

Pancreatic Imaging with ^{11}C -Dihydratetabenazine PET: A Perspective

Historically, the pancreas has been a difficult organ to image because of its retroperitoneal location and overlying visceral organs. Over the past 2 decades, however, the advent of CT and MRI has allowed clinicians to correlate clinical symptoms with anatomic structure. These additional anatomic data revolutionized the evaluation of many disease processes of the pancreas, such as pancreatitis. Unfortunately, these imaging modalities do not describe organ function or easily separate the endocrine from the exocrine pancreas. Specifically, the ability to quantify and monitor β -cell mass (BCM) is of particular

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importance to the study of diabetes. Although many investigations have focused on this area, to date there is no reliable noninvasive method for quantifying BCM.

Diabetes mellitus (DM) and movement disorders such as Parkinson's disease (PD) are caused by loss of β -cells and dopaminergic neurons, respectively. Also, several gene products, including some that are related to monoamine transport and metabolism, are common to these cell types. Thus, tracers that have been used for studying monoamine physiology in movement disorders may be useful for evaluating β -cell function in DM. PET and SPECT of monoamine transport for the evaluation of patients with PD and other

movement disorders (1) have been performed with 3 types of ligands. The first type is agents that bind to the pre-synaptic cellular membrane, such as ^{11}C -labeled 2-carbomethoxy-3-(4-fluorophenyl) tropane (2), ^{11}C -methylphenidate (3), and $^{123}\text{I}/^{11}\text{C}$ -labeled 2 β -carbomethoxy-3 β -(4-fluorophenyl)-*N*-(1-iodoprop-1-en-3-yl)nortropine (4). The second type of tracers that target the vesicular monoamine transporter system includes agents such as ^{11}C -dihydratetabenazine, ^{11}C -DTBZ (5). The third type is agents that reflect dopamine decarboxylase activity, such as ^{18}F -labeled 3,4 dihydroxyphenylalanine, ^{18}F -DOPA (1). Recently, the scope of monoamine imaging has been extended to patients with pancreatic pathology.

Although by far the largest number of clinical and research studies of monoamine transport and metabolism in neurodegenerative diseases have used ^{18}F -DOPA, tracers with selectivities for the dopamine transporter (2–4, 6–8) and the vesicular monoamine transporter, VMAT2 (5,8), have also been used for PET assessment of the status of nigrostriatal neurons in PD patients. In a recent study, striatal uptake of FD as an index of DOPA decarboxylase activity was compared with striatal uptake of ^{11}C -labeled methylphenidate and dihydratetabenazine, which are tracers of dopamine transporter and VMAT2 densities, respectively (9). In this investigation, 3 consecutive PET studies with the 3 ligands were performed on 35 PD patients and 16 age-matched healthy subjects. The results demonstrated that the reduction in binding potential (maximum number of binding sites divided by the dissociation constant) in the PD patients was much greater with ^{11}C -methylphenidate than with ^{11}C -DTBZ, whereas the

FD influx constant was least affected, consistent with the tendency of residual striatal cells in PD patients to maintain synaptic dopamine concentrations by upregulation of DOPA decarboxylase activity and downregulation of the dopamine transporter. These findings suggest that although dopamine transporter ligands are probably the most sensitive tracers for detecting early PD, VMAT2 ligands may provide the best fidelity for quantifying the number of residual dopaminergic cells.

Similar to the loss of dopaminergic neurons in PD and other movement disorders, DM results from either an absolute or a relative reduction in BCM that leads to inadequate insulin secretion and hyperglycemia. Currently, measurement of insulin secretory capacity is used as a surrogate measure of BCM. Although these measurements are of some value, serum insulin levels are an imprecise index of BCM. Direct measurement of insulin levels in blood draining from the pancreas is a more accurate procedure but is invasive and difficult to perform. Clearly, a noninvasive PET method for evaluating BCM would be of great value both clinically and for evaluating new therapies for treating DM.

Despite their different embryologic origins, many gene products that display functional similarities are common to β -cells and dopaminergic neurons. Specific examples of these proteins include DOPA decarboxylase (a key enzyme in monoamine biosynthesis), monoamine transporters (concentrate monoamines from the extracellular space to the cytosol), and vesicular monoamine transporters (concentrate monoamines into storage granules).

To date, only 2 PET tracers have been used for imaging β -cell function and mass. Although several studies using

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the DOPA decarboxylase substrate ^{18}F -DOPA have been reported, it remains unclear whether this tracer is of value for imaging normal β -cells in adults. However, hyperinsulinemia of infancy, a neuroendocrine condition characterized by either focal adenomatous hyperplasia or diffusely increased insulin secretion by the pancreas, is clearly evaluable with this ligand. Ribeiro et al. (10–12) were the first to report on the use of ^{18}F -DOPA PET for differentiating between focal and diffuse hyperinsulinemia of infancy, and their findings were subsequently verified by other investigators (13–18). When uptake of ^{18}F -DOPA was focal, immunocytochemical analysis of surgical specimens confirmed the diagnosis of focal disease. In contrast, when a diffuse pattern of ^{18}F -DOPA uptake was observed, immunocytochemical analysis revealed distribution of abnormal β -cells throughout the pancreas. In general, the immunocytochemical results closely matched the PET data and demonstrated colocalization of proinsulin and DOPA decarboxylase.

These findings clearly establish the value of ^{18}F -DOPA in the evaluation of hyperinsulinemia of infancy. Unfortunately, however, ^{18}F -DOPA has several disadvantages as a tracer: a complex procedure is required for its preparation, synthetic yields are poor, and target-to-background ratios tend to be low. Other tracers, such as ligands that target VMAT2 (i.e., ^{11}C -DTBZ), could be of even greater value for studying hyperinsulinemia of infancy, and additional studies with these agents are warranted.

PET studies of VMAT2 pathophysiology are in their infancy; however, several important studies have been published by the group at Columbia University (19–21). In an investigation (19) with ^{11}C -DTBZ, they demonstrated decreased radioligand uptake in the pancreas of Lewis rats with streptozotocin-induced diabetes, compared with euglycemic historical controls. This study suggested that quantitation of VMAT2 expression in β -cells with ^{11}C -DTBZ and PET represents a method for noninvasive longitudinal estimates of changes

in BCM that may be of value in the study and treatment of diabetes. In another study (20), they used ^{11}C -DTBZ to estimate BCM in a rat model of spontaneous type 1 DM (the bio-breeding diabetes-prone rat). In longitudinal PET studies, they demonstrated a significant decrease in pancreatic uptake of ^{11}C -DTBZ that anticipated loss of glycemic control. Comparisons of standardized uptake values (SUVs) of ^{11}C -DTBZ and blood glucose concentrations demonstrated that a 65% decrease in baseline SUV correlated significantly with the development of persistent hyperglycemia. These studies further supported the notion that PET-based quantitation of VMAT2 provides a noninvasive measurement of BCM that may be useful for studying the pathogenesis of diabetes and monitoring therapeutic interventions. In a PET study of ^{11}C -DTBZ in baboons (21), these investigators demonstrated that most of the injected tracer localized to liver and lungs, followed by the intestines, brain, and kidneys. The highest estimated absorbed radiation dose was in the stomach wall, and the dosimetry of doses proposed for human imaging was determined to be safe.

In this issue of *The Journal of Nuclear Medicine* (22), the same group of investigators extend their studies to healthy human volunteers ($n = 9$) and patients with long-standing type 1 DM ($n = 6$). In this study, VMAT2 binding potential (BP_{ND}) was estimated voxel-wise using renal cortex as reference tissue, and the functional binding capacity (the sum of voxel $BP_{\text{ND}} \times$ voxel volume) was calculated as an index of total pancreatic VMAT2. Pancreatic BP_{ND} , functional binding capacity, and stimulated insulin secretion measurements were compared between groups. The results of this study demonstrated that mean pancreatic BP_{ND} was decreased to 86% of control values in type 1 DM (1.86 ± 0.05 vs. 2.14 ± 0.08 , $P = 0.01$), and BP_{ND} correlated with stimulated insulin secretion in controls but not in type 1 DM ($r^2 = 0.50$, $P = 0.03$). In addition, mean functional binding capacity was decreased by at least 40% in

patients with type 1 DM, compared with controls ($P = 0.001$). The decreases in functional binding capacity and BP_{ND} were significantly less ($P = 0.001$) than the near-complete loss of stimulated insulin secretion observed in type 1 DM. In general, it was concluded that PET with ^{11}C -DTBZ can be used to quantify VMAT2 binding in the human pancreas. However, given the near-complete depletion of BMC in long-standing type 1 DM (detected by tissue sampling), BP_{ND} and functional binding capacity appeared to overestimate BCM. This overestimation may be due to higher nonspecific binding in pancreas than in renal cortex. In this context, it is not clear why the authors dismissed skeletal muscle as a reference tissue. As correctly pointed out by the authors, ^{18}F -labeled VMAT2 ligands with lower nonspecific binding and the potential for delayed imaging may be more suitable for the clinical evaluation of BCM.

Although not as yet investigated, ^{18}F -DOPA could also be useful for studying BCM in type 1 DM. However, with this tracer the same issues related to reference tissue selection exist. Moreover, as in the case of using ^{18}F -DOPA for the evaluation of patients with movement disorders, upregulation of DOPA decarboxylase activity in residual β -cells in patients with long-standing type 1 DM could diminish the expected reduction in tracer uptake. Similar considerations might exist for studies with ligands that are specific for membrane monoamine transports. Although these membrane proteins tend to be down-regulated in movement disorders in order to maintain monoamine levels in the synaptic cleft, this may not be the case in pancreatic tissue of patients with type 1 DM; in fact, there may be upregulation. These issues definitely require further investigation.

Neurofunctional imaging appears to be a new approach that may overcome many of the deficiencies found with other imaging techniques. The combination of ^{11}C -DTBZ and PET appears to represent a noninvasive means to monitor BCM quantitatively. This technique may represent a modality to

monitor the endocrine pancreas in real time. The ability to accurately monitor BCM in vivo may allow for more insightful investigation of agents that stimulate β -cell regeneration or inhibit β -cell destruction. In the future, this noninvasive technique may complement or ultimately replace other pancreatic imaging modalities used to identify abnormal or aberrant BCMs.

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