Beta-Cell Imaging: Opportunities and Limitations

TO THE EDITOR: We read with interest the review by Ichise and Harris (*1*), who proposed ^{11}C-dihydrotetrabenazine (^{11}C-DTBZ) PET as a potentially useful method for imaging β-cells in the native pancreas. ^{11}C-DTBZ targets the vesicular monoamine transporter type 2, which is expressed by β-cells but is absent from the exocrine pancreas. Although the authors have discussed several limitations of this method, they have not addressed the one that is perhaps most important and precludes the use of ^{11}C-DTBZ PET for imaging β-cells in the native pancreas. β-cells represent only 1%–2% of pancreatic volume and are clustered in islets of Langerhans throughout the pancreas. Islets are very small (~50–400 μm in diameter (*2*))—a problem that cannot be resolved by current noninvasive in vivo imaging methods, including PET. Equally important, the islets and pancreas of patients with diabetes are atrophic, compared with those of healthy controls (*2*). The combination of the relatively low spatial resolution of PET and islet/pancreas atrophy in diabetes will result in underestimation of the true concentration of a certain compound (in this case ^{11}C-DTBZ), if not corrected for partial-volume effects (*3,4*). In fact, if one corrects for partial-volume effects, there will be no differences in degree of uptake of a certain β-cell–specific tracer between patients (with a substantial degree of atrophy) and controls.

Sweet et al. (*5*) reported that the low-volume fraction of β-cells within the exocrine pancreas (about 1:100) requires that β-cells retain labeled imaging agents at least 1,000-fold more strongly than exocrine cells, in order for β-cell imaging in the pancreas to succeed by quantitative techniques. However, this level of retention is almost impossible and is not achievable with any existing agents. In addition, the high concentration of such compounds will result in significant radiation toxicity to the β-cells. Therefore, we believe it is ill conceived that β-cell imaging in the native pancreas be considered feasible with the technologies available today. However, the contrary is true for imaging the fate of transplanted pancreatic islets. Particularly, subcutaneous islet transplants may be reasonable, quantifiable targets for PET. The advantage of transplanting islets subcutaneously is that this site suffers considerably less from accumulation and uptake of certain compounds in non–β-cells than do other organs or structures, such as the liver and kidneys. The high concentration of β-cells at a known location and the opportunity to perform partial-volume correction of acquired PET data (*3,4*) make it possible to calculate the exact standardized uptake value at this site.

Besides radiolabeled DTBZ, which was discussed by Ichise and Harris (*1*), other promising PET radiotracers for β-cell imaging, including ^{18}F-L-dihydroxyphenaline (*6*) and sulfonylurea receptor ligands (*7*), deserve further investigation. We foresee an important role for ^{18}F-FDG in the evaluation of islet transplants, complementary to β-cell–specific tracers (*8*). ^{18}F-FDG may be used as a tracer to image immune activation associated with the rejection of islet grafts in the subcutaneous space (*8*). Early detection of subcutaneous islet cell rejection by increased trapping of ^{18}F-FDG and decreased trapping of β-cell–specific tracers (which are taken up only by functioning islets) leads to a window for potential intervention before frank biochemical failure and rescue of the subcutaneous islet graft.

We hope that this communication will eliminate some important misconceptions about β-cell imaging and stimulate meaningful investigations in this increasingly important field.

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REPLY: We would like to thank Dr. Kwee et al. for their interest and comments about our review on PET imaging of β-cell mass (*1*). They raise a major concern that PET with its limited spatial resolution may not be able to resolve small islets containing β-cells that are scattered throughout the pancreas. To address this concern, we would like to point out first that the ultimate goal of PET using radioligands such as ^{11}C-dihydrotetrabenazine (^{11}C-DTBZ) that target transporters and receptor proteins is to estimate average target protein density per unit volume of the tissue (pancreas) in which the target proteins are found (B_{avail}, in units of

molar [often nmol·L^{-1}, that is, nanomoles of receptor or transporter per 1,000 cm^{-3} tissue]) (*2*). Here, we are not estimating vesicular monoamine transporter 2 (VMAT2) per individual islet volume. The goal is to estimate VMAT2 density per unit pancreatic tissue volume or total pancreatic VMAT2 content (β-cell mass). To further clarify this point, an analogy can be made to PET imaging of neuroreceptors and transporters in the brain.

VMAT2 and dopamine transporters are found in the dopaminergic terminals in the striatum. It has been well established that PET using high-affinity radioligands such as ^{11}C-DTBZ can quantify the binding potential that correlates with the number of target sites per unit volume of striatal tissue (B_{avail}) (*3*). The volume of the human striatum (caudate nucleus and putamen) is about 5.5 cm^3 (*4*). Clusters (150–300 μm in diameter) of intrastriatal neurons (96% are medium spiny neurons) make up about 15% of the volume of the striatum and are embedded in surrounding "matrix," which makes up about 85% of the volume of the striatum. This larger matrix compartment consists of a mesh of extensive dendritic trees of medium spiny neurons and afferent axonal terminals, as well as efferent axons. Each branch of these dendritic trees is packed with numerous small spines that receive several different afferent inputs including glutamatergic, dopaminergic, GABAergic, and cholinergic terminals. The major massive input in terms of quantity of axons is not dopaminergic but glutamatergic corticostriatal projections.

Scattered patches of nigrostriatal dopaminergic terminals (0.1–0.5 μm in diameter) are a minor component of this matrix in terms of the volume contribution and are almost homogeneously dispersed throughout the matrix of the striatum (*5*). Therefore, VMAT2 and dopamine transporters containing dopaminergic terminals are by no means densely packed in the striatum. Yet PET with high-affinity radioligands for these sites allows detection of excellent binding signals, and kinetic model–based quantification allows for the estimation of binding potential, which correlates with the VMAT2 or dopamine transporter density (B_{avail} = number of transporter sites per unit volume of striatal tissue).

On the other hand, the volume of the normal pancreas is about 80 cm^3 (15 times the volume of the striatum) (*6*). The major component of the pancreas in terms of volume is exocrine tissue, and exocrine cells account for 98%–99% of the pancreatic parenchyma. The endocrine component of the pancreas is organized into clusters of islets of Langerhans containing 4 major cell types (producing different hormones), α-cells (glucagon), β-cells (insulin), δ-cells (somatostatin), and pancreatic polypeptide-producing cells. The islets (average 150 μm in diameter) are scattered almost homogeneously within the exocrine tissue and represent 1%–2% of the parenchyma (*7*).

From this analogy, it is apparent that the pancreas resembles the stratum in terms of the miniscule volumes of VMAT2 binding sites that are scattered in the tissue of interest. The volume of the pancreas is, however, about 15 times larger than that of the striatum. The target tissue volume is important, as pointed out by Kwee et al., for the recovery of PET signal (partial-volume effects) from the target tissue (pancreas or striatum) because of the limited spatial resolution of the PET system. Another important factor that influences the accuracy of the PET measurements relates to PET signal intensity. With ^{11}C-DTBZ PET, the average peak pancreatic standardized uptake value was 9, which is comparable to that of ^{18}F-FDG in the gray matter of the brain.

Our group recently started using ^{18}F-fluoropropyl-(+)-DTBZ, which has high binding affinity for VMAT2 (inhibition constant, 0.11 nM) and is superior to ^{11}C-DTBZ with lower affinity (higher inhibition constant) (0.97 nM) (*8,9*). In addition, this tracer can be shipped from a remote central radiopharmacy thanks to the much longer half-life of ^{18}F (110 min). Our preliminary human data (unpublished) indicate that the average peak standardized uptake value of ^{18}F-fluoropropyl-DTBZ in the human pancreas is 21, more than double that of ^{11}C-DTBZ. Our VMAT2 PET brain and pancreas imaging studies using ^{18}F-fluoropropyl-DTBZ in baboons suggest that the pancreas-specific VMAT2 binding signal is approximately 85% that of the striatum of the brain, suggesting that VMAT2 density in the pancreas is similar to that in the striatum (*10*). One important point here is that the pancreatic PET signal represents a combination of specific VMAT2 binding signal and nondisplaceable background signal consisting of free tissue and nonspecific binding signal from both endocrine and islet tissues of the pancreas (the latter accounting for up to 40% of the total pancreatic signal). ^{18}F-fluoropropyl-DTBZ thus provides exquisitely intense target tissue (pancreas) signal of high PET image quality (high signal-to-noise ratios).

The discussion so far has not directly addressed the partial-volume effect in PET quantification of VMAT2 in the pancreas, or in the striatum for that matter. Given that our current PET/CT system (Biograph HD; Siemens) has a full width at half maximum of 2.5–4.0 mm, voxel signal at the periphery of the pancreas suffers from the partial-volume effect. However, signal from the islets located more centrally is completely recovered, because radioactivity sampling is performed over all voxels of the pancreas. Here, we are not quantifying signal from individual islets. Unlike the situation with detection by ^{18}F-FDG PET of small lung nodules surrounded by air-filled lung tissue containing practically no activity, the pancreas is in the abdomen, and surrounding soft-tissue background activity mitigates the partial-volume effect for the peripheral voxels. However, implementation of partial-volume correction or resolution recovery would improve the accuracy of PET quantification of the pancreas. For PET of the brain, particularly for the thin cortical gray matter, partial-volume correction should improve the quality of PET brain images. For example, absolute quantification of glucose utilization of the thin cortical gray matter in tiny mouse brains (each brain measuring about 1 g) using small-animal ^{18}F-FDG PET (1.5 mm in full width at half maximum) underestimated slightly by 8% that quantified by the autographic 2-^{14}C-deoxyglucose method in the same animals (*11*).

Finally, we agree that ^{18}F-FDG PET is an excellent method for tracking the viability of transplanted islet cells in the subcutaneous space. Although the subcutaneous location of the transplant is favorable in minimizing the partial-volume effects, the signal intensity of ^{18}F-FDG uptake in the transplant is relatively low (standardized uptake value of 1–3). We believe that one key consideration for successful and accurate PET that targets islets and, more specifically, β-cells within the islets is the availability of tracers that can show high target-to-noise ratios. Our preclinical experiments suggest that PET targeting VMAT2 is also feasible for imaging transplanted islets and does not suffer from the need to label islets before transplantation (*12*).

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Errata

In the article "Assessment of Tumoricidal Efficacy and Response to Treatment with ^{18}F-FDG PET/CT After Intraarterial Infusion with the Antiglycolytic Agent 3-Bromopyruvate in the VX2 Model of Liver Tumor," by Liapi et al. (*J Nucl Med*. 2011;52:225–230), an acknowledgment of support from the Abdulrahman A. Abdulmalik Research Fund was inadvertently omitted. The authors regret the omission.

In the article "SNM Practice Guideline for Sodium ^{18}F-Fluoride PET/CT Bone Scans 1.0," by Segall et al. (*J Nucl Med.* 2010;51:1813–1820), the first paragraph of Section III, Definitions, incorrectly states that no applications for an Investigational New Drug have been filed with the U.S. Food and Drug Administration for ^{18}F. The corrected paragraph is shown below. The authors regret the error.

^{18}F is a diagnostic molecular imaging agent used for identification of new bone formation. ^{18}F, administered as intravenous Na^{18}F, was approved by the U.S. Food and Drug Administration in 1972 but has been listed as a discontinued drug since 1984. In 2000, the Food and Drug Administration listed it in the Orange Book for discontinued drug products. The original approval in 1972 may be used as a basis to reapply for marketing approval via a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA). Several clinical trials are currently using Na^{18}F with Investigational New Drug exemptions. In December 2008, the National Cancer Institute filed an NDA for a different potency and dose from the original NDA. Presently, Na^{18}F is manufactured and distributed for clinical use by authorized user prescription under state laws of pharmacy. In December 2011, Na^{18}F for clinical use will have to be prepared under an NDA or ANDA and meet the cGMP requirements of 21 CFR 212.