Cold-induced metabolic activity in brown fat and its contribution to thermogenesis

The thermogenic capacity of brown fat is associated with uncoupling. Uncoupling protein-1 (UCP1) is responsible for heat production by promoting proton leak in the inner membrane of mitochondria and thus uncoupling the ATP production. As for UCP1 expression is triggered by the intracellular signal cascade which is activated by binding of noradrenaline or other adrenergic mimetics to cell membranous adrenergic receptors, mainly β_3-receptors (Fig. 2). Relative UCP1 expression level is several 100- or 1000-fold in human brown fat samples to white fat samples [3]. Thus, thermogenic capacity exists in human adults' brown fat, but is not functional in all of us such as in morbid obesity [21]. Whether this is a result of expansion of intracellular triglyceride stores and/or non-functional UCP1 or other factors such as PCG1α in the signal cascade in brown fat is not yet known.

At fasting and in normal room temperature brown fat metabolism is silent and comparable to white adipose tissue metabolic activity [3,10,22]. Cold seems to be the most potent and natural, and also most used inducer of brown fat metabolic activity and thermogenesis in human studies to date [2,4,10,11]. However, the contribution of brown fat to whole body thermogenesis is still somewhat obscure.

Mild acute cold exposure decreases skin temperature [2,23]. However, the temperature of supraclavicular skin area in subjects with functionally active BAT did not decrease significantly indicating heat production [23]. A study by Lee et al. [24] using infrared thermograph also showed that the temperature of supraclavicular fossa is not decreased. These findings and peripheral vasoconstriction in relation to slight increase in core temperature suggest a possible role of BAT activation for heat transport to the body core [2,21].

Resting energy expenditure (REE) has shown to increase in several cold exposure studies [2,4,10,12,20,21]. REE is measured by indirect calorimetry [25] using either chamber [2,26] or canopy hood (e.g. [10,20]) at whole body level. Resting metabolic rate is increased especially in those subjects with increased metabolic activity, i.e. increased glucose uptake or perfusion in BAT in cold [20,21].

At least 10-fold increase in BAT metabolic activity as measured with ^{18}FDG-PET is found during cold exposure [3,10] which in perfusion dependent manner is also thought to reflect the increase in thermogenesis. Glucose uptake by the cold-activated BAT may be increased as a result of a rapid need of fuel for mitochondrial heat production, and for glucose oxidation and lactate production but probably also for simultaneous storage of glucose in the form of triglycerides in small lipid droplets inside the cell in close vicinity with mitochondria. Glucose uptake by BAT is, however, estimated to be only approximately 10% of the total energy need of the tissue during cold exposure based on animal studies [27]. In animals this contribution is suggested to be significant but also in humans the contribution of glucose uptake as a part of thermogenesis is considered remarkable — only a few tissues are able to increase their metabolic rate at least 10-fold during short stimulation. Glucose uptake in BAT is almost as high as cerebral glucose uptake [28]. In addition to brown adipocytes skeletal muscle cells are able to increase their metabolism, especially glucose uptake, several 10-folds during acute exercise.

BAT oxidative metabolism, as measured with ^{11}C-acetate-PET is clearly activated by acute cold exposure suggesting a role of BAT in non-shivering thermogenesis without relying in much more energy consuming muscle shivering [12,20]. Perfusion of BAT is also elevated significantly; approximately two-fold during acute cold exposure [10] further supporting the increased oxidative role of BAT in cold. Oxygen consumption itself is 50% higher in the subjects with active BAT — their BAT oxygen consumption is also higher in resting state when compared to controls with nonfunctional BAT [20]. In addition, perfusion is closely related with BAT glucose uptake and whole body energy expenditure suggesting a perfusion dependent manner of energy expenditure in cold [10].

4. Brown fat is an insulin sensitive tissue

Insulin activates the sympathetic nervous system (SNS) which subsequently activates BAT thermogenesis. In addition to well-known insulin effects on skeletal muscle insulin may also be involved in meal-associated thermogenesis mainly indirectly via central nervous system, CNS [29].

Insulin stimulation – produced by euglycemic hyperinsulinemic clamp technique – increases BAT glucose uptake as well, in average 5-fold to fasting condition [10]. Insulin-stimulated glucose uptake in

Please cite this article as: K.A. Virtanen, et al., Brown adipose tissue functions in humans, Biochim. Biophys. Acta (2013), http://dx.doi.org/10.1016/j.bbalip.2012.12.011