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PET Imaging of Human Brown Adipose Tissue with the TSPO Tracer [¹¹C]PBR28

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Abstract

Purpose: Brown adipose tissue (BAT) in adult humans has been recently rediscovered and intensively investigated as a new potential therapeutic target for obesity and type 2 diabetes (T2D). However, reliable assessment of BAT mass *in vivo* represents a considerable challenge. The purpose of this investigation is to demonstrate for the first time that human BAT depots can be imaged with a translocator protein (TSPO)-specific positron emission tomography (PET) tracer [¹¹C]PBR28 under thermoneutral conditions.

Procedures: In this retrospective analysis, we analyzed the images of three healthy volunteers who underwent PET/magnetic resonance (MR) imaging after injection of 14 m Ci of [¹¹C]PBR28 at room temperature. Thirty-minute static PET images were reconstructed from the data obtained 60–90 min after the injection of the tracer.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Results: [^{11}C]PBR28 uptake in the neck/supraclavicular regions was identified, which was parallel to the known distribution pattern of human BAT depots. These areas co-localized with the areas of hyperintensity and corresponded to fat on T1-weighted MR images. Standardized uptake value (SUV) was used to quantify [^{11}C]PBR28 signal in BAT depots. The average ($\pm$ SD) SUV_(mean) and SUV_{max} for BAT depots was 2.13 ($\pm$ 0.33) and 3.19 ($\pm$ 0.34), respectively, while the average SUV_(mean) for muscle and subcutaneous adipose tissue was 0.79 ($\pm$ 0.1) and 0.18 ($\pm$ 0.04), respectively.

Conclusions: In this brief article, we provide the first evidence suggesting that [^{11}C]PBR28, a widely available TSPO-specific PET tracer, can be used for imaging human BAT mass under thermoneutral conditions.

Keywords

Brown adipose tissue; TSPO; C-11 PBR28; Metabolic disease; Thermoneutral conditions

Introduction

Brown adipose tissue (BAT) plays an important role in metabolism and energy expenditure [1], and its most distinct features include a large number of mitochondria, abundant expression of uncoupling protein-1 (UCP-1), and numerous small oil droplets in a single cell [1, 2]. BAT was previously considered to have no physiologic relevance in adult humans, even though it is highly abundant at embryonic and early postnatal stages. However, since 2009, this dogmatic view has been overturned by several large clinical studies [3–8]. Cypess et al. analyzed 3640 2-deoxy-2- ^{18}F fluoro-D-glucose (^{18}F FDG) positron emission tomography (PET)/X-ray computed tomography (CT) scans of 1972 patients, and found that the body mass index (BMI) was inversely correlated with the presence of BAT on PET/CT images [3], suggesting that BAT could represent a target for novel therapies for the treatment of obesity and associated metabolic disorders such as type 2 diabetes (T2D) [9, 10]. Other studies have also confirmed the clinical significance of BAT [4–8]. Potential benefits of BAT have been strengthened by the observation that white adipose tissue (WAT) could undergo browning under various stimuli [10–20]. Manipulating BAT *via* browning has sparked renewed interest in BAT as a therapeutic target to treat obesity and associated metabolic disorders [10–20].

PET/CT with ^{18}F FDG is currently the gold standard technique for imaging BAT [21–23]. However, the BAT depots of only a small number of adults can be visualized with ^{18}F FDG if no cold or drug stimulation is applied. Conversely, ^{18}F FDG PET/CT studies performed under stimulation suggest that BAT is present in the majority of adults [4, 15, 24]. This remarkable difference suggests that ^{18}F FDG can only identify activated BAT but not BAT mass. Because no specific imaging biomarker for BAT has been reported, accurately quantifying BAT mass is a challenge for imaging scientists, as most of the current imaging methods are BAT-activation dependent [21, 25–28]. MRI has been used for imaging BAT; however, MRI lacks specificity, and multiple MRI protocols and techniques exist which have not been adequately validated in human cohorts [16, 29–33]. Other PET probes for BAT thermogenesis have been reported; however, the reported PET signal of ^{18}F FBnTP was inversely correlated with BAT activation [34]. Eriksson, et al. reported that cannabinoid

receptor-1 PET tracer [^{18}F]FMPEP-d2 could be used to image BAT in rats under thermoneutral conditions; but no human BAT imaging results have been reported [35]. Ding, et al. demonstrated that [^{11}C]MRB could be used to assess BAT in its basal state [36, 37]; however, [^{11}C]MRB reflects only sympathetic innervation of BAT due to its binding to the norepinephrine transporter. Our group has recently reported that near infrared fluorescence (NIRF) probe CRANAD-X ($X = -2, -3$, and -29) could be used for BAT mass imaging [38], and Cerenkov luminescence imaging with [^{18}F]FDG could be applied to image BAT in mice [39]. However, NIRF imaging and Cerenkov imaging are currently not widely used clinical modalities. Clearly, imaging probes that can consistently detect BAT mass for preclinical and clinical applications are highly desirable.

Our recent study suggests that BAT can be visualized *via* synthesis-free PET imaging with a combination of disulfiram, a FDA-approved drug for alcoholism, and $^{64}\text{CuCl}_2$ (termed [^{64}Cu]-Dis) [40]. In this study, we identified an 18 kDa translocator protein (TSPO) as a potential imaging biomarker for BAT. TSPO, previously known as the peripheral benzodiazepine receptor (PBR), is a five transmembrane domain protein situated mainly on the outer membrane of mitochondria [41, 42]. TSPO has been an important imaging target for central nervous system (CNS) indications such as glial activation in the brain [43–46]. In the healthy brain, TSPO is constitutively expressed by glial cells, as well as by some neurons, but only at low levels. During neuroinflammatory responses, however, TSPO is substantially upregulated, predominantly in glial cells [43–47]. For that reason, TSPO has been extensively used for the imaging of glial activation in the brains of patients with various conditions, spanning from neurodegenerative disorders to chronic pain [48–51]. Currently, several TSPO radio-ligands have been developed for animal and/or human use, including [^{11}C]PK11195, [^{11}C]PBR28, [^{11}C]vinpocetine, [^{11}C]DAC, [^{18}F]PBR06 and [^{18}F]DPA714 [43–46].

While TSPO has been extensively investigated as a target in the CNS, only a few reports have explored its implications in the periphery [52, 53]. We hypothesized that TSPO might serve as a potential imaging marker for BAT mass, because one of the distinct features of BAT is the high abundance of mitochondria, where TSPO is located on the outer membrane. Indeed, our data from previous animal studies support this hypothesis [40]. Western blot and immunohistological data indicated that the protein expression level of TSPO in BAT was considerably higher than that found in WAT. *In vivo* PET imaging with [^{18}F]DPA [54], a newly developed TSPO tracer, showed remarkably high uptake in BAT depots ($\sim 15\%$ ID/g), which was consistent with *ex vivo* bio-distribution data [40]. Based on the evidence described above, we conducted a retrospective imaging analysis of PET images obtained after injection of [^{11}C]PBR28 (a widely used TSPO tracer) in healthy volunteers.

Methods

Simultaneous PET/MR imaging was performed using a 3T Siemens Biograph mMR system (Siemens Medical Solutions USA, Inc., Malvern, PA, USA). Integrated PET/MRI is capable of collecting structural MR images simultaneously with PET data. [^{11}C]PBR28 was produced in-house using a procedure modified in [55]. A T1-weighted (T1W) two-point Dixon 3D volumetric interpolated breath-hold examination (VIBE) sequence was acquired

with the following parameters: parallel acquisition technique (PAT) GRAPPA factor 2, repetition time (TR) = 3.60s, echo time 1 (TE1) = 1.23 ms, TE2 = 2.46 ms, flip angle (FA) = 10°, slice thickness = 3.12 mm, and in-plane resolution = 4.1 × 2.6 mm. The resulting images were segmented in-line to create a mumap for MR-based attenuation correction (MRAC) of the PET data. MRAC scans were acquired immediately prior to the initiation of PET scans. PET images were used for the placement of volume-of-interest (VOIs). [¹¹C]PBR28 was then injected as an intravenous bolus of 14.4 (± 0.3) m Ci in healthy volunteers, *n* = 3 (see description in Table 1). Image acquisition (30-min static scan) was conducted 60–90 min after [¹¹C]PBR28 injection in a single bed position with the field of view (FOV) centered on the C5 vertebra. PET data were stored in a list-mode format.

Results

In this retrospective analysis, we present imaging data from three healthy volunteers, who were imaged under thermoneutral conditions with [¹¹C]PBR28, a TSPO PET tracer that has been widely used for both preclinical and clinical investigations [44, 50]. The mean age was 39.7 (± 5.1) years, and the mean weight of the subjects was 72.3 (± 13) kg. PET images were obtained using 30-min static scans at 60–90 min after [¹¹C]PBR28 injection. We identified [¹¹C]PBR28 uptake in the neck (supraclavicular (Fig. 1)), paralleling the known distribution pattern of human BAT depots [4]. These areas co-localized with the areas of hyperintensity corresponded to fat on T1-weighted MR images. To quantify the uptake of [¹¹C]PBR28 in BAT depots, SUV from 60 to 90 min summed images was used. The average (± SD) SUV_(mean) and SUV_{max} was 2.13 (± 0.33) and 3.19 (± 0.34), respectively, and the average VOI was 5.93 (± 0.53) ml (Table 1). The value of standard uptake value ratio (SUV_R) that used the cerebellum as the reference area [23] was 2.87 (± 0.71) (Table 1). Moreover, clear PET signal could be easily identified in the paravertebral regions around the neck (Fig. 2a, b), with the accumulation pattern similar to that from [¹⁸F]FDG imaging performed under cold exposure [4]. As expected, we found that the uptake of [¹¹C]PBR28 in other adipose tissues was considerably lower (SUV_(mean) = 0.18 (± 0.04) and 0.54 (± 0.07) for subcutaneous fat and peri-adrenal fat, respectively (Table 1, Fig. 2c, d), indicating that [¹¹C]PBR28 has excellent selectivity for BAT over WAT. Additionally, we analyzed the tracer uptake in muscle tissues and found that average SUV_(mean) of deltoid muscle was 0.79 (± 0.1) (Table 1), suggesting that the tracer uptake in muscle was low. Taken together, these findings suggest that BAT mass can be imaged with the TSPO PET tracer [¹¹C]PBR28 under thermoneutral conditions in humans.

Discussion

In this brief report, we presented preliminary human BAT imaging data from a retrospective analysis, suggesting that TSPO might serve as an imaging biomarker for BAT mass. However, additional work is needed to confirm that [¹¹C]PBR28 can reliably assess BAT mass.

Promoting BAT mass, *via* browning, has been considered one of the potential approaches to fight the escalating obesity epidemic [2, 10, 56, 57]. Identifying a PET tracer that can reliably monitor browning and changes in BAT mass in both clinical and basic research

settings would be of high significance. Therefore, future studies are warranted to investigate the advantages and disadvantages of TSPO PET tracers for preclinical and clinical BAT imaging.

This retrospective analysis has several limitations. Primarily, this investigation could not provide BAT imaging data under cold exposure, which is essential to assess whether the uptake of [^{11}C]PBR28 was not activation-dependent. Second, though BAT is highly vascularized and [^{11}C]PBR28 retention in endothelial vessels has been reported [58], this analysis could not provide information regarding signal contribution from the vessels in BAT. Future research is needed to determine the sources contributing to TSPO signal in BAT. In addition, the short half-life of [^{11}C]PBR28 (~ 20 min) is a potential disadvantage. However, the fact that we observed [^{11}C]PBR28 signal in the regions previously thought to possess large BAT content suggests that, even with a relatively short half-life, we could detect a physiologically meaningful signal. In future studies, these limitations could be easily overcome with the optimized imaging condition of [^{11}C]PBR28 or alternative F-18 labeled TSPO PET tracers, which may provide similar imaging results or even better BAT contrast and selectivity.

Conclusion

In this brief article, we provide the first evidence suggesting that [^{11}C]PBR28, a widely available TSPO-specific PET tracer, can be used for imaging human BAT mass under thermoneutral conditions.

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Fig. 1. Representative images of a healthy volunteer who underwent PET/MRI using [^{11}C]PBR28. The images were obtained 60–90 min after 14 m Ci of [^{11}C]PBR28 injection. The supraclavicular BAT depots are indicated with arrows.

Fig. 2.
a–b PET/MRI images of paravertebral regions of a healthy volunteer after $[^{11}\text{C}]\text{PBR28}$ injection. Representative paravertebral BAT depots are indicated with white arrows. **c–d** PET/MRI images of periadrenal regions of a healthy volunteer after $[^{11}\text{C}]\text{PBR28}$ injection.

Table 1. Demographical and image analysis data from healthy volunteers. Cerebellum was used as a reference for SUVR calculation

Subject	Age	Gender	Height (cm)	Body weight (Kg)	BMI	Injection dose (m Ci)	BAT SUV _(mean)	BAT SUV _{max}	BAT SUVR _(mean)	BAT SUVR _{max}	Subcutaneous fat SUV _(mean)	Periadrenal fat SUV _(mean)	Neck muscle SUV _(mean)	Deltoid muscle SUV _(mean)
No. 1	34	F	155	63.5	26.4	14.65	2.47	3.56	3.60	2.93	0.15	0.51	0.77	0.76
No. 2	44	M	173	87.5	29.2	14.12	1.81	2.86	2.20	1.44	0.16	0.50	0.59	0.72
No. 3	41	M	174	65.7	21.7	14.46	2.04	3.04	2.62	1.84	0.22	0.63	0.58	0.88