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

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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/m2), 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 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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123I-MIBG injection, whereas a time interval of 24 h after injection is used to visualize tumors from neuroendocrine origin (11,12). Therefore, we compared 123I-MIBG SPECT/CT images obtained 4 and 24 h after 123I-MIBG administration and determined which time interval resulted in an optimal correlation with 18F-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/m²). 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 18F-FDG PET/CT and two 123I-MIBG SPECT/CT scans at 4 and 24 h after administration of 123I-MIBG. The interval between the 18F-FDG PET/CT and the 123I-MIBG scintigraphy was set between 1 and 2 wk. To minimize the possibility of order bias, 5 subjects first underwent 18F-FDG PET/CT, followed by 123I-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.

18F-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 18F-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 18F-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 123I-MIBG 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 becuquers per milliliter within the region of interest divided by injected dose in becuquers 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 18F-FDG of at least 2.0 g/mL was considered indicative of BAT (11).

123I-MIBG SPECT/CT: Scanning Protocol
All subjects were pretreated with potassium iodide to block thyroid uptake of 123I-MIBG.
Again, the subjects were exposed to mild cold for 2 h. After 1 h of cold exposure, approximately 185 MBq of 123I-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 123I-MIBG injection. The next day, 24 h after administration of 123I-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 PET/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 123I (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 123I-MIBG was identified by SPECT and the presence of fat was identified by CT, semiquantitative uptake of 123I-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 18F-FDG PET/CT and 123I-MIBG SPECT/CT
The 18F-FDG PET/CT and 123I-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 18F-FDG PET/CT in which metabolically active BAT was present (i.e., an SUVmax of 18F-FDG ≥ 2.0 g/mL) were copied to the aligned 123I-MIBG SPECT/CT images. Subsequently, the semiquantitative uptake of 123I-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 123I-MIBG between the 4- and 24-h acquisitions were determined with a paired-sample t test. The correlation between semiquantitative uptake of 123I-MIBG (4 and 24 h after administration) and the SUVmax of 18F-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/m². 18F-FDG uptake in BAT was visually observed in 8 of 10 subjects, whereas 123I-MIBG uptake in BAT was observed in 7 of 10 subjects in both the SPECT/CT scans acquired 4 h after 123I-MIBG administration and the SPECT/CT scans acquired 24 h after 123I-MIBG administration. The mean semiquantitative uptake value of 123I-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 123I-MIBG uptake in the reference region and not of a higher 123I-MIBG uptake in BAT itself (Table 1).

All subjects who showed 123I-MIBG uptake in BAT also showed 18F-FDG uptake in BAT in the same anatomic location (Figs. 1 and 2). The SUVmax of 18F-FDG and semiquantitative uptake values of 123I-MIBG at 4 and 24 h after administration were normally distributed. There was no statistically significant
A strong positive correlation was found between the SUVmax of 18F-FDG and the semi-quantitative uptake of 123I-MIBG at 24 h after administration ($r = 0.64$, $P = 0.04$) (Fig. 3). Semiquantitative uptake of 123I-MIBG in BAT 24 h after administration explained approximately 40% of the variance in the SUVmax of 18F-FDG in BAT ($R^2 = 0.407$).

**DISCUSSION**

123I-MIBG SPECT/CT, as a marker of sympathetic activity, and 18F-FDG PET/CT, as a marker of metabolic activity, identified the same anatomic regions as being active BAT. Moreover, when 123I-MIBG SPECT/CT was performed 24 h after administration of 123I-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 18F-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 18F-FDG PET/CT, which is in line with previous publications (3).

The opportunity to identify BAT with 123I-MIBG scintigraphy has previously been described in rats (10,13). Okuyama et al. retrospectively investigated 123I-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, 123I-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 123I-MIBG was deemed to be related to active BAT (9). In addition,
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 18F-FDG PET/CT for known or suspected pheochromocytoma; 10 of the patients had undergone a 123I-MIBG SPECT scan as well (13). In 3 of these 10 patients, BAT was observed on both 123I-MIBG and 18F-FDG images. In the remaining 7 patients, BAT was detected with 18F-FDG PET/CT only (n = 3), 123I-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.

To our knowledge, this study is the first to visualize sympathetic activity of BAT with 123I-MIBG after cold exposure in adult humans. Furthermore, we do not know of any studies that (semiquantitatively) compared BAT activity measured by 123I-MIBG SPECT/CT and 18F-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 123I-MIBG both identified the same anatomic regions as being active BAT as did the 18F-FDG PET/CT scans. However, the semiquantitative uptake value of 123I-MIBG was higher after 24 h than after 4 h. As mentioned earlier, this was the result of a relatively lower 123I-MIBG uptake in the reference region (i.e., lower background activity) and not of a higher 123I-MIBG uptake in BAT itself (i.e., higher absolute uptake of 123I-MIBG). We found a strongly positive correlation between 18F-FDG SUVmax and the semiquantitative uptake of 123I-MIBG only after 24 h (and not after 4 h). This finding suggests that the higher signal-to-noise-ratio in 123I-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 18F-FDG and the semiquantitative uptake of 123I-MIBG after 24 h.

In our study, 18F-FDG and 123I-MIBG were not administered simultaneously, because we did not want the 123I-MIBG SPECT/CT scan obtained 4 h after administration to be influenced by the still-radioactive 18F-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 18F-FDG PET/CT and the 123I-MIBG SPECT/CT images. Because we demonstrated that a time interval of 24 h between 123I-MIBG administration and SPECT/CT is preferable over a 4-h interval to visualize sympathetic BAT activity, 18F-FDG and 123I-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

123I-MIBG SPECT/CT and 18F-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 123I-MIBG SPECT/CT as a method to visualize and quantify the sympathetic stimulation of BAT.

DISCLOSURE

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REFERENCES