[18F]6-fluoro-3-O-methyl-L-3,4-dihydroxyphenylalanine

[^{18}F]OMFD

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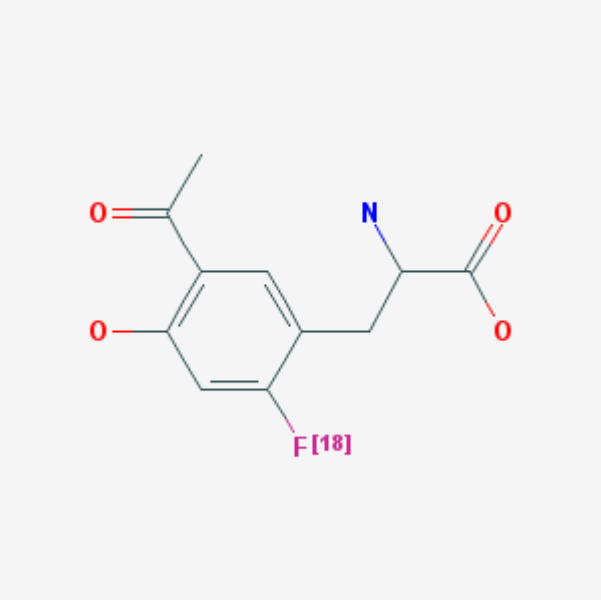
Chemical name:	[^{18}F]6-fluoro-3-*O*-methyl-L-3,4-dihydroxyphenylalanine
Abbreviated name:	[^{18}F]OMFD
Synonym:	3-*O*-methyl-6-[^{18}F]-fluoro-L-DOPA
Agent Category:	Compound
Target:	L amino acid transporters (LAT)
Target Category:	Binding
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Non-Primate Mammals • Humans



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Background

[PubMed]

Although ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is considered the gold standard for the detection of tumors using positron emission tomography (PET), the use of this agent as a tumor diagnostic agent has a limitation (1, 2): the uptake of ^{18}F-FDG by cells is based on the glucose transport system. An increased glucose metabolism is a characteristic feature of cancer cells, so this feature can be used to distinguish the neoplastic from normal cells. However, because the uptake of ^{18}F-FDG is nonspecific, use of this agent does not distinguish between cells that are cancerous and those that take up ^{18}F-FDG because of other etiologies such as inflammation, infection, or even brown fat or granulomas, etc (2). Also, slow-growing malignant tissues (such as prostate tumors) might not show an increased glucose metabolism and thus can not be detected with ^{18}F-FDG (3). As a consequence, many other radiolabeled ligands, such as amino acids or their derivatives, have been developed and used for the detection and diagnosis of malignant tumors (1).

In this regard, methionine labeled with radioactive carbon (as ^{11}C) has been developed and extensively evaluated for the detection of neoplastic lesions. However, because the label has a short half-life, several ^{18}F amino acid analogs have been generated and studied for the diagnosis of neoplastic lesions with PET (4). An increased uptake of amino acids that correlated with upregulation of the amino acid transport system in proliferating cells was observed, and this resulted in a high tumor/normal tissue ratio regardless of the cell cycle phase (4, 5). In the pursuit of developing agents for the detection of cancers, investigators have evaluated a phenylalanine derivative, 3-*O*-methyl-6-^{18}F-fluoro-L-3,4-dihydroxyphenylalanine (^{18}F-OMFD), for tumor imaging (6, 7). ^{18}F-OMFD was shown to be taken up by neoplastic cells and has been suggested to be suitable for the detection of squamous cell head and neck carcinoma by imaging (8).

Synthesis

[PubMed]

The synthesis of ^{18}F-OMFD has been detailed by Füchtner and Steinbach (9). Briefly, a precursor of ^{18}F-OMFD, *N*-formyl-3-*O*-methyl-4-*O*-ditert-butyldicarbonate-6-trimethyl-stannyl-L-dihydroxyphenylalanine-ethyl ester was derived from *N*-formyl-3,4-*O*-ditert-butyldicarbonate-6-trimethylstannyl-L-dihydroxyphenylalanine-ethyl ester as described by Namavari et al. (10). The precursor was dissolved in trichlorofluoromethane at room temperature and reacted with gaseous ^{18}F-fluorine while the temperature was decreased to -20^{o}C. Subsequently, 12 M hydrochloric acid was added to the reaction mixture and the temperature was increased to 70^{o}C. Excess solvent was evaporated by blowing gaseous nitrogen through the mixture. The reaction vessel was then closed, and a partial hydrolysis of the products was allowed to proceed at 130^{o}C for 10 min at an elevated pressure. Subsequently, ^{18}F-OMFD was separated from the reaction mixture by high-performance liquid chromatography on a C-8 column. The total time taken for preparation at the end

of bombardment was 50 min with a yield of 20–25% (decay corrected, as related to ^{18}F-fluorine). The radiochemical purity of ^{18}F-OMFD was >98% with a specific activity of ~20 GBq/mmol (540 mCi/mmol) in ~50 preparations (9).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The *in vitro* uptake of ^{18}F-OMFD was investigated in HT-29 (of human colon adenocarcinoma origin), FaDu (of squamous cell carcinoma origin), and RBE4 (of rat brain origin) cell lines in the presence or absence of a competitive transport inhibitor such as 2-aminobicyclo-[2,2,1]-heptane-2-carboxylic acid and α-(methylamino)isobutyric acid plus serine and with or without sodium (6). The transport of ^{18}F-OMFD was shown to be mediated primarily through a high-capacity, sodium-independent, amino acid transport system, and the FaDu cells showed the highest uptake.

Animal Studies

Rodents

[PubMed]

Using PET, Haase et al. investigated the uptake of ^{18}F-OMFD in mice bearing FaDu or HT-29 cell xenograft tumors (8). Maximum radioactivity was observed to accumulate in the tumors and the pancreas in both tumor models. The uptake was higher in the FaDu tumors with a standardized uptake value (SUV) of 3.07 ± 0.66 compared to 1.19 ± 0.26 for the HT-29 cell tumors. From this study the investigators concluded that ^{18}F-OMFD could be used for the detection of poorly differentiated, squamous cell tumors in the head and neck (8).

Other Non-Primate Mammals

[PubMed]

The transport of ^{18}F-OMFD and ^{18}F-dihydroxyphenylalanine (^{18}F-DOPA) across the blood–brain barrier (BBB) was investigated with PET in pigs of different ages (11). The transport rate of both neutral amino acids across the BBB was observed to decrease as the brains of the animals developed, but the cerebral blood flow and the plasma concentrations of these amino acids did not change during brain development. The transport of ^{18}F-OMFD and ^{18}F-DOPA was mediated primarily by the L amino acid transporter 1. Data from the study indicated that developmental changes of the transporter system for neutral amino acids in these animals after birth lead to a decrease in the BBB permeability for these amino acids during brain development.

Non-Human Primates

[PubMed]

No references are currently available

Human Studies

[PubMed]

The use of ^{18}F-OMFD for brain tumor imaging and whole-body biodistribution was studied using PET in humans (7). With this technique, 16 of 19 studied patients were suspected to have viable brain tumors with a standardized uptake value of 3.0 ± 0.8 and a tumor/non-tumor ratio of 1.9 ± 0.5. Maximum uptake of the label was observed between 15 and 30 min after administration with a subsequent slow decrease in uptake. The label did not accumulate in any specific organ and was eliminated through the urinary system (7). The investigators caution that, although ^{18}F-OMFD appears to be a suitable agent to image brain tumors, because it has been evaluated in only a small number of patients it remains to be demonstrated that it is as specific as *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine to differentiate between a tumor and inflammation or as promising as 3-[^{18}F]fluoro-L-α-methyl-tyrosine to image malignant tumors (7).

In another study, the use of ^{18}F-OMFD was compared to that of ^{18}F-FDG and ^{18}F-DOPA for the diagnosis of metastatic medullary thyroid carcinoma (MTC) (12). With results from this study the investigators concluded that, although ^{18}F-FDG and ^{18}F-DOPA could detect highly suspicious foci, suggesting local recurrence or metastasis of MTC, the foci were not detected with ^{18}F-OMFD.

Supplemental Information

[Disclaimers]

References

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