Combining ^{123}I-Metaiodobenzylguanidine SPECT/CT and ^{18}F-FDG PET/CT for the Assessment of Brown Adipose Tissue Activity in Humans During Cold Exposure

Wanda M. Admiraal[1], Frits Holleman[1], Lonneke Bahler[1], Maarten R. Soeters[2], Joost B. Hoekstra[1], and Hein J. Verberne[3]

[1]Department of Internal Medicine, Academic Medical Center, Amsterdam, The Netherlands; [2]Department of Endocrinology and Metabolism, Academic Medical Center, Amsterdam, The Netherlands; and [3]Department of Nuclear Medicine, Academic Medical Center, Amsterdam, The Netherlands

Brown adipose tissue (BAT) has become a focus of research in the hope of finding a new target to fight obesity. Metabolic BAT activity can be visualized with ^{18}F-FDG PET/CT. Furthermore, the sympathetic innervation of BAT can be visualized with the radiolabeled norepinephrine analog ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG). We aimed to determine whether ^{123}I-MIBG SPECT/CT and ^{18}F-FDG PET/CT identify the same anatomic regions as active BAT in adult humans. Furthermore, we investigated whether the magnitude of BAT activity measured by these techniques correlated. Finally, we tried to establish the optimal time interval between ^{123}I-MIBG administration and subsequent SPECT/CT acquisition to visualize sympathetic stimulation of BAT. **Methods:** Ten lean (body mass index, 19–25 kg/m^2), healthy Caucasian men (age, 18–32 y) underwent one ^{18}F-FDG PET/CT and two ^{123}I-MIBG-SPECT/CT scans within a 2-wk interval. On 2 separate occasions, the subjects were exposed to mild cold (17°C) for 2 h after an overnight fast. After 1 h of cold exposure, ^{18}F-FDG (one occasion) or ^{123}I-MIBG (other occasion) was administered. ^{18}F-FDG PET/CT was performed at 1 h after ^{18}F-FDG administration, and ^{123}I-MIBG-SPECT/CT was performed at 4 and 24 h after ^{123}I-MIBG injection. **Results:** ^{18}F-FDG uptake in BAT was observed in 8 of 10 subjects, whereas ^{123}I-MIBG uptake was observed in 7 of 10 subjects in both the SPECT/CT scans acquired at 4 h after ^{123}I-MIBG administration and the SPECT/CT scans acquired at 24 h after ^{123}I-MIBG administration. All subjects who showed ^{123}I-MIBG uptake in BAT also showed ^{18}F-FDG uptake in BAT. There was no statistically significant correlation between maximal standardized uptake value of ^{18}F-FDG and semiquantitative uptake of ^{123}I-MIBG at 4 h after administration. However, a positive correlation was found between the maximal standardized uptake value of ^{18}F-FDG and semiquantitative uptake of ^{123}I-MIBG at 24 h after administration ($r = 0.64$, $P = 0.04$). **Conclusion:** ^{123}I-MIBG SPECT/CT, as a marker of sympathetic activity, and ^{18}F-FDG PET/CT, as a marker of metabolic activity, identified the same anatomic regions as active BAT. Moreover, when ^{123}I-MIBG SPECT/CT was performed at 24 h after ^{123}I-MIBG administration, the magnitude of BAT activity measured with these techniques correlated strongly. This finding not only supports that BAT activity in humans is sympathetically influenced but also identifies ^{123}I-MIBG SPECT/CT, when performed 24 h after ^{123}I-MIBG injection, as a method to visualize and quantify sympathetic stimulation of BAT.

Key Words: brown adipose tissue; ^{18}F-FDG; ^{123}I-MIBG

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Given its high capacity to dissipate excess energy, brown adipose tissue (BAT) has become a focus of research in the hope that activation of BAT may be a new target to fight obesity (*1–4*). However, knowledge of mechanisms regulating BAT activity in humans is still limited.

BAT can be assessed with various radiolabeled metabolic substrates, of which ^{18}F-FDG PET/CT is most commonly used, typically under conditions of mild cold exposure (*1–5*).

On the basis of animal data and observational studies in humans, BAT is likely to be activated by the sympathetic nervous system (*2*). ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG), a radiolabeled norepinephrine analog, is commonly used for scintigraphic assessment of neuroendocrine tumors and cardiac sympathetic activity (*6–8*). Uptake of ^{123}I-MIBG does not always correspond to tumor localization and is known to correspond with the typical distribution pattern of BAT (*9*). ^{123}I-MIBG scintigraphy has already been used specifically to localize BAT in rats (*10*).

The aim of this study was to determine whether ^{123}I-MIBG SPECT/CT, as a measure of sympathetic stimulation and activation, and ^{18}F-FDG PET/CT, as a marker of metabolic activity, identify the same anatomic location of BAT in adult lean humans. Furthermore, we investigated whether the magnitude of BAT activity measured by these 2 techniques correlated.

Finally, we tried to establish the optimal time interval between ^{123}I-MIBG administration and subsequent acquisition to visualize and quantify sympathetic stimulation and activation of BAT. In clinical practice, imaging of the cardiac sympathetic nerves is commonly performed 4 h after

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For correspondence or reprints contact: Wanda Admiraal, Academic Medical Center, Department of Internal Medicine F4-255, P.O. Box 22660, 1100DD Amsterdam, The Netherlands.
E-mail: w.m.admiraal@amc.uva.nl
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^{123}I-MIBG injection, whereas a time interval of 24 h after injection is used to visualize tumors from neuroendocrine origin (*11,12*). Therefore, we compared ^{123}I-MIBG SPECT/CT images obtained 4 and 24 h after ^{123}I-MIBG administration and determined which time interval resulted in an optimal correlation with ^{18}F-FDG PET/CT–assessed BAT activity.

MATERIALS AND METHODS

We studied a group of 10 healthy, lean Caucasian male volunteers (age, 18–32 y; body mass index [BMI], 19–25 kg/m^2). The institutional ethics committee of the Academic Medical Center approved the study protocol, and all subjects provided written informed consent. Subjects were recruited through public advertisements; all underwent a physical examination, and a fasting blood sample was drawn. Each of the 10 subjects underwent one ^{18}F-FDG PET/CT and two ^{123}I-MIBG SPECT/CT scans at 4 and 24 h after administration of ^{123}I-MIBG. The interval between the ^{18}F-FDG PET/CT and the ^{123}I-MIBG scintigraphy was set between 1 and 2 wk. To minimize the possibility of order bias, 5 subjects first underwent ^{18}F-FDG PET/CT, followed by ^{123}I-MIBG-SPECT/CT; the order was reversed in the other 5 subjects. All subjects were scanned after an overnight fast.

Anthropometric and Laboratory Measurements

Patients, wearing light clothing, had their weight measured on a mechanical scale (SECA) to the nearest 100 g, and their heights recorded to the nearest 0.01 m. Patients' blood pressure was measured while they were seated (M5-1; Omron). Furthermore, fasting plasma glucose levels were assessed.

^{18}F-FDG PET/CT: Scanning Protocol

All subjects were exposed to mild cold (~17°C, controlled by use of a ventilation system [Airco]) for 2 h. Shivering was neither reported by subjects nor noticed by research staff. After 1 h of cold exposure, approximately 200 MBq of ^{18}F-FDG were administered intravenously and exposure to cold was continued for another hour. Upper-body (from the base of the skull to groin) static PET acquisition was performed 60 min after ^{18}F-FDG injection.

PET/CT images were acquired with a Gemini time-of-flight multidetector helical PET/CT scanner (2 min/bed position) (Philips). In areas in which uptake of ^{18}F-FDG was identified by PET and the presence of fat was identified by CT (Hounsfield units between −250 and −50), the maximal standardized uptake values (SUVmax), defined as activity in becquerels per milliliter within the region of interest divided by injected dose in becquerels per gram of body weight, were determined (Hybrid Viewer; HERMES Medical Solutions). Anatomic regions of interest were cervical, supraclavicular, and superior mediastinal depots. In these areas, an SUVmax of ^{18}F-FDG of at least 2.0 g/mL was considered indicative of BAT (*1*).

^{123}I-MIBG SPECT/CT: Scanning Protocol

All subjects were pretreated with potassium iodide to block thyroid uptake of ^{123}I-MIBG.

Again, the subjects were exposed to mild cold for 2 h. After 1 h of cold exposure, approximately 185 MBq of ^{123}I-MIBG were administered intravenously and exposure to cold was continued for another hour. Thereafter, the subjects resided in a thermoneutral environment for another 3 h. Subsequently, an upper-body SPECT/CT image was acquired at 4 h after ^{123}I-MIBG injection. The next day, 24 h after administration of ^{123}I-MIBG, a second SPECT/CT scan was obtained for the same anatomic region.

The SPECT/CT images were acquired with the use of an Infinia SPECT/CT scanner (GE Healthcare) with a medium-energy all-purpose collimator and a 128 × 128 matrix. A 15% window was set for the main energy peak of ^{123}I (159 keV). SPECT images were iteratively reconstructed (ordered-subset expectation maximization) and corrected for attenuation using low-dose CT (no intravenous contrast). In areas in which uptake of ^{123}I-MIBG was identified by SPECT and the presence of fat was identified by CT, semiquantitative uptake of ^{123}I-MIBG was calculated as the maximum (decay-corrected) count per voxel in the volumes of interest (VOIs) divided by the mean count per voxel in a reference region (i.e., the mediastinum) (Hybrid Viewer; HERMES Medical Solutions).

Alignment of ^{18}F-FDG PET/CT and ^{123}I-MIBG SPECT/CT

The ^{18}F-FDG PET/CT and ^{123}I-MIBG SPECT/CT scans were aligned using the CT images with Hybrid Viewer. The results of this automated nonrigid registration algorithm were visually validated. The specific VOIs on the anatomic images of ^{18}F-FDG PET/CT in which metabolically active BAT was present (i.e., an SUVmax of ^{18}F-FDG ≥ 2.0 g/mL) were copied to the aligned ^{123}I-MIBG SPECT/CT images. Subsequently, the semiquantitative uptake of ^{123}I-MIBG in these VOIs was calculated.

Statistical Analysis

Depending on the distribution of the data, the characteristics of the study subjects are reported as mean ± SD or median with interquartile range. *P* values for differences in semiquantitative uptake of ^{123}I-MIBG between the 4- and 24-h acquisitions were determined with a paired-sample *t* test. The correlation between semiquantitative uptake of ^{123}I-MIBG (4 and 24 h after administration) and the SUVmax of ^{18}F-FDG was determined with a Pearson correlation coefficient. Data analysis was performed using SPSS software (version 16.0; IBM). *P* values of less than 0.05 were considered statistically significant.

RESULTS

Table 1 shows the characteristics of the 10 volunteers. The median age of the participants was 22.5 y (interquartile range, 21.2–25.1 y), and the mean BMI ± SD was 22.2 ± 1.2 kg/m^2. ^{18}F-FDG uptake in BAT was visually observed in 8 of 10 subjects, whereas ^{123}I-MIBG uptake in BAT was observed in 7 of 10 subjects in both the SPECT/CT scans acquired 4 h after ^{123}I-MIBG administration and the SPECT/CT scans acquired 24 h after ^{123}I-MIBG administration. The mean semiquantitative uptake value of ^{123}I-MIBG was higher 24 h after administration than it was 4 h after administration (mean counts ± SD per voxel, 3.11 ± 1.05 vs. 1.8 ± 0.51; P = 0.002). This difference was the result of a relatively lower ^{123}I-MIBG uptake in the reference region and not of a higher ^{123}I-MIBG uptake in BAT itself (Table 1).

All subjects who showed ^{123}I-MIBG uptake in BAT also showed ^{18}F-FDG uptake in BAT in the same anatomic location (Figs. 1 and 2).

The SUVmax of ^{18}F-FDG and semiquantitative uptake values of ^{123}I-MIBG at 4 and 24 h after administration were normally distributed. There was no statistically significant

TABLE 1
Characteristics of Male Volunteers

Characteristic	Data (study population = 10)
Age (y)	
Median	22.5
Interquartile range	21.2–25.1
Body mass index (mean ± SD) (kg/m^2)	22.2 ± 1.2
Systolic blood pressure (mean ± SD) (mm Hg)	117 ± 7
Diastolic blood pressure (mm Hg)	
Median	75
Interquartile range	72–77
Fasting plasma glucose (mean ± SD) (mmol/L)	4.6 ± 0.3
Presence of BAT based on ^{18}F-FDG PET/CT (*n*)	8
SUVmax of ^{18}F-FDG (mean ± SD) (g/L)*	5.8 ± 4.58
Presence of BAT based on 4-h ^{123}I-MIBG SPECT/CT (*n*)†	7
Uptake of ^{123}I-MIBG in reference region (mean counts per voxel) after 4 h‡,§ (mean ± SD)	21.0 ± 5.6
Absolute uptake of ^{123}I-MIBG in BAT after 4 h (mean maximum counts per VOI)§,‖ (mean ± SD)	37.4 ± 14.1
Semiquantitative uptake of ^{123}I-MIBG (mean ± SD) after 4 h¶	1.8 ± 0.51
Presence of BAT based on 24-h ^{123}I-MIBG SPECT/CT (*n*)*	7
Uptake of ^{123}I-MIBG in reference region (mean counts per voxel) after 24 h‡,§ (mean ± SD)	3.2 ± 0.5
Absolute uptake of ^{123}I-MIBG in BAT after 24 h (mean maximum counts per VOI)§,‖ (mean ± SD)	9.8 ± 3.10
Semiquantitative uptake of ^{123}I-MIBG (mean ± SD) after 24 h¶	3.1 ± 1.1

*SUVmax of ^{18}F-FDG, defined as activity in becquerels per milliliter within region of interest divided by injected dose in becquerels per gram of body weight.

†Presence of BAT was determined visually.

‡Uptake of ^{123}I-MIBG in reference region (i.e., mediastinum) was calculated as mean counts per voxel in this reference region.

§Decay-corrected.

‖Uptake of ^{123}I-MIBG in BAT was calculated as maximum count per voxel in VOI.

¶Semiquantitative uptake of ^{123}I-MIBG was calculated as maximum count in anatomic volumes of interest divided by mean count per voxel in reference region (i.e., mediastinum).

correlation between the SUVmax of ^{18}F-FDG and the semiquantitative uptake of ^{123}I-MIBG at 4 h after administration ($r = 0.35$, $P = 0.33$). However, a strong positive correlation was found between the SUVmax of ^{18}F-FDG and the semiquantitative uptake of ^{123}I-MIBG at 24 h after administration ($r = 0.64$, $P = 0.04$) (Fig. 3). Semiquantitative uptake of ^{123}I-MIBG in BAT 24 h after administration explained approximately 40% of the variance in the SUVmax of ^{18}F-FDG in BAT ($R^2 = 0.407$).

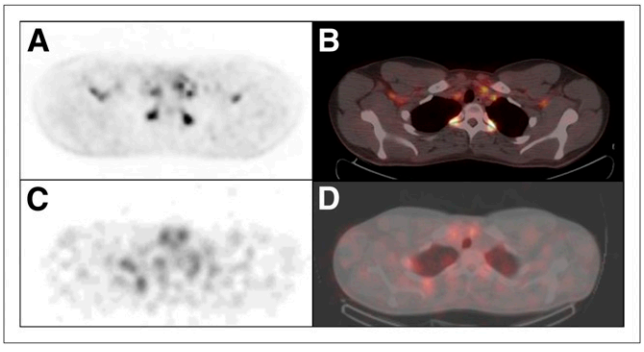

FIGURE 1. Brown adipose tissue visualized with ^{123}I-MIBG SPECT/CT (C and D) and ^{18}F-FDG PET/CT (A and B). ^{18}F-FDG and ^{123}I-MIBG uptake on corresponding transversal PET and SPECT images is suggestive of BAT and is superimposed on adipose tissue on correlated transversal CT images.

DISCUSSION

^{123}I-MIBG SPECT/CT, as a marker of sympathetic activity, and ^{18}F-FDG PET/CT, as a marker of metabolic activity, identified the same anatomic regions as being active BAT. Moreover, when ^{123}I-MIBG SPECT/CT was performed 24 h after administration of ^{123}I-MIBG, the correlation between these 2 techniques was strongly positive. These findings support the notion that metabolic BAT activity in humans is influenced by the sympathetic nervous system.

The ability to visualize metabolically active BAT in humans with ^{18}F-FDG PET/CT under conditions of mild cold exposure has been reported in several studies (*1–5*). In our study, metabolically active BAT was found in 80% of the subjects after 2 h of cold exposure (16°C–18°C) with ^{18}F-FDG PET/CT, which is in line with previous publications (*3*).

The opportunity to identify BAT with ^{123}I-MIBG scintigraphy has previously been described in rats (*10,13*). Okuyama et al. retrospectively investigated ^{123}I-MIBG scans obtained in 266 pediatric patients who had been treated for, or who were suspected of having, neuroendocrine tumors (*9*). In 22 of these patients, ^{123}I-MIBG accumulation was observed in the nape-of-the-neck region not corresponding to tumor tissue. Because all 22 scans were obtained during winter, this accumulation of ^{123}I-MIBG was deemed to be related to active BAT (*9*). In addition,

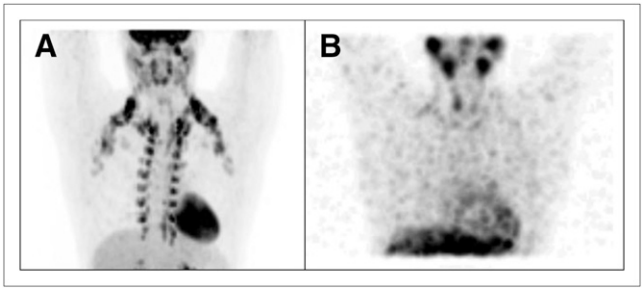

FIGURE 2. BAT visualized with ^{123}I-MIBG SPECT/CT (B) and ^{18}F-FDG PET/CT (A). Images demonstrate clear association between ^{18}F-FDG uptake in BAT and ^{123}I-MIBG, both showing increased uptake in BAT (maximum-intensity-projection images).

because these images were not combined with CT, no definite conclusion on the presence of BAT could be made. In another study, Hadi et al. retrospectively reviewed images of 83 patients evaluated with ^{18}F-FDG PET/CT for known or suspected pheochromocytoma; 10 of the patients had undergone a ^{123}I-MIBG SPECT scan as well (*13*). In 3 of these 10 patients, BAT was observed on both ^{123}I-MIBG and ^{18}F-FDG images. In the remaining 7 patients, BAT was detected with ^{18}F-FDG PET/CT only ($n = 3$), ^{123}I-MIBG only ($n = 1$), or neither modality ($n = 2$).

There is an inherent problem with retrospective studies on BAT activity, because the reported BAT in retrospective studies is only the incidentally detected BAT (*14*). As mentioned earlier, BAT is optimally visualized during cold exposure. Inactive BAT will not be visible on PET scans (*14*). Because the patients included in the retrospective studies were not specifically exposed to cold, it is a likely assumption that BAT, although present, was not detected in some of these patients.

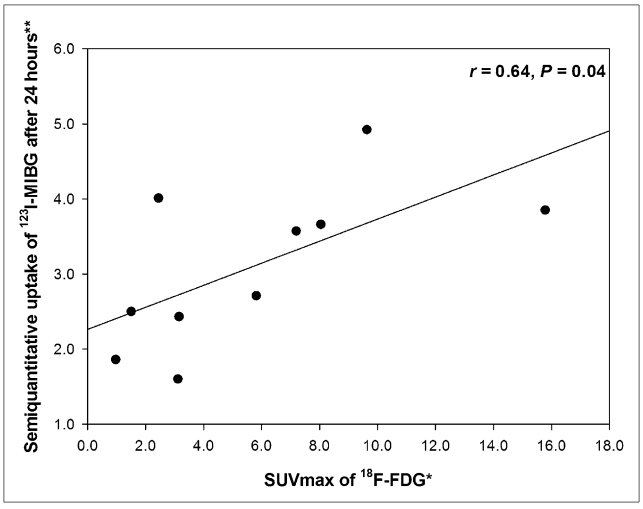

FIGURE 3. Correlation between SUVmax of ^{18}F-FDG and semiquantitative uptake of ^{123}I-MIBG 24 h after administration. Correlations between SUVmax of ^{18}F-FDG and semiquantitative uptake of ^{123}I-MIBG with corresponding *P* values were determined with Pearson correlation coefficient. *SUVmax of ^{18}F-FDG was defined as activity in becquerels per milliliter within region of interest divided by injected dose in becquerels per gram of body weight. **Semiquantitative uptake of ^{123}I-MIBG was calculated as maximum count in anatomic VOIs divided by mean count per voxel in reference region (i.e., mediastinum).

To our knowledge, this study is the first to visualize sympathetic activity of BAT with ^{123}I-MIBG after cold exposure in adult humans. Furthermore, we do not know of any studies that (semiquantitatively) compared BAT activity measured by ^{123}I-MIBG SPECT/CT and ^{18}F-FDG PET/CT that were performed in the same period in the same individuals.

In our study, the SPECT/CT scans obtained 4 and 24 h after administration of ^{123}I-MIBG both identified the same anatomic regions as being active BAT as did the ^{18}F-FDG PET/CT scans. However, the semiquantitative uptake value of ^{123}I-MIBG was higher after 24 h than after 4 h. As mentioned earlier, this was the result of a relatively lower ^{123}I-MIBG uptake in the reference region (i.e., lower background activity) and not of a higher ^{123}I-MIBG uptake in BAT itself (i.e., higher absolute uptake of ^{123}I-MIBG). We found a strongly positive correlation between ^{18}F-FDG SUVmax and the semiquantitative uptake of ^{123}I-MIBG only after 24 h (and not after 4 h). This finding suggests that the higher signal-to-noise-ratio in ^{123}I-MIBG SPECT/CT images obtained after 24 h, when compared with images obtained after 4 h, results in a more accurate assessment of sympathetic stimulation of BAT.

A limitation of the study may be the relatively small sample size. For this reason, caution must be applied when extrapolating these results to the broader community. However, despite this small sample size, we still found a statistically significant and strongly positive correlation between the SUVmax of ^{18}F-FDG and the semiquantitative uptake of ^{123}I-MIBG after 24 h.

In our study, ^{18}F-FDG and ^{123}I-MIBG were not administered simultaneously, because we did not want the ^{123}I-MIBG SPECT/CT scan obtained 4 h after administration to be influenced by the still-radioactive ^{18}F-FDG, which has a half-life of 109.8 min (*15*). Although the procedure of exposing the subjects to cold was performed in exactly the same way, the fact that the subjects were studied on separate days might have influenced the comparability of the ^{18}F-FDG PET/CT and the ^{123}I-MIBG SPECT/CT images. Because we demonstrated that a time interval of 24 h between ^{123}I-MIBG administration and SPECT/CT is preferable over a 4-h interval to visualize sympathetic BAT activity, ^{18}F-FDG and ^{123}I-MIBG can be administered simultaneously in future studies, thereby limiting the cold exposure of subjects to only one time and reducing subject-related sources of variability.

As mentioned earlier, BAT has become a focus of research in the hope that activation of BAT may be a new target to fight obesity (*1–5*). Several studies have shown that BAT activity is much lower in obese people than in their lean peers (*1,3,16*). The ability to quantify sympathetic stimulation of BAT in humans makes it possible to investigate the extent to which metabolic BAT activity is

attributable to central activation, as opposed to peripheral factors (such as hormones or intrinsic cellular factors, i.e., sensitivity of BAT to sympathetic stimulation). In future studies, we will simultaneously visualize and quantify sympathetic and metabolic activation to elucidate the mechanisms behind a diminished BAT activity in obese people.

CONCLUSION

^{123}I-MIBG SPECT/CT and ^{18}F-FDG PET/CT identify the same anatomic regions as active BAT. Moreover, the magnitude of BAT activity measured with these techniques correlates strongly. This finding not only supports the notion that BAT activity in humans is influenced by the sympathetic nervous system but also identifies ^{123}I-MIBG SPECT/CT as a method to visualize and quantify the sympathetic stimulation of BAT.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734. No potential conflict of interest relevant to this article was reported.

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