

Brown Adipose Tissue and Nuclear Medicine Imaging

During the last 2 years, brown adipose tissue (BAT) has received considerable attention in the field of nuclear medicine. BAT has been shown to accumulate ^{18}F -FDG (1–4), metaiodobenzylguanidine (MIBG) (5,6), and tetrofosmin (7). The first description of BAT is, however, generally attributed to the Swiss physician and naturalist Konrad Gessner, who detected BAT in hibernating marmots more than 450 years ago. Nevertheless, the function of this tissue remained unknown until the second half of the 20th century. At that time it became evident that BAT is a highly specialized thermogenic tissue that plays an important role in the regulation of body temperature in newborn and hibernating mammals (8).

Morphologically, BAT differs from regular or white adipose tissue by its rich vascularization and its high density of mitochondria. These features are also responsible for the brownish color of BAT. Functionally, BAT is characterized by a unique metabolic pathway whose only purpose is the generation of heat. In tissues other than BAT, oxygen consumption by the mitochondria is closely coupled to adenosine triphosphate (ATP) synthesis. The β -oxidation of fatty acids and the citric acid cycle lead to formation of 2 energy-rich electron donors, reduced nicotinamide adenine dinucleotide (NADH) and NADH phosphate (NADPH), in the mitochondrial matrix. The enzymes of the respiratory

chain in the inner mitochondrial membrane transfer electrons from NADH and NADPH to oxygen. In this process, oxygen is reduced to water, and protons (H^+) are transported from the mitochondrial matrix across the inner mitochondrial membrane. Because the inner mitochondrial membrane is generally impermeable to charged molecules, a proton gradient is generated across this membrane. Protons can enter the mitochondrial matrix only by the ATP-synthase complex. In this enzyme complex, energy derived from the flow of protons entering the mitochondrial matrix drives the phosphorylation of adenosine diphosphate to ATP (8). This mechanism ensures that oxygen consumption is tightly coupled to ATP synthesis. BAT cells, however, express an “uncoupling protein,” which allows protons to enter the mitochondrial matrix without ATP’s being synthesized (9). This means that ATP synthesis is uncoupled from oxygen consumption and that energy released from the oxidation of NADH and NADPH is completely converted to heat.

Heat production by BAT is triggered by the sympathetic nervous system. Norepinephrine released from sympathetic nerve terminals binds to β_3 -receptors on the surfaces of BAT cells and causes, in a cyclic adenosine monophosphate-mediated process, activation of the enzyme hormone-sensitive lipase. Hormone-sensitive lipase degrades cytoplasmic triglycerides, and the free fatty acids generated from this process enter β -oxidation in the mitochondria and initiate heat production (8). Furthermore, norepinephrine activates, in an insulin-independent manner, glucose transport by glucose transporter 1 and potentially also by glucose transporter 4 (10,11). Norepi-

nephrine also causes a remarkable increase in the perfusion of BAT. Microsphere studies on rats have shown a perfusion as high as 11 mL/min/g for norepinephrine-stimulated BAT (12). Thus, the biologic mechanisms for the accumulation of MIBG, ^{18}F -FDG, and tetrofosmin by activated BAT are well defined: MIBG is concentrated in the sympathetic nerve terminals in the BAT, ^{18}F -FDG uptake is mediated by increased activity of glucose transporters, and tetrofosmin uptake is due to the high perfusion of activated BAT and probably also to its high density of mitochondria.

What do we learn in this context from the study of Tatsumi et al. (13), which is reported on pages 1189–1193 of this issue of *The Journal of Nuclear Medicine*? The authors have evaluated ^{18}F -FDG uptake in the BAT of rats stimulated by cold exposure and the anesthetic ketamine, which has sympathomimetic properties. They found that both stimuli cause a marked increase in ^{18}F -FDG uptake by BAT—an increase that is well visualized by PET/CT imaging. Pretreatment with propranolol and reserpine, both of which inhibit the sympathetic stimulation of BAT, significantly reduced ^{18}F -FDG uptake in BAT, whereas diazepam had no significant effect. These findings have implications regarding the acquisition protocols of ^{18}F -FDG PET studies but also suggest potential new research applications of ^{18}F -FDG PET.

First, the study demonstrates that animal handling may markedly influence the results of ^{18}F -FDG PET in rodents. In the study of Tatsumi et al. (13), injection of ketamine (a commonly used anesthetic for rodents) caused ^{18}F -FDG uptake by the BAT of Lewis rats to increase to 2.8 %ID/g of tissue/kg of body weight (15 %ID/g for

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an 185-g rat). The amount of BAT in rats can be estimated to be at least 0.75% of the total body weight (12). This means that at least 20% of the total amount of ^{18}F -FDG injected was accumulated by BAT. Thus, at least in this rat strain, activation of BAT can quantitatively change the whole-body distribution of ^{18}F -FDG. In addition, ^{18}F -FDG uptake by BAT will markedly decrease image contrast for tumors implanted at the shoulder of the animals. Further studies are needed to determine whether ketamine has such a pronounced effect on ^{18}F -FDG biodistribution also in other rat or mouse strains. A more than 8-fold increase in the ^{18}F -FDG uptake of BAT has previously been reported in mice sedated with chlorpromazine, which has no distinct sympathomimetic properties (14). Thus, hypothermia induced by sedation or anesthesia may by itself cause marked BAT activation. Therefore, the body temperature of mice or rats should be carefully controlled during ^{18}F -FDG PET studies (e.g., by heating pads) regardless of the type of anesthesia applied. This need is also emphasized by the data of Tatsumi et al., who found that cold exposure of rats caused a 4–5 times increase in ^{18}F -FDG uptake by BAT.

Second, for the clinical application of ^{18}F -FDG PET, it is interesting to note that diazepam, which is frequently used clinically to reduce ^{18}F -FDG uptake in the upper supraclavicular area, had a considerably lower effect on ^{18}F -FDG uptake than did propranolol. Thus, treatment with β -blockers may be preferable to administration of diazepam to decrease ^{18}F -FDG accumulation by BAT. However, as the authors point out, species differences may exist and the optimal clinical patient preparations still need to be determined. The affinity of propranolol is approximately 100 times lower for the β_3 -receptor found in BAT than for the common β_1 - and β_2 -receptors (15). Therefore, further studies are needed to determine whether clinically safe doses of propranolol can efficiently decrease ^{18}F -FDG uptake in BAT.

Finally, the study of Tatsumi et al. (13) and previous clinical studies suggest that ^{18}F -FDG PET may also be used as a research tool in studies evaluating the mechanism of human obesity and potential therapeutic approaches for obese patients. In several animals, BAT is stimulated not only by cold exposure but also by a high-calorie diet. By this mechanism, BAT serves as a buffer for the metabolic needs of the animal, and the weight gain induced by a high-calorie diet is reduced. BAT serves as a buffer for the metabolic needs of the animal. Loss of this buffer function of BAT in humans has been suggested as a mechanism for obesity (16). Activation and expansion of BAT (e.g., by β_3 -agonists) is therefore being discussed as a new form of treatment for obese patients. However, despite more than 5,000 publications on BAT, this theory of human obesity is still controversial (8). A large part of this controversy is caused by the lack of a noninvasive test that allows us to assess quantitatively the amount and activity of BAT in serial studies. The study by Tatsumi et al. and the previous clinical studies now provide considerable evidence that ^{18}F -FDG PET/CT may be helpful in clarifying the role of BAT in human obesity.

Independent of the interesting biochemical properties of BAT and the potential new applications of ^{18}F -FDG, MIBG, and tetrofosmin, an intriguing question remains: Why did it take so long for ^{18}F -FDG, MIBG, and tetrofosmin uptake in BAT to be recognized? All 3 tracers have been used clinically in large numbers of patients for several years, but only recently was their accumulation by BAT noted. In fact, ^{18}F -FDG uptake in the area of the neck had already been described in 1996 (17). However, this finding was generally considered to represent uptake by muscle tissue, although the pattern of tracer uptake was in many cases hardly consistent with the anatomic configuration of muscles in the head and neck area. BAT was probably not considered, because it was generally believed that BAT is not present in relevant amounts in adults, except after pro-

longed exposure to cold (18), after a chronic increase in plasma catecholamine levels (19,20), or in cachectic patients (21). Only with in-line PET/CT systems could ^{18}F -FDG uptake be localized with the certainty required to exclude muscle as the site of increased tracer uptake and to clearly attribute ^{18}F -FDG uptake to fat tissue. This observation has then stimulated further research on the uptake of ^{18}F -FDG and other tracers by BAT. Thus, the “BAT story” is a good example of how functional imaging benefits from morphologic information but also illustrates that “the most difficult of all is to see with your eyes, what is in front of your eyes.” [Johann Wolfgang von Goethe, “Xenien aus dem Nachlass”]

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