p-(2-[^{18}F]Fluoroethyl)-L-phenylalanine

[^{18}F]FEP

Kam Leung, PhD[1]

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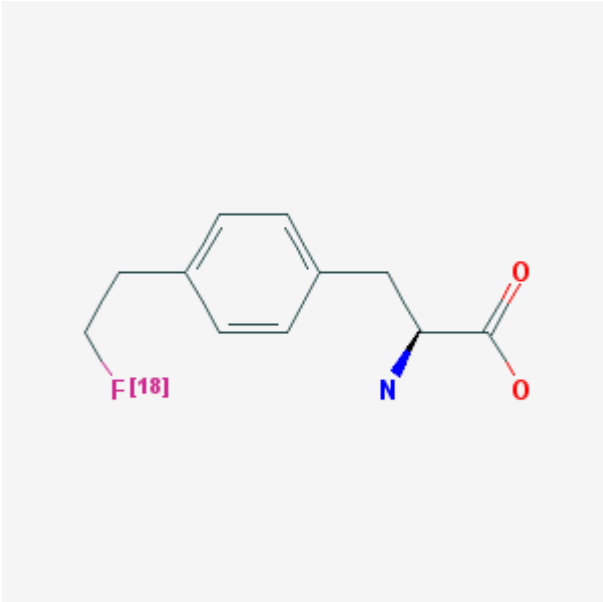
Chemical name:	*p*-(2-[^{18}F]Fluoroethyl)-L-phenylalanine
Abbreviated name:	[^{18}F]FEP
Synonym:	
Agent category:	Compound
Target:	L-type amino acid transporter system
Target category:	Transporter
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



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Background

[PubMed]

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

[1] National Center for Biotechnology Information, NLM, NIH, Bethesda, MD; Email: micad@ncbi.nlm.nih.gov.

Corresponding author.

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increased uptake of amino acids compared with uptake in normal brain tissue. 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. ^{123}I-Labeled amino acids are also used for imaging in oncology although no radiolabeled amino acid is approved at present (1, 3, 4).

More than twenty 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 Na-dependent transporter system A, as well as through a Na^+-dependent system B^0 (5). The amino acids are retained in tumor cells due to their high metabolic activities, including incorporation into proteins, which are higher than metabolic activities of 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 overexpressed transporter systems (6). L-[^{11}C]MET, [^{18}F]fluorotyrosine, L-[^{11}C]leucine, and [^{18}F]fluoro-α-methyl tyrosine have been widely used in the detection of tumors (2, 5), but they are not approved by the United States Food and Drug Administration. These radiolabels are moved into cells by various amino acid transporters and are incorporated into proteins although only leucine is quantitatively incorporated into protein. The fraction of radiolabeled amino acids that is incorporated into proteins is usually small compared to the total amount taken up into the cell. Imaging techniques that use natural amino acids are based on amino acid transport and protein incorporation.

Non-natural amino acids are not incorporated into proteins (2, 7); instead, they are rapidly transported into tumor cells. They are retained inside the tumor cells because of their high cellular metabolism and the high activity of the amino acid transporters. 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.[^{18}F]FET has a higher specificity than [^{18}F]FDG. Recently, a new L-phenylalanine analog, *p*-(2-[^{18}F]fluoroethyl)-L-phenylalanine ([^{18}F]FEP), was synthesized and evaluated as an amino acid PET tracer for the detection of brain tumors (8). FEP is a substrate for the L-type amino acid transporter system. Therefore, [^{18}F]FEP 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]

Wang et al. (8) reported the synthesis of [^{18}F]FEP using the tosylate precursor in a two-step reaction. Nucleophilic [^{18}F]fluorination was performed in the presence of *tetra*-butyl ammonium bicarbonate, with subsequent acidic hydrolysis to remove the protecting groups. The specific activity of [^{18}F]FEP was 31–69 GBq/μmol (0.84–1.84 Ci/μmol) at the end of synthesis, with a total synthesis time of 90 min and a radiochemical decay-corrected yield of 27%–37%. Radiochemical purity was >95%.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Wang et al. (8) showed that [^{18}F]FEP entered rat 9L gliosarcoma tumor cells in culture with 13.3% incubation dose/0.1 mg protein (n = 3) after 30 min of incubation. [^{18}F]FEP uptake into rat 9L gliosarcoma tumor cells in culture was reduced by 90%, 5%, and 50% by the presence of 1 mM 2-aminobicyclo[2.2.1]heptane-2-carboxylic acid (an L-type transporter inhibitor), *N*-methyl-α-aminoisobutyric acid (an A-type transporter inhibitor), and serine, respectively. The data suggest that [^{18}F]FEP is predominantly transported into 9L cells *via* the L-type transporter.

Animal Studies

Rodents

[PubMed]

The biodistribution of [^{18}F]FEP was studied in 9L glioma-bearing rats (n = 6) (88). Moderate uptake of [^{18}F]FEP was observed in most organs, such as kidneys, liver, lung, blood, brain, and heart (0.52%–0.65% ID/g), with the highest uptake in the pancreas (2.45% ID/g) at 60 min after injection. The tumor uptake of [^{18}F]FEP was 0.90% ID/g, and accumulation was low in the bone (0.41% ID/g). The tumor/blood and tumor/muscle ratios were 1.73 and 1.45, respectively. PET imaging dynamic scans were performed with [^{18}F]FEP in comparison to [^{18}F]FET at 5–120 min after injection. Both tracers showed rapid tumor accumulation at 5 min and reached a plateau at ~20 min. The tumor/muscle ratios (~5) of these two tracers were similar at 20 min after injection. No blocking studies were performed.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

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