O-(2-[^{18}F]Fluoroethyl)-L-tyrosine

[^{18}F]FET

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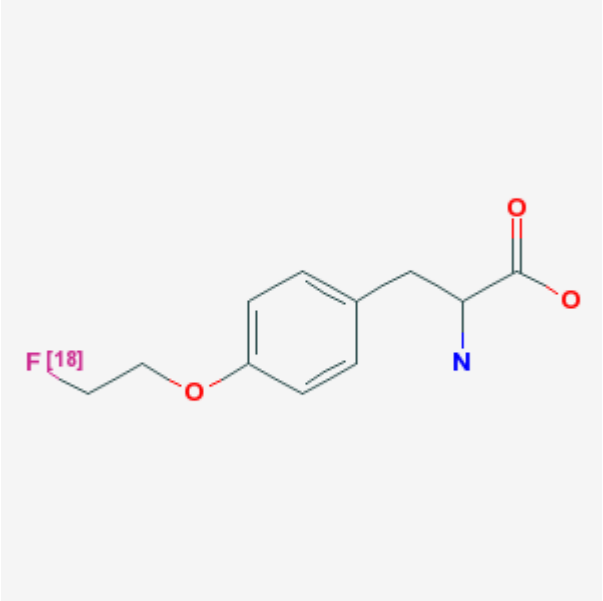
Chemical name:	*O*-(2-[^{18}F]Fluoroethyl)-L-tyrosine
Abbreviated name:	FET, [^{18}F]FET
Synonym:	
Agent category:	Compound
Target:	L-type amino acid transporter system and Na^+-dependent system B^0
Target category:	Transporter
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Humans



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Background

[PubMed]

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A variety of [^{11}C] and [^{18}F] labeled amino acids have been studied for potential use in positron emission tomography (PET) oncology (1, 2). Most brain tumors show an increased uptake of amino acids as compared with normal brain (3). These amino acids are composed of naturally occurring amino acids such as, L-[^{11}C]leucine, L-[^{11}C]methionine (MET), and L-[^{11}C]tyrosine and non-natural amino acids such as [^{11}C]aminoisobutyric acid, [^{11}C]1-aminocyclopentane-1-carboxylic acid, and [^{11}C]1-aminocyclobutane-1-carboxylic acid. There are also ^{123}I-labeled amino acids used in imaging in oncology (1, 4, 5).

Some 20 amino acid transporter systems have been identified (1). Most of the amino acids are taken up by tumor cells through an energy-independent L-type amino acid transporter system and a sodium-dependent transporter system A but also a Na^+-dependent system B^0 (6). They are retained in tumor cells due to their higher metabolic activities including incorporation into proteins than most normal cells (1). Malignant transformation increases the use of amino acids for energy, protein synthesis and cell division. Tumor cells were found to have over-expressed transporter systems (7). L-[^{11}C]MET, [^{18}F]fluorotyrosine, L-[^{11}C]leucine, and [^{18}F]fluoro-α-methyl tyrosine have been widely used in detection of tumors (2, 6) but are not approved by the FDA. They are moved into cells by various amino acid transporters and are incorporated into proteins. The fraction of radiolabeled amino acid that is incorporated into protein is usually small compared to the total amount taken up into the cell. These natural amino acid images are based on amino acid transport and protein incorporation.

None of the non-natural amino acids is incorporated into proteins (2, 8). These amino acids are rapidly transported into tumor cells. They are retained inside the tumor cells because of their high cellular metabolism and their high activity of the amino acid transporters. Recently, a new L-tyrosine analog, *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine ([^{18}F]FET), was synthesized and evaluated as an amino acid PET tracer for the detection of brain tumors with a higher specificity as compared with [^{18}F]FDG. Therefore, [^{18}F]FET could be a useful tracer in brain tumor imaging based solely on amino acid transport.

Related Resource Links:

- Chapters in MICAD (Amino acid transporters)
- Gene information in NCBI (L-type amino acid transporter, A-type amino acid transporter)
- Articles in Online Mendelian Inheritance in Man (OMIM) (Amino acid transporters)
- Clinical trials (Amino acid transporters)
- Drug information in FDA (Amino acid transporters)

Synthesis

[PubMed]

[^{18}F]FET was synthesized by a direct alkylation of tyrosine with [^{18}F]fluoroethyltosylate as previously reported by Wester et al. (8). [^{18}F]fluoroethyltosylate was prepared by [^{18}F]fluorination of ethylene glycol-1,2-ditosylate with [^{18}F] potassium Kryptofix complex. This two-step synthesis provided [^{18}F]FET with a 40% overall radiochemical yield and a radiochemical purity >97% with a total synthesis time of 50 min.

An automated synthesis of [^{18}F]FET was reported using *O*-(2-tosyloxyethyl)-*N*-trityl-L-tyrosine *tert*-butylester as a precursor for one-step nucleophilic [^{18}F]fluorination in the presence of *tetra*-butyl ammonium hydrogen carbonate/carbonate (9). The specific activity of [^{18}F]FET was 18 GBq/μmol (0.49 Ci/μmol) with a total synthesis time of 80 min and a radiochemical yield of 55-60%. This method provided a radiochemical purity >99%.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

[^{18}F]FET was shown to be transported mainly (80%) by the L-type amino acid transporter system, which was inhibited by 2-amino-2-norbornanecarboxylic acid (BCH) and not incorporated into proteins in human SW707 colon carcinoma cells (10). [^{18}F]FET showed a fast accumulation into SW707 cells for the first 6 min, followed by a plateau of nearly constant radioactivity up to 30 min. There was no significant accumulation of D-[^{18}F]FET. [^{18}F]FET was found to be transported into F98 rat gliomas similarly to L-[^{3}H]methionine mainly by system L and also (30%) by the Na^{+}-dependent system B^{0} (6). No significant incorporation of FET into proteins was detected.

[^{18}F]FET showed a fast-increasing uptake into F98 rat glioma cells in the first 10 min (0.475%) in culture, followed by a plateau of nearly constant radioactivity up to 60 min of incubation (11). On the other hand, [^{18}F]fluoro-2-deoxy-2-D-glucose (FDG) was increasingly accumulated into the cells over 60 min (1.07% at 60 min).

Animal Studies

Rodents

[PubMed]

Biodistribution studies in mice bearing SW707 colon carcinomas showed a high uptake of radioactivity in the pancreas (18% injected dose (ID)/g) at 60 min after injection of [^{18}F]FET (8). The brain (2.17% ID/g) and the tumors (6.37% ID/g) showed moderate uptakes of the tracer. Low radioactivity was observed in bone tissue, indicating little defluorination. The liver, kidney, and blood showed a fast distribution of [^{18}F]FET, completed in less than 5 min. The other organs showed little elevated uptake with time. [^{18}F]FET remained intact in the tissue homogenates of pancreas, brain, and tumor and plasma samples. No incorporation of [^{18}F]FET into proteins was detected in the tissue homogenates.

The biodistribution of [^{18}F]FET was determined in brain F98 glioma-bearing rats and compared with FDG (11). A moderate uptake and a long retention time of [^{18}F]FET in most organs, such as kidneys, liver, lung, blood, and heart, whereas a low uptake were found in normal brain. The maximum uptake of [^{18}F]FET and FDG in the F98 tumor was observed at 60 min after injection (1.49% and 2.77% ID/g), respectively. The tumor-to-brain ratios were 3.15 for [^{18}F]FET and 1.44 for FDG. Both PET images and autoradiograms of [^{18}F]FET showed high tracer uptake and contrast in the brain tumor, whereas FDG showed poor brain tumor images because of high uptake in the normal brain. [^{18}F]FET seems to be a useful amino acid tracer for brain tumor imaging with PET.

[^{18}F]FET did not accumulate significantly in inflammatory tissues (12). Tumor-infiltrated lymph nodes could be differentiated from inflammatory lymph nodes (13), and radiation necrosis could be differentiated from tumor recurrence (14). [^{18}F]FET was found to be a better tracer than [^{11}C]MET, [^{18}F]fluorocholine, or FDG in these circumstances because [^{18}F]FET does not accumulate in macrophages as compared with [^{18}F]fluorocholine and FDG.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

Human dosimetry was estimated based on human dynamic PET scans after injection of 400 MBq (10.8 mCi) [^{18}F]FET at 70 and 200 min (15). The urinary bladder received the highest dose (0.060 mGy/MBq or 222 mrad/mCi). Other organs, the uterus (0.022 mGy/MBq or 81 mrad/mCi) and kidney (0.020 mGy/MBq or 74 mrad/mCi), received moderate doses. No increased uptake was seen in the liver, bone, intestine, lung, heart, or pancreas. The effective dose was 0.0165 mSv/MBq (61 mrem/mCi). The effective dose based on biodistribution data of mice was estimated to be 0.009 mSv/MBq (33 mrem/mCi) (16).

A series of peripheral tumors were compared with [^{18}F]FET and FDG PET scans in 38 cancer patients (17). [^{18}F]FET was positive in 13 of 38 patients, whereas FDG was positive in 37 of 38 patients. However, in patients with squamous cell carcinomas, [^{18}F]FET provided better discrimination than FDG between lesions and inflammatory tissues.

Initial clinical studies of [18F]FET in comparison with [11C]MET were carried out in 16 patients with intracerebral lesions, showing brain tumor images in 13 patients (18). There were few differences in uptake and image contrast between [11C]MET and [18F]FET. In a different study, 20 patients with suspected brain tumors were imaged by [18F]FET PET, 3-[123I]-iodo-α-methyl-L-tyrosine (IMT) SPECT, and magnetic resonance imaging (MRI) (19). [18F]FET and IMT showed similar uptakes in brain lesions. However, [18F]FET exhibited a significant higher tumor-to-brain ratio than IMT and an improved discrimination of anatomic structures over IMT. In a later study, [18F]FET PET improved the specificity of MRI from 53% to 94% in diagnostic assessment of cerebral gliomas in 31 patients (20). These and other studies [PubMed] have demonstrated that [18F]FET PET provides accurate delineation of brain tumor metastases, detection of brain tumor recurrence, and identification of brain lesions.

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