Methods xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Methods

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

Brown adipose tissue and lipid metabolism imaging ☆

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ARTICLE INFO

Article history:
Received 30 November 2016
Received in revised form 28 April 2017
Accepted 5 May 2017
Available online xxxx

Keywords:
Adipose tissue imaging
Lipid metabolism
Nuclear imaging
Optical imaging
MRI

ABSTRACT

Purpose: Brown adipose tissue (BAT) research has evolved from an underestimated to a fast developing field. Its assumed curing properties for the world wide epidemic obesity, and its related diseases, makes this tissue an interesting target for a broad amount of non-invasive molecular BAT tracers. Apart from ^{18}F-FDG PET/CT there are several methods to detect BAT and measure its metabolism in a more appropriate way. Especially interesting is the measure of lipid turnover, because fatty acids comprise the main fuel for active BAT. This review outlines different imaging modalities suitable for BAT imaging with the overall goal to explain the yet not completely understood mechanism in BAT and its quantitative contribution to whole body lipid and energy metabolism.
Methods: Publications with focus on brown adipose tissue and lipid metabolism imaging are analyzed, different imaging approaches are introduced and promising BAT tracers are presented.
Results: Radiolabelled and fluorescent fatty acids, labelled particles, ^{3}H-Triolein and ADIFAB staining can give information about the inflow and therefore about the utilization of fatty acids which represents the activation state *in vivo*/*in vitro*. Non-invasive scanning with CT or MRI is a useful addition to those techniques.
Conclusion: Lipid metabolism imaging offers the opportunity to visualize and quantify yet undiscovered aspects of BAT metabolic activities and is key to completely clarify its role in whole body lipid and energy metabolism.

Contents

Abbreviations: BAT, brown adipose tissue; WAT, white adipose tissue; PET, positron emission tomography; FDG, 2-fluor-2-desoxy-D-glucose; LCFA, long chain fatty acids; FA, fatty acids; TG, triglycerides; UCP1, uncoupling protein 1; TRLs, triglyceride-rich lipoproteins; LPL, lipoprotein lipase; FTHA, 14(*R*,*S*)-fluoro-6-thia-heptadecanoic acid; C-palmitate, C-hexadecanoic acid; BMIPP, 15-(4-iodophenyl)-3-methyl-pentadecanoic acid.

☆ This work was supported by the Weijerhorst Foundation.

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http://dx.doi.org/10.1016/j.ymeth.2017.05.001
1046-2023/

1. Introduction

1.1. Background

The function and presence of BAT in adults was neglected until two decades ago. Now the investigation of BAT using molecular imaging has matured to one of the most interesting and fast developing research topics in endocrine research. Because obesity – and its related metabolic syndrome – is reaching epidemic proportions in the western world [1] and may even become a more severe problem in the near future for the worldwide population, more attention is drawn to adipose tissue metabolism. A turning point was the discovery that WAT, apart from storing energy (fat), is able to secret leptin, an important hormone controlling the energy balance [2]. Other substances [3] (autocrine and endocrine) released by WAT have been found and by that the consideration of the impact of adipose tissue on whole body metabolism rose continuously. In retrospective PET studies with FDG, it could be shown that besides WAT, another form of adipose tissue exists in adult humans [4–6]. In these studies, symmetrical accumulations of FDG appeared in the supraclavicular region, which were originally thought to be attributed to uptake in cervical muscles. Later, scans with PET/CT indicated that these "artifacts" correlate with Hounsfield units of fat [6]. By these FDG studies it could be proven that BAT is functionally present in adults and is metabolically active. BAT, named after its darker color resulting from higher mitochondria expression within the cell and increased blood circulation [7], was previously thought to be absent in adult humans and only be present in newborns to maintain their body temperature [8]. The results of the PET scans indicate a chance of observing BAT in 5–8% of standard clinical routine PET scans [4,9] and a total contribution to body mass of 0,05–0,01% [10]. These findings could be confirmed later by dedicated cold exposure studies where a direct correlation between cold exposure and BAT metabolic activity, measured through FDG uptake, was reported [11–13]. Assuming a fixed relative contribution of glucose and fatty acids and that mainly fatty acids and glucose contribute to energy expenditure [12,14], an increase in metabolic activity of BAT would result in an increase of total body energy expenditure of 2–28% [15]. Therefore activation of BAT with unchanged food uptake, may lead to significant weight loss, offering an additional treatment option to obese patients. Another field of application would be in patients with pheochromocytoma. It was found that catecholamine secreting tumors activate BAT and lead to an increase in metabolic activity characterized by FA and glucose uptake [16–18]. In these studies BAT activity was inversely correlated to body mass index and in general patients with cancer cachexia are often suffering from body weight loss and depletion of muscular and adipose tissue [19].

However, in order to actually calculate the metabolic activity of BAT in humans, in addition to FDG PET/CT, other tracers and techniques are needed. Through the upcoming interest in this tissue, several new activation, targeting and imaging strategies have been developed to visualize BAT's functions. FDG has set the stage; several attributions of BAT have been defined. Non-invasive visualization of lipid metabolism could give more insight since lipid turnover is one of the major features of BAT. This review summarizes early as well as the newest inventions of lipid metabolism imaging linked to BAT and describes how visualization of lipid fate and adipose tissue activity has evolved.

1.2. Activation of brown adipose tissue and fatty acid metabolism

First observations of BAT in humans were performed with FDG [4–6] which visualizes metabolic active tissue in terms of glucose uptake. It was observed that through cold exposure the chance of visualizing BAT increased in animals and lean subjects [11–13]. Besides, it was shown that BAT is activated through norepinephrine binding to β3-adrenoeceptor [20,21]. Recently it was observed for the first time that BAT takes up an increased amount of glucose in obese humans after cold acclimation. This led to the conclusion that significant amounts of BAT can be recruited during repeated cold exposure [22]. Glucose is mainly taken up by protein transporters of the GLUT family, mainly the fat muscle specific isoform GLUT4 [23,24]. Glucose is processed in different pathways e.g. in citric acid cycle [25] or it is conversed to FA [26,27]. Nevertheless LCFA are the main "fuel" for BAT. Tracers based on fatty acids, quantify the metabolic activity of BAT in a better way than glucose does.

Through the norepinephrine activation process FA stored as TG in lipid droplets are consumed in the mitochondria to produce heat and new FA are taken up [28,29]. This identifies FA as the main metabolized substance in BAT and makes them and other compounds targeting lipid metabolism a powerful tool to visualize BAT and its functions within the body.

Usually mitochondria oxidize fatty acids and ATP is produced to store the nascent energy but BAT mitochondria contain the BAT specific UCP1 which gives them the ability to uncouple the oxidation process and to produce heat instead of ATP [30–33]. This process is responsible for nonshivering thermogenesis [15,34]. Fedorenko et al. showed that LCFA (>12 carbon atoms [35]) are essential for the uncoupling process as they work as a carrier for H^+ through the UCP1 and that LCFA are also produced within the inner mitochondria membrane by PLA2 [36]. In BAT cells UCP1 is inhibited by purine nucleotides, mainly ATP. The UCP1 channel is blocked by the nucleotides from the cytosolic side [37–40]. It was shown that LCFA can overcome the blocking of UCP1 and