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Médecine Nucléaire 40 (2016) 20–30
Médecine Nucléaire
Imagerie Fonctionnelle et Métabolique

General Review

The current role of ^{18}F-FDOPA PET for neuroendocrine tumor imaging

Place actuelle de la TEP à la ^{18}F-FDOPA dans les tumeurs neuroendocrines

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Received 26 November 2015; accepted 4 January 2016
Available online 4 February 2016

Abstract

This review discusses the clinical value of ^{18}F-dihydroxyphenylalanine positron emission tomography-computed tomography (^{18}F-FDOPA PET/CT) across the spectrum of neuroendocrine tumors (NETs). The rationale for ^{18}F-FDOPA imaging is generally based on the ability of NETs to take up and decarboxylate amine precursors. The kinetics of tumor uptake and retention varies according to tumor type. For some tumor types, the imaging protocol might include early-time acquisitions in order not to miss cases with rapid washout, or carbidopa premedication to overcome physiological pancreatic uptake. The roles of ^{18}F-FDOPA PET/CT imaging will be examined in diverse settings of patients with MTC, digestive NET, congenital hyperinsulinism and pheochromocytomas/paragangliomas. In each clinical setting, the diagnostic accuracy of ^{18}F-FDOPA PET/CT is compared to that offered by conventional imaging methods or other PET tracers, such as ^{68}Ga-labeled somatostatin analogs or ^{18}F-FDG.

Keywords: ^{18}F-FDOPA; PET; Neuroendocrine; Gastroenteropancreatic tumors; Medullary thyroid carcinoma; Paraganglioma; Congenital hyperinsulinism

Résumé

Cet article de revue discute le rôle de la TEP à la ^{18}F-dihydroxyphénylalanine (^{18}F-FDOPA-TEP/TDM) dans le champ large des tumeurs endocrines. Le rationnel de l'utilisation de la ^{18}F-FDOPA est la capacité que présentent certaines tumeurs endocrines à capter et décarboxyler les amines et leurs précurseurs, d'où le terme système APUD (*amine precursor uptake and decarboxylation*). Toutefois, les cinétiques de captation et de rétention de la ^{18}F-FDOPA varient fortement selon le type tumoral. Ainsi, pour certaines tumeurs endocrines, la réalisation d'images précoces est nécessaire pour ne pas méconnaître une tumeur à relargage rapide (*rapid washout*). Par ailleurs, une prémédication par la carbidopa est utile

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http://dx.doi.org/10.1016/j.mednuc.2016.01.003

dans certaines indications pour diminuer la captation pancréatique physiologique. Les indications actuelles de la TEP/TDM à la ^{18}F-FDOPA seront examinées en fonction des différents contextes cliniques tels que : cancer médullaire de la thyroïde, tumeurs endocrines gastro-entéro-pancréatiques, hyperinsulinisme congénital et insulinome, phéochromocytome/paragangliome. Les valeurs diagnostiques de la TEP/TDM à la ^{18}F-FDOPA seront comparées à celles offertes par les moyens d'imagerie « conventionnelle » ou par d'autres traceurs TEP comme les analogues de la somatostatine marqués au gallium-68 et le ^{18}F-FDG.

Mots clés : ^{18}F-FDOPA ; TEP ; Tumeurs neuroendocrines ; Tumeurs gastro-entéro-pancréatiques ; Cancer médullaire de la thyroïde ; Paragangliome ; Hyperinsulinisme congénital

1. Introduction

In the past two decades, we have experienced a progressive development of nuclear medicine imaging techniques for neuroendocrine tumours (NETs) mainly related to the better understanding of tumoral properties, the introduction of new radiolabeled probes and the growing availability of high-resolution SPECT/CT and PET/CT instruments allowing hybrid ''morpho-functional'' imaging.

The cellular ability to take up, accumulate, and decarboxylate amine precursors and amino acids have been taken into account for the development of diagnostic radiotracers for nuclear medicine imaging [1]. Accordingly, radiolabeled amino acids such as dihydroxyphenylalanine (DOPA) have been successfully proposed as imaging agents for in vivo tumor visualization [2]. For nuclear imaging of NETs, DOPA is labelled with ^{18}F (^{18}F-FDOPA). Once internalized, ^{18}F-FDOPA is decarboxylated to ^{18}F-dopamine in some tumors (i.e., PGLs, midgut NET), transported and stored into secretory vesicles. Therefore, the high uptake of ^{18}F-FDOPA in NETs is the result of the increased synthesis, storage and secretion of biogenic amines such as dopamine and serotonin [3,4].

^{18}F-FDOPA was initially developed to investigate the striatal system and the dopaminergic neurotransmission pathways. Later, we observed a progressive utilization of ^{18}F-FDOPA positron emission tomography (PET) to image a variety of NETs and pancreatic β-cell hyperplasia. At present, ^{18}F-FDOPA PET is recommended and largely used in several clinical situations [4,5], directly influencing patient management with good outcomes. Due to the wide clinical interest and demand, currently, ^{18}F-FDOPA is a commercial radiotracer largely available in Europe from different suppliers in the setting of the marketing authorization (MA).

The present review focuses on the main clinical applications of ^{18}F-FDOPA PET while also discussing its strengths and limitations in comparison to the other nuclear medicine techniques that are currently available for the clinical management of patients with NETs.

2. ^{18}F-FDOPA molecular, pharmacological and radiochemical issues for NET imaging

The accumulation of amine precursors relies on the well-known ability of NETs to decarboxylate such substrates due to the aromatic L-amino acid decarboxylase (AADC) enzyme. This metabolic pathway was first described in 1969 as APUD (amine precursor uptake and decarboxylation) [1]. Increased expression of AADC has been found to be a hallmark for some NETs [6]. ^{18}F-FDOPA accumulation in NET cells encompasses the entrance of the tracer through the L-amino transporter (mainly the LAT-1 and LAT-2), which is up-regulated to cover the increased demand for precursors. Later, the decarboxylation by the AADC leads to the formation of ^{18}F-Fdopamine, which is subsequently stored in intracellular vesicles through vesicular transporters (VMATs) [7] (Fig. 1). However, it has been suggested that this storage method might not be effective in all NET cells [8]. Other amino acid tracers that use the same transmembrane transport system such as ^{11}C-methionine, ^{11}C-tyrosine, and ^{123}I-methyltyrosine do not accumulate to the same extent in NET cells, which strongly suggests that overexpression of LATs is not the only factor that leads to the high uptake of ^{18}F-FDOPA. It seems that metabolism by AADC plays a central role [9]. Thus, the oral premedication by carbidopa (CD), a peripheral AADC inhibitor, should be regarded as an important issue [10]. A recent animal study [11] reported that different pharmacological inhibitors of the catecholamine-0-methyl transferase (COMT), the monoamine oxidase (MAO) or the VMAT lead to specific metabolite uptake patterns that may have certain clinical applications. Finally, a novel synthetic radiochemical approach may allow a better understanding of ^{18}F-FDOPA molecular pathways. Electrophilic substitution strategy for the production of ^{18}F-FDOPA is the conventional labeling method, which has suffered from a quite low radiochemical yield due to the difficulty of generating and handling $18F_2$ [12]. Moreover, a large amount of carrier ^{19}F-FDOPA is generated during the electrophilic process, which in turn leads to relative low specific activity. Radiopharmaceutical manufacturers are on their way to implement a new nucleophilic substitution radiosynthesis process that should be easier, more reliable and that will reduce the total mass administered (no carrier added and higher specific activity). A recent study by Kuik et al. [12] reported slight uptake differences between low and high specific activity of ^{18}F-FDOPA in vitro (BON cells). The authors reported a significantly higher uptake for high specific activity ^{18}F-FDOPA in these cells after tetrabenazine pretreatment (a VMAT inhibitor), which may be due to a differential filling degree of the vesicles since the tracer might be present at lower concentrations than endogenous substrates. Although ^{18}F-FDOPA should be