5-(2-[^{18}F]Fluoroethoxy)-L-tryphan

[^{18}F]-L-FEHTP

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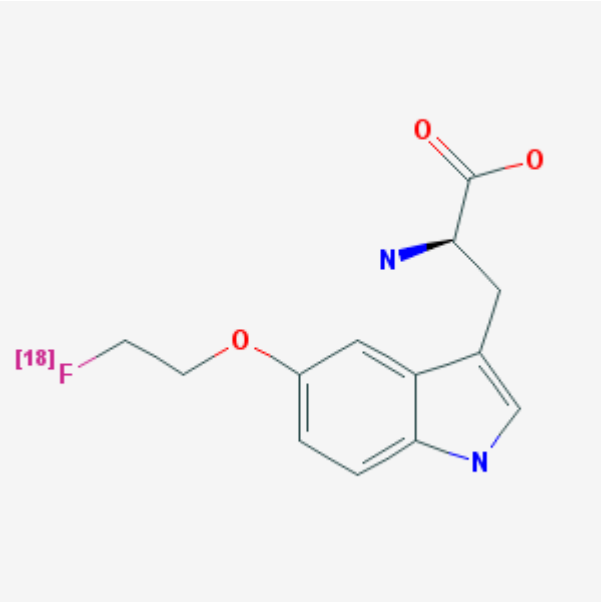
Chemical name:	5-(2-[^{18}F]Fluoroethoxy)-L-tryphan
Abbreviated name:	[^{18}F]-L-FEHTP, 5-^{18}FEHTP
Synonym:	L-5-(2-[^{18}F]Fluoroethoxy)tryphan
Agent category:	Compound
Target:	L-type amino acid transporter 1 (LAT1)
Target category:	Amino acid uptake
Method of detection:	Positron emission tomography (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

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increased uptake of amino acids as compared with normal brain tissues (3). These amino acids are composed of naturally occurring amino acids, such as L-[^{11}C]leucine, *S*-[^{11}C]methyl-L-methionine ([^{11}C]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 in oncological imaging (1, 4, 5).

Some 20 amino acid transporter systems have been identified (1). Most amino acids are taken up by tumor cells through an energy-independent L-type amino acid transporter (LAT) system, a Na-dependent transporter system A, or a Na^+-dependent system B^0 (6). They are retained in tumor cells due to their metabolic activities, including incorporation into proteins, which are higher than most normal cells (1). Malignant transformation increases the use of amino acids for energy, protein synthesis, and cell division. Tumor cells have been found to have overexpressed 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 the detection of tumors (2, 6) but are not approved by the United States Food and Drug Administration. These agents 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, except for leucine which is incorporated into proteins, quantitatively. These natural amino acid images are based on amino acid transport and protein incorporation.

5-(2-[^{18}F]Fluoroethoxy)-L-tryphan ([^{18}F]-L-FEHTP), unlike L-3,4-dihydroxy-6-[^{18}F]fluorophenylalanine ([^{18}F]FDOPA), is only a substrate of LAT1 and is not a substrate of aromatic L-amino acid decarboxylase (AADC). [^{18}F]-L-FEHTP was evaluated as a PET tumor imaging agent in mice with comparison to [^{18}F]fluoro-2-deoxy-2-D-glucose ([18F]FDG) and [^{18}F]FDOPA (8, 9).

Related Resource Links:

- Chapters in MICAD (Amino acid transporters)
- Gene information in NCBI (L-type amino acid transporter 1, L-type amino acid transporter 2, A-type amino acid transporter)
- Articles in Online Mendelian Inheritance in Man (OMIM) (Amino acid transporters)
- Clinical trials (Amino acid transporters, L-[^{11}C]methionine)
- Drug information in FDA (Amino acid transporters, L-[^{11}C]methionine)

Synthesis

[PubMed]

[^{18}F]-L-FEHTP was synthesized by direct alkylation of 5-hydroxy-L-tryptophan with [^{18}F]fluoroethyltosylate for 10 min at 90°C (9). [^{18}F]Fluoroethyltosylate was prepared by [^{18}F]-fluorination of ethylene glycol-1,2-ditosylate with [^{18}F]-potassium Kryptofix complex for 15 min at 100°C. This two-step automated synthesis provided [^{18}F]-L-

FEHTP with 12%–16% overall yield and a radiochemical purity >98% with a total synthesis time of ~40 min. The specific activities of [^{18}F]-L-FEHTP was 50–150 GBq/μmol (1.35–4.05 Ci/μmol).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Kramer et al. (8) showed that [^{18}F]-L-FEHTP accumulation in NCI-H69 endocrine small cell lung cancer cells, PC-3 prostate cancer cells, and MDA-MB-231 breast cancer cells was reduced by >95% in the presence of 10 mM 2-aminobicyclo[2.2.1]heptane-2-carboxylic acid (BCH, an L-type transporter inhibitor). The radioactivity accumulation of [^{18}F]-L-FEHTP was 48%–113% incubation dose (ID)/mg protein in the absence of BCH. The ADCC inhibitor *S*-carbidopa had little effect on the [^{18}F]-L-FEHTP accumulation in these cells, suggesting that decarboxylation was not involved in the accumulation. On the other hand, *S*-carbidopa almost completely abolished the accumulation of [^{18}F]FDOPA (26%–53% ID/mg protein).

Animal Studies

Rodents

[PubMed]

Ex vivo tissue accumulation of [^{18}F]-L-FEHTP was studied in mice (n = 6/group) bearing S180 fibrosarcoma at 15, 30, 60, and 120 min after injection of 0.74 MBq (0.02 mCi) of the tracer as reported by Li et al. (9). The tumor accumulation of radioactivity was 3.07 ± 1.04% injected dose (ID)/g, 4.61 ± 1.18% ID/g, 5.19 ± 0.79% ID/g, and 2.37 ± 0.23% ID/g at 15, 30, 60, and 120 min, respectively. The tissue with the highest uptake was the liver (4.59%), followed by the kidney (4.05% ID/g), lung (3.86% ID/g), small intestine (3.65% ID/g), brain (3.18% ID/g), spleen (3.15% ID/g), heart (2.41% ID/g), muscle (2.04% ID/g), bone (1.94% ID/g), and blood (1.91% ID/g) at 30 min. All tissues showed moderate washout. The maximal tumor/blood and tumor/muscle ratios at 60 min were 2.87 and 2.79, respectively. [^{18}F]-L-FEHTP remained >95% intact and no other radioactive metabolites were detected in the blood, brain, and tumors at 15 and 60 min after injection. No blocking studies were performed.

In a separate study, accumulation of [^{18}F]-L-FEHTP (n = 4) and [^{18}F]FDG (n = 4) was compared in mice with tumors and *Staphylococcus aureus*-induced inflammation in thigh muscle. [^{18}F]-L-FEHTP exhibited tumor/muscle and inflammation/muscle ratios of 2.79 and 0.94, respectively, at 60 min after injection. On the other hand, [^{18}F]FDG exhibited tumor/muscle and inflammation/muscle ratios of 2.91 and 3.17, respectively, at 60 min after injection. Whole-body PET imaging at 60 min after injection showed high [^{18}F]-L-FEHTP and [^{18}F]FDG accumulation in the tumors, whereas low [^{18}F]-L-FEHTP and high [^{18}F]FDG accumulation were observed in the inflammation.

Kramer et al. (8) performed *ex vivo* biodistribution studies in nude mice bearing NCI-H69 (n = 3) or PC-3 xenografts (n = 4) at 70 min after injection of [^{18}F]-L-FEHTP. The tumor accumulation of radioactivity (standard uptake value (SUV)) was 1.58 ± 0.48 and 1.40 ± 0.35 in the NCI-H69 and PC-3 tumors, respectively. The tissue with the highest SUV was the pancreas (8.50), followed by the kidney (2.05), spleen (0.88), brain (0.84), liver (0.81), heart (0.78), and blood (0.75). Pretreatment with tryptophan (25 mg/kg, 10 min) resulted in a slight decrease (not significant) of tissue accumulation in the NCI-H69 tumors, brain, and kidneys but had little effect on the other tissues.

Kramer et al. (8) performed PET imaging studies in mice (n = 3–7/group) bearing NCI-H69 or PC-3 tumors after injection of [^{18}F]-L-FEHTP or [^{18}F]FDOPA. Dynamic and static PET scans showed the accumulation of both tracers in the two tumors with SUV of ~1.5. Pretreatment with *S*-carbidopa 60 min before [^{18}F]FDOPA decreased the radioactivity levels in the PC-3 tumors by ~50%, whereas no decrease was observed in the accumulation of [^{18}F]-L-FEHTP.

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.

References

1. Jager P.L., Vaalburg W., Pruim J., de Vries E.G., Langen K.J., Piers D.A. *Radiolabeled amino acids: basic aspects and clinical applications in oncology.* J Nucl Med. 2001;42(3): 432–45. PubMed PMID: 11337520.
2. Laverman P., Boerman O.C., Corstens F.H., Oyen W.J. *Fluorinated amino acids for tumour imaging with positron emission tomography.* Eur J Nucl Med Mol Imaging. 2002;29(5):681–90. PubMed PMID: 11976809.
3. Herholz K., Heiss W.D. *Positron emission tomography in clinical neurology.* Mol Imaging Biol. 2004;6(4):239–69. PubMed PMID: 15262239.
4. Langen K.J., Pauleit D., Coenen H.H. *3-[(123)I]Iodo-alpha-methyl-L-tyrosine: uptake mechanisms and clinical applications.* Nucl Med Biol. 2002;29(6):625–31. PubMed PMID: 12234586.

5. Lahoutte T., Caveliers V., Camargo S.M., Franca R., Ramadan T., Veljkovic E., Mertens J., Bossuyt A., Verrey F. *SPECT and PET amino acid tracer influx via system L (h4F2hc-hLAT1) and its transstimulation.* J Nucl Med. 2004;45(9):1591–6. PubMed PMID: 15347729.
6. Langen K.J., Jarosch M., Muhlensiepen H., Hamacher K., Broer S., Jansen P., Zilles K., Coenen H.H. *Comparison of fluorotyrosines and methionine uptake in F98 rat gliomas.* Nucl Med Biol. 2003;30(5):501–8. PubMed PMID: 12831987.
7. Saier M.H., Daniels G.A., Boerner P., Lin J. *Neutral amino acid transport systems in animal cells: potential targets of oncogene action and regulators of cellular growth.* J Membr Biol. 1988;104(1):1–20. PubMed PMID: 3054116.
8. Kramer S.D., Mu L., Muller A., Keller C., Kuznetsova O.F., Schweinsberg C., Franck D., Muller C., Ross T.L., Schibli R., Ametamey S.M. *5-(2-18F-fluoroethoxy)-L-tryptophan as a substrate of system L transport for tumor imaging by PET.* J Nucl Med. 2012;53(3):434–42. PubMed PMID: 22331220.
9. Li R., Wu S.C., Wang S.C., Fu Z., Dang Y., Huo L. *Synthesis and evaluation of l-5-(2-[(18)F]fluoroethoxy)tryptophan as a new PET tracer.* Appl Radiat Isot. 2010;68(2):303–8. PubMed PMID: 19906535.