[^{18}F]Fluoromethyl-D-tyrosine

D-[^{18}F]FMT

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Chemical name:	[^{18}F]Fluoromethyl- D-tyrosine	
Abbreviated name:	D-[^{18}F]FMT	
Synonym:		
Agent Category:	Compound	
Target:	L-amino acid transporter 1	
Target Category:	Transporter	
Method of detection:	Positron emission tomography (PET)	
Source of signal / contrast:	^{18}F	
Activation:	No	
Studies:	• *In vitro* • Rodents	Structure not available in PubChem.

Background

[PubMed]

Cancerous tumors are formed by characteristically high levels of proliferating cells that have a constant high requirement for basic building blocks such as carbohydrates, nucleotides, and amino acids (AA) to maintain a suitable metabolic rate and to continue the synthesis of macromolecules such as DNA and proteins to sustain their phenotype (1). Because of the high carbohydrate demand of tumor cells, (^{18}F)fluorodeoxy-glucose ((^{18}F)FDG), which is not metabolized by the cells and as a consequence accumulates in neoplastic tumors, was developed to screen for cancers using positron emission tomography (PET) imaging. Although shown to be suitable for the detection of certain cancers (2), the main limitation of using (^{18}F)FDG to detect tumors is that it tends to accumulate in some normal tissues (e.g., brain and heart) and inflamed tissues (3-5).

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Therefore, several ^{11}C- and ^{18}F-labeled AAs and their analogs, including L- and D-methyl-^{11}C-methionine (L- and D-(^{11}C)MET) and L- and D-*O*-(^{18}F)fluoromethyl-tyrosine (L- and D-(^{18}F)FMT), were developed as an alternative and have been evaluated for the uptake by and PET imaging of normal and tumor tissues (6, 7).

Radiolabeled L-isomers of AAs behave like the naturally occurring compounds in a biological system, can be used for protein synthesis, are easily metabolized by mammalian cells, and have been shown to accumulate in non-target tissue in addition to tumors (8). In contrast, the D-isomers are unnatural and, compared with the L-isomers, ^{14}C-labeled D-amino acids have been shown to have a higher tumor accumulation (9-12). Although different AA transport systems are involved in the uptake of AAs, the AAs are transported primarily by the L AA transport systems (designated as LAT1 and LAT2), which are not sodium-dependent and can transport both the L- and D-isomers (7, 13), including those containing a branched chain or an aromatic moiety (14). Also, the LAT1 was reported to be expressed in the brain, spleen, placenta, and the testis (15) and was reported to be overexpressed in malignant tumors (16, 17). Tsukada et al. reported the tumor/blood uptake of the D-isomers of (^{18}F)FMT, (^{18}F)fluoroethyl-tyrosine, and (^{18}F)fluoropropyl-tyrosine in tumor-bearing mice was 181%, 137%, and 101%, respectively, compared with their L homologs, indicating that the D-isomers could be potential PET imaging agents (13). In another study, D-(^{18}F)FMT was suggested to be a better PET tracer than the L- and D-isomers of (^{11}C)MET because it showed lower accumulation in various normal organs and, compared with (^{18}F)FDG, did not accumulate in inflamed tissue (7). Urakami et al. studied the uptake of L- and D-(^{18}F)FMT in cultured cells under *in vitro* conditions and evaluated the use of these radiolabeled compounds for the imaging of abdominal and brain tumors in rats and mice, respectively (18).

Synthesis

[PubMed]

The L- and D-isomers of tyrosine were reacted with (^{18}F)fluoromethyl bromide to generate (^{18}F)FMT as described elsewhere (7, 13). Purity of the two enantiomers was determined with high-performance liquid chromatography using a CHIOBIOTIC T column with ethanol:water (1:1) as the eluent. (^{18}F)FDG was produced as detailed by Oberdorfer et al. (19). The specific activities of D-(^{18}F)FMT, L-(^{18}F)FMT, and (^{18}F)FDG were 115 ± 10, 126 ± 12, and 144 ± 21 GBq/μmol, respectively (3.10 ± 0.27, 3.40 ± 0.32, and 3.89 ± 0.56 Ci/μmol, respectively) (18). The radiochemical purities of D-(^{18}F)FMT, L-(^{18}F)FMT, and (^{18}F)FDG were 99.6 ± 0.4%, 99.8 ± 0.3%, and 100.0 ± 0.0%, respectively (18). The average time of radiochemical synthesis and the yield of these labeled compounds were not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Urakami et al. studied the uptake of d-(18F)FMT and l-(18F)FMT in rat C6 glioma and HeLa cells at select time points for up to 30 min after exposure to the radiochemicals (18). Both cell lines were reported to show a higher uptake of the l-isomer, and the uptake was not saturated even at 60 min. The release of both labeled isomers was studied using HeLa cells loaded with the l- and d-isomers, respectively, in AA-free medium and in presence or absence of excess l-leucine (100 μM) (18). Presence of l-leucine was reported to accelerate the release of both labeled isomers from the loaded HeLa cells. The uptake and release study indicated that the transport of the labeled d-isomer was lower than the transport of the l-isomer under in vitro conditions. In another study, the uptake of both labeled isomers in C6 glioma cells was reported to be inhibited by the presence of excess (1 mM) l-isomers of methionine, phenylalanine, and tyrosine. Uptake of the two labeled isomers was also inhibited by 2-aminobicyclo-(2,2,1)-heptane-2-carboxylic acid, a selective inhibitor of the l AA transport system, but no inhibition was observed with l-glycine. These results indicated that both the labeled isomers were transported by the l AA transport system (18). This observation was confirmed with a reverse-transcriptase polymerase chain reaction analysis of the C6 glioma and HeLa cells, and it was observed that only the LAT1 mRNA was expressed in both the cell lines.

Animal Studies

Rodents

[PubMed]

Urakami et al. evaluated the use of D-(^{18}F)FMT, L-(^{18}F)FMT, and (^{18}F)FDG, respectively, for PET imaging in normal tissue (left leg) and HeLa cell xenograft tumors (right leg) in mice (n > 3 animals for each radiocompound) (18). The standard uptake values (SUV) for D-(^{18}F)FMT and L-(^{18}F)FMT in the tumor tissue were 1.33 and 1.642, respectively, but these values were 0.488 and 0.874, respectively, in the normal tissue. Therefore, among these labeled compounds, D-(^{18}F)FMT was reported to show a more clear difference between the normal tissue and tumor tissue. Under the same experimental conditions, (^{18}F)FDG was reported to have a lower accumulation in the tumor compared with either (^{18}F)FMT isomer, and an uptake of the labeled carbohydrate derivative was also observed in the normal brain and heart of the animals.

Another study performed to image C6 glioma tumors in mouse brain (n = 5 animals per labeled compound) also showed that D-(^{18}F)FMT was a superior PET imaging agent compared with either L-(^{18}F)FMT or (^{18}F)FDG (18).

Tsukada et al. compared the use of D-(^{18}F)FMT to the use of O-^{11}C-methyl-D-tyrosine (D-(^{11}C)CMT) and to D- and L-(^{11}C)MET for the PET imaging of HeLa tumors in mice (n = 5 animals per labeled AA) (7). Although the tumor SUV levels of D-isomers of (^{11}C)MET, (^{11}C)CMT, and (^{18}F)FMT were 261%, 72%, and 95%, respectively, of the corresponding L-isomer of the AAs at 60 min after administration, the tumor/blood ratios of the D-isomers were reported to be 130%, 140%, and 182%, respectively, of the L-isomers. Also,

the D-isomers of the various labeled AAs had a much lower uptake in the abdominal organs compared with L-isomers of AAs. The investigators also compared the uptake of D- and L-(^{11}C)MET, D-(^{11}C)CMT, and D-(^{18}F)FMT to (^{18}F)FDG for the visualization of turpentine-induced inflammatory tissue in these animals (n = 5 mice per labeled AA) (7). Among these labeled compounds, only (^{18}F)FDG was reported to show a high accumulation in the inflamed tissue. From these studies the investigators concluded that the D-isomers of (^{11}C)CMT and (^{18}F)FMT were probably superior to L- and D-(^{11}C)MET for tumor imaging using PET.

Other Non-Primate Mammals

[PubMed]

No references are currently available.

Non-Human Primates

[PubMed]

No references are currently available.

Human Studies

[PubMed]

No references are currently available.

Supplemental Information

[Disclaimer]

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