^{18}F-DOPA PET and PET/CT

In the study of Timmers et al. (*1*) published in this issue of *The Journal of Nuclear Medicine,* 11 patients with pheochromocytoma and extraadrenal abdominal paraganglioma were evaluated with ^{18}F-dihydroxyphenylalanine (DOPA) PET at baseline and after carbidopa administration. This inhibitor of peripheral aromatic amino acid decarboxylase is already known to increase tracer availability in the striatum for central nervous system studies, but preliminary results from Timmers et al. indicate that it also enhances ^{18}F-DOPA PET sensitivity (from 47.4% to 50%) for the detection of neoplastic lesions.

Since the 1980s, ^{18}F-DOPA has been synthesized and used as a positron-emitting compound for PET examination of patients affected by Parkinson's disease (*2*). Subsequently, other clinical applications have arisen, beginning in the field of oncology (brain tumors and neuroendocrine tumors) and continuing up to the newest applications, such as the evaluation of primary hyperinsulinemia in pediatric patients. Despite ^{18}F-DOPA's being a promising PET radiopharmaceutical, precise clinical indications have not yet been assessed, and the published literature is based on preliminary results and small

patient populations both for applications in neurology and for applications in oncology.

L-DOPA (L-dihydroxyphenylalanine) is the immediate precursor of dopamine, a neurotransmitter in the central nervous system predominantly found in the nigrostriatal region, and defects in this region are strongly related to neurodegenerative and movement disorders (*3*). Although dopamine in the circulation does not cross the blood–brain barrier, L-DOPA is carried into the brain by the large neutral amino acid transport system, converted into dopamine by the action of L-aromatic amino acid decarboxylase (*4*), and then stored in intraneuronal vesicles, from which it is released when the nerve cell fires. Because ^{18}F-DOPA is an analog of L-DOPA, this positron-emitting compound is clinically used to trace the dopaminergic pathway and to evaluate striatal dopaminergic presynaptic function (*5–7*).

The large neutral amino acid transport system is highly expressed not only in the nigrostriatal region as a physiologic feature of normal brain but also in brain tumors as a pathologic feature, causing an increased uptake of amino acids, compared with that in normal brain. Because of this observation, some researchers have used ^{18}F-DOPA for the functional evaluation of brain neoplasms (*8,9*).

A similar characteristic is present in extracranial APUD tumors. APUD, or "amine precursor uptake and decarboxylation," indicates the capacity to take up amino acids and transform them into biogenic amines by means of decarboxylation. Having that capacity is why APUD tumors show a markedly increased uptake of ^{18}F-DOPA and can be evaluated by means of ^{18}F-DOPA PET (*10*). Like APUD tumors, normal islets in the pancreas also take up a small amount of ^{18}F-DOPA and decarboxylate it to produce insulin. In hyperfunctioning islets (as in cases of insulinomas or primary hyperinsulinemia), the uptake can be quite pronounced, and ^{18}F-DOPA PET can be of value for evaluating those patients (*11*).

Parkinson's disease is a slowly progressive disorder characterized by degeneration of dopaminergic neurons in the substantia nigra. In the early phase of disease, clinical signs may be subtle or can be confused with other, parkinsonism-related disorders, such as multiple-system atrophy, progressive supranuclear palsy, corticobasal degeneration, or essential tremor. Furthermore, the clinical diagnosis can be influenced and complicated by symptomatic medication. Considering these factors, in vivo markers of dopaminergic degeneration are important for the early diagnosis and monitoring of disease progression, and neuroimaging procedures (e.g., ^{18}F-DOPA PET and ^{123}I-*N*-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)nortropane [FP-CIT] SPECT for the presynaptic dopaminergic system) can help clinicians in selected cases.

Although ^{18}F-DOPA is used less frequently than ^{123}I-FP-CIT in the clinical setting because of the need for a cyclotron-based radiopharmacy and the relative complexity of the synthesis (*12*), ^{18}F-DOPA has been shown to be as accurate as ^{123}I-FP-CIT and to reasonably correlate with motor scores and disease duration (*13*). ^{18}F-DOPA and ^{123}I-FP-CIT, in fact, demonstrate 2 different aspects of the presynaptic dopaminergic system, the first reflecting the activity of the decarboxylating enzyme and the storage capacity of dopamine (*5,14*) and the second reflecting the activity of the transmembrane dopamine transporter (*15*). For

this reason, some authors avoid comparing these methods with each other.

Despite discordant results in the literature, it seems that in the early phases of Parkinson's disease the decarboxylating enzyme can be upregulated as a compensatory phenomenon, and the uptake of ^{18}F-DOPA may be normal even in parkinsonian patients. In contrast, the dopamine transporter is downregulated, making ^{123}I-FP-CIT SPECT more sensitive for the early detection of Parkinson's disease (16). For monitoring disease progression, the 2 compounds are theoretically equivalent, and ^{18}F-DOPA, despite significantly higher costs, may have advantages over ^{123}I-FP-CIT in the length of the procedure and the quality of the images.

The second major application of ^{18}F-DOPA PET is in oncology, for the evaluation of neuroendocrine tumors. Neuroendocrine tumors have an increased L-DOPA decarboxylase activity and therefore show marked ^{18}F-DOPA uptake on PET examinations. The first example of neuroendocrine tumor visualization using a DOPA-labeled tracer goes back to 1995, but published papers on this topic are still few. The widespread and effective application of ^{123}I/^{131}I-MIBG and ^{111}In-pentetreotide in clinical practice probably reduces the need for another tracer specific for neuroendocrine tumors, and the high cost and difficulty of the radiochemical synthesis of ^{18}F-DOPA prevent the routine use of this compound.

Preliminary studies by some research groups have shown that ^{18}F-DOPA PET is useful for detecting primary and metastatic neoplastic diseases of neuroendocrine differentiation (carcinoids, gastroenteropancreatic tumors, glomus tumors, medullary thyroid cancer, small cell lung cancer, and pheochromocytoma) (10,17–22), but larger studies are needed to assess the sensitivity, specificity, and accuracy of this new diagnostic procedure, especially in comparison to the well-established use of ^{123}I/^{131}I-metaiodobenzylguanidine and ^{111}In-pentetreotide.

^{18}F-DOPA PET/CT hybrid systems and the related positron-emitting compounds are characterized by a significantly higher spatial resolution than that of SPECT γ-emitting compounds and allow accurate localization of hot spots because of the anatomic map provided by CT. Thus, a possible clinical indication for PET could be patients whose clinical symptoms and biochemical analysis are strongly consistent with neuroendocrine tumor but for whom conventional imaging procedures (^{123}I/^{131}I-metaiodobenzyl-guanidine, ^{111}In-pentetreotide, and contrast-enhanced CT and MRI) have failed to identify a tumor. Furthermore, because the examination is short (the whole procedure from injection to end of acquisition lasts less than 2 h), ^{18}F-DOPA PET could be performed on weaker patients.

Another rising application of ^{18}F-DOPA PET is the evaluation of congenital hyperinsulinemia, which is the most common cause of persistent hypoglycemia in infants and is associated with a recessive mutation of the β-cell ATP-sensitive potassium channel. The channel is encoded by 2 adjacent genes: A diffuse disease involving the whole pancreas develops when both genes are mutated, whereas a recessive mutation may cause focal adenomatosis. The result is a dysregulation of the production of insulin (23,24). Surgical intervention is frequently necessary to control the disorder but is curative only for focal lesions. Functional tests cannot distinguish between the 2 forms, and imaging techniques (contrast-enhanced CT, MRI, ^{111}In-pentetreotide, and transabdominal or intraoperative ultrasound) do not detect focal adenomas, which are rarely identifiable even during surgical intervention.

In view of the ability of pancreatic β-cells to take up amino acids, ^{18}F-DOPA PET/CT was studied for the ability to distinguish diffuse from focal hyperinsulinemia and to localize the areas of disease to be removed. The preliminary results were encouraging, and the accuracy of this technique seemed to range from 96% to 100% for the diagnosis of focal or diffuse disease and for the localization of focal lesions (11).

^{18}F-DOPA PET has also been studied for applications such as the detection of brain tumors and the localization of adenoma in patients with primary hyperparathyroidism, but incomplete or negative results precluded an eventual clinical application (8,25). According to the published literature, despite its high potential, ^{18}F-DOPA PET and PET/CT are still underused in clinical practice for oncologic purposes, although wider application of the techniques is being considered for movement disorders.

In their paper, Timmers et al. (1) highlight the importance of administering carbidopa not only for ^{18}F-DOPA-PET studies of the central nervous system but also for oncologic studies. The finding of increased sensitivity after carbidopa is of great importance and should stimulate further studies of ways to maximize the sensitivity of PET.

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