Functional imaging of brown adipose tissue

Kirsi A. Virtanen[a] and Pirjo Nuutila[a,b]
[a]Turku PET Centre, University of Turku, and [b]Department of Medicine, Turku University Hospital, Turku, Finland

Correspondence: Dr Kirsi A. Virtanen, Turku PET Centre, Kiinamyllynkatu 4–8, 20520 Turku, Finland. Tel: +358 2 3131878; fax: +358 2 2318191; e-mail: kirsi.virtanen@utu.fi

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Abstract

Human brown adipose tissue (BAT) has been found to be functionally highly active, especially when exposed to cold. Although combined positron emission tomography (PET) and computed tomography (CT) is an expensive method, it has provided new and important data on the role of BAT in human physiology and metabolism. Currently, PET seems to be the only option for the study of BAT function and its interaction with other tissues at the whole-body level. Further studies are needed to evaluate the importance of BAT in human physiology, and to evaluate the possible manipulation of BAT activation. ■ *Heart Metab.* 2010;48:15–17.

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Human brown adipose tissue (BAT) has recently been re-discovered as a tissue of interest, and it has been found to be functionally and metabolically highly active when exposed to cold [1,2]. Advanced imaging technology – namely the development of hybrid positron emission tomography (PET)/computed tomography (CT) scanners – has been the key to the progress that has been made.

Metabolic activity during oncological diagnostic [^{18}F]2-fluoro-D-deoxyglucose* (FDG)-PET scanning has been recognized in the upper chest and neck region for a long time; in the1990 s this activity was considered to represent muscle tension in the neck area. The launch of hybrid PET/CT scanners in the 2000s enabled the precise co-localization of PET images with anatomical CT images in non cerebral regions also. When symmetrical uptake of FDG in the neck and upper chest region during PET/CT scanning was carefully analyzed, the metabolic activity was clearly localized in adipose tissue [3]. However, similar accumulation of FDG may occur in the case of inflammation, which cannot be excluded in severely sick cancer patients – especially since the fat area in the supraclavicular region consists of several other structures (such as blood vessels and lymphatic tissue). Thus it was essential to find an answer to the questions whether healthy adults have functionally active BAT in regions of high uptake of FDG, and whether this activated tissue expresses biochemical characteristics typical of BAT.

Increased uptake of FDG in the supraclavicular region has been described more often in cold seasons than during the summer [4]. Saito et al [5] demonstrated a similar kind of accumulation in the neck, supraclavicular, and paravertebral regions in experimental settings in which the study individuals were exposed to acute cold before and during PET/CT scanning. We followed a similar protocol whereby healthy adults were exposed to temperatures of 15–19°C for 2 hours, before undergoing a PET/CT scan during which one foot was intermittently placed into cold water (5–10°C). In addition to detecting any increase in FDG uptake during the cold exposure, we quantified glucose uptake in the suspected BAT regions (in most cases supraclavicular), in order to compare tissue uptake of glucose in the different cold and warm settings. The method of quantification of glucose uptake in human adipose tissue used in our laboratory has been validated previously [6]. Glucose uptake was found to be more than 10 times greater under conditions of cold than that in the scan performed at normal room temperature [1].

The probability of observing increased uptake of FDG in the neck region ranges from 0.6% to 25% [3,4,7–9], the highest probabilities being found during the cold season in females [4]. In our small study population of 27 normal-weight adults, FDG uptake was activated in 60% of cases during experimental exposure to cold.

Although cold is a very effective activator of BAT metabolism and thermogenesis, humans do not spend much time in cold environments. A related alternative condition of everyday life that merits consideration is the postprandial state, in which many of us spend most of our waking hours. Eating is considered to be the trigger for ''true'' thermogenesis, although the importance of diet-induced thermogenesis in humans has been debated [10]. Furthermore, available data concerning BAT metabolism in postprandial humans are very sparse. Williams and Kolodny [11] have shown that, although uptake of FDG is high in BAT during fasting, this could be abolished by giving two high-fat, very-low-carbohydrate, protein-permitted meals twice, before the scan and during the previous evening. This suggests that the function of the Randle cycle in BAT is similar to that in other tissues, such as skeletal muscle.

The important question is whether the postprandial thermogenic effect is local or systemic. Regarding the small amount of BAT in healthy normal-weight adults – 1–60 g in the supraclavicular region – we would support the concept of a local release of heat, in view of our own experience from cold exposure studies in which we have not found any change in the skin temperature. Therefore, in the postprandial state, activation of thermogenesis in the supraclavicular and neck regions would secure the delivery of warm blood to the brain during the period when the peripheral circulation was concentrated mostly in the gastrointestinal tract.

One of the hormones secreted simultaneously with eating is insulin, from the pancreatic β cells. Our preliminary data suggest that insulin may have a considerable role in human BAT metabolism [12]. Uptake of glucose by this tissue is measured by FDG-PET, and insulin stimulation is induced using the euglycemic hyperinsulinemic clamp technique (1 mU/kg per min) [13], whereby the plasma insulin concentration is increased to the postprandial insulin concentration. The insulin-stimulated rate of uptake of glucose is comparable to that which has been measured in skeletal muscle [12]. In the future, it will be intriguing to learn what other factors, such as gut hormones, participate in the function of BAT in human physiology.

PET has become a more common technique in the Western world, but remains very expensive. The need for tracers other than FDG is obvious: it is the tracer most commonly used worldwide (90% of PET scans are performed using FDG), and is currently the only tracer used in the study of human BAT function; this

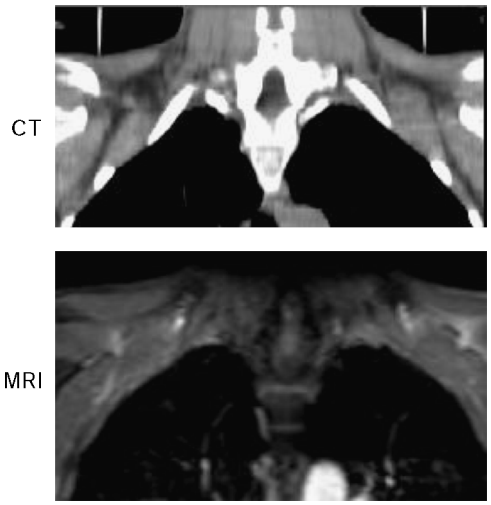

Figure 1. Example images (coronal slices) from computed tomography (CT) (upper image) and magnetic resonance imaging (MRI) (lower image). Adipose tissue stands out as dark gray both in CT and in MRI images. On the basis of CT and MRI findings, white and brown adipose tissues cannot be distinguished from each other.

may lead to bias. Even when fully activated, BAT derives only about 10% of its energy source from glucose [14]. For the study of BAT function in human metabolism, it would be highly desirable to utilize new tracers that could increase our understanding, for example, of adrenergic receptor density or fatty acid metabolism in BAT. However, other modalities for the imaging of BAT function remain to be developed. To date, magnetic resonance imaging (MRI) has not been able to fulfill the criteria for sensitivity, and for the present MRI is comparable to CT in imaging anatomy, but is not able to distinguish between white and brown fat in humans (*Figure 1*). Functional MRI could

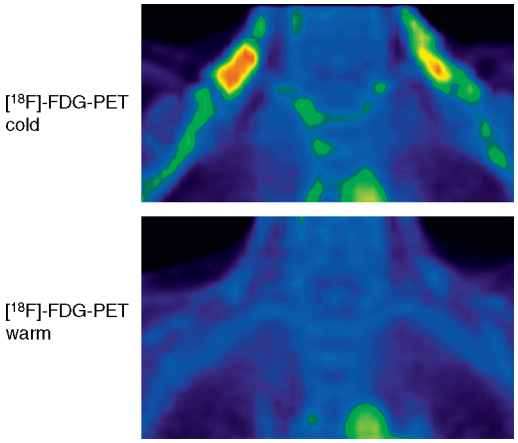

Figure 2. Example images (coronal slices) of [^{18}F]2-fluoro-D-deoxyglucose-positron emission tomography (FDG-PET) during cold exposure (upper image) and during normal room temperature (warm; lower image) in the same individual as in Figure 1. During cold exposure, an intense increase in FDG uptake can be detected in the neck region (red color), whereas during warm exposure such an increase can not be found.

be an option for the future, although with the same provisos as for PET: the imaging conditions (warm/cold/fasting/postprandial) need to be taken carefully into account before conclusions are drawn. We found this to be crucial when an increase in uptake of FDG in BAT during exposure to cold was observed in 60% of study individuals, but none showed any activation of BAT glucose uptake in warm temperatures (*Figure 2*) [1].

Conclusion

PET is a highly sensitive, non invasive tool for the in-vivo imaging of BAT in humans, providing unique information on the basic function and physiology of BAT. Currently, PET seems to be only option for the study of BAT function and its interaction with other tissues at the whole-body level.

*see glossary for definition of this term. ■

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