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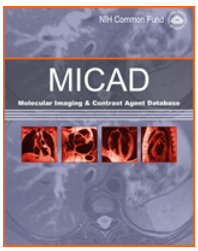

anti-1-Amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid

anti-[^{18}F]FACBC

Kam Leung, PhD[1]

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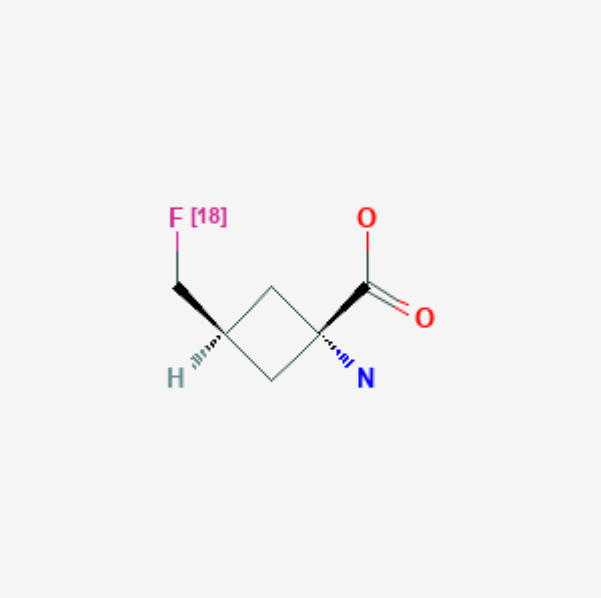
Chemical name:	*anti*-1-Amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid
Abbreviated name:	*anti*-[^{18}F]FACBC, *anti*-3-[^{18}F]FACBC
Synonym:	
Agent category:	Compound
Target:	L-type amino acid transporter
Target category:	Transporter
Method of detection:	PET
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Humans



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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 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, 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 (4-6).The natural amino

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

Corresponding author.

acids are taken up by tumor cells through an energy-independent L-type amino acid transporter system and retained in tumor cells because of their higher metabolic pathways, including incorporation into proteins than most normal cells (4). L-[^{11}C]Methionine and [^{18}F]fluorotyrosine have been widely used in the detection of tumors. On the other hand, the non-natural amino acids are not metabolized. Their uptakes are through both the L-type transporter and the energy-dependent A-type transporter (7). Therefore, they can be accumulated intracellularly in high concentrations. *anti*-1-Amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid (*anti*-[^{18}F]FACBC) was shown to have a high tumor/brain ratio (8). Therefore, *anti*-[^{18}F]FACBC could be a useful tracer in PET tumor imaging.

Related Resource Links:

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

Synthesis

[PubMed]

Nucleophilic fluorination of *syn*-1-t-butyl-carbamate-3-trifluromethanesulfonoxy-1-cyclobutane-1-carboxylic acid methyl ester with K[^{18}F]F/Kryptofix2.2.2 and subsequent hydrolysis and purification provided a radiosynthesis yield of 12% of *anti*-[^{18}F]FACBC at the end of bombardment (8). A radiochemical purity of 99% was obtained. The total synthesis time was 60 min. An automated radiosynthesis of *anti*-[^{18}F]FACBC was reported with a radiosynthesis yield of 24% and a radiochemical purity of 99% (9). The specific activity was 137-192 GBq/mmol (3.7-5.2 Ci/mmol).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

anti-[^{18}F]FACBC showed a fast-increasing uptake into human DU-145 prostate tumor cells in the first 5 min in culture with ~6% injected dose (10)/10^5 cells, followed by a peak (~8% ID/10^5 cells) at 15 min and a gradual decrease to 3% ID/10^5 cells at 60 min (10). The uptake was blocked by the presence of excess natural amino acids to <0.2% ID/10^5 cells. On the other hand, uptake of 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG) increased with time from ~1% ID/10^5 cells at 5 min to 9% ID/10^5 cells at 60 min. The uptake was blocked by the presence of excess glucose to <0.5% ID/10^5 cells.

Yu et al. (11) showed that *anti*-[^{18}F]FACBC uptake into rat 9L gliosarcoma tumor cells in culture was reduced by 76%, 6%, and 98% by the presence of 10 mM of BCH, MeAIB, and ACS, respectively. The data suggest that *anti*-[^{18}F]FACBC is predominantly a L-type transporter substrate .

Animal Studies

Rodents

[PubMed]

Uptake of *anti*-[^{18}F]FACBC and [^{18}F]FDG were compared in rats implanted intracerebrally with 9L gliosarcoma (8). Accumulation of *anti*-[^{18}F]FACBC in the spleen, lungs, liver, and kidneys was greater than in the heart, tumor, blood, and brain at 5 min after injection. The uptake in the brain (0.11% ID/g) was low and increased

slightly to 0.26% ID/g at 60 min. The uptake in the tumor increased from 0.62% ID/g to 1.72% ID/g. Most of the other tissues showed a decrease in radioactivity at 60 min, except for the liver, which showed an increase. Accumulation of [^{18}F]FDG in the kidneys, liver, heart, brain tumor and blood was from 0.91%ID/g to 1.3% ID/g at 5 min. However, there was little difference in the uptake between the brain and tumor at 5 min and 60 min. The tumor-to-brain ratio at 60 min was 6.6 and 0.84 for *anti*-[^{18}F]FACBC and [^{18}F]FDG, respectively.

Oka et al. (10) compared the biodistribution of *anti*-[^{18}F]FACBC and [^{18}F]FDG in rats transplanted with DU-145 tumor cells orthotopically in the prostate (OPCT). In the brain, heart, small intestine, testis, mesenteric lymph nodes, and urinary bladder, the accumulation of [^{18}F]FDG was higher than that of *anti*-[^{18}F]FACBC at 15 and 60 min after injection. On the other hand, *anti*-[^{18}F]FACBC uptake into the liver, muscle, and pancreas was higher than [^{18}F]FDG uptake into these organs at 15 and 60 min. The uptake of *anti*-[^{18}F]FACBC (1.58 ± 0.40% ID/cm^3) and [^{18}F]FDG (1.48 ± 0.90% ID/cm^3) into the prostate cancer tissue was similar at 60 min. In contrast, [^{18}F]FDG (0.55 ± 0.18% ID/cm^3) uptake into the normal prostate regions was significantly higher than *anti*-[^{18}F]FACBC (0.37 ± 0.06% ID/cm^3) ($P < 0.05$). The accumulation of *anti*-[^{18}F]FACBC (3.09 ± 1.43% ID/cm^3) was significantly lower than [^{18}F]FDG (69.31 ± 16.55% ID/cm^3) in the urinary bladder at 60 min ($P < 0.05$).

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

PET imaging using *anti*-[^{18}F]FACBC was taken one week after a patient had undergone surgery to remove a tumor in the brain (8). The uptake of *anti*-[^{18}F]FACBC in normal brain tissue was 21 nCi/ml and 29 nCi/ml at 5 min and 60 min, respectively. The uptake in tumor was 110 nCi/ml at 5 min and 130 nCi/ml at 60 min. Human dosimetry was estimated by Nye et al. (12) using the biodistribution data from 6 healthy volunteers. The liver received the highest dose of radioactivity, followed by the pancreas, heart wall, kidneys, and spleen. The effective dose equivalent is 0.0164 mSv/MBq (60.6 mrem/mCi).

Schuster et al. (13) studied 15 patients with a recent diagnosis of prostate carcinoma (n = 9) or suspected recurrence (n = 6) underwent 65-min dynamic PET/CT of the pelvis after injection of 300-410 MBq (8.1-11.1 mCi) *anti*-[^{18}F]FACBC followed by static body images. In the 8 patients with newly diagnosed prostate carcinoma who underwent dynamic scanning, visual analysis correctly identified the presence or absence of focal cancer lesions in 40 of 48 prostate sextants. Pelvic nodal status correlated with *anti*-[^{18}F]FACBC findings in 7 of 9 patients and was indeterminate in 2 of 9. Visual analysis was successful in identifying disease in all 4 patients with proven recurrence.

Savir-Baruch et al. (14) studied five patients with elevated prostate-specific antigen level after curative therapy for prostate carcinoma underwent 60-min dynamic PET/CT of the pelvis after injection of 193-340 MBq (5.2-9.3 mCi) *anti*-[^{18}F]FACBC. Average standard uptake value (SUV) of malignant lesions was 4.3 ± 1.1 and 3.4 ± 0.8 at 5 and 20 min, respectively. The lesion/blood ratios were 3.0 ± 0.9 at 5 min, whereas lesions/urinary bladder ratio was 2.3 ± 1.4 at 20 min.

References

1. Coleman R.E., Hoffman J.M., Hanson M.W., Sostman H.D., Schold S.C. *Clinical application of PET for the evaluation of brain tumors.* . J Nucl Med. 1991;32(4):616–22. PubMed PMID: 2013802.
2. Kaschten B., Stevenaert A., Sadzot B., Deprez M., Degueldre C., Del Fiore G., Luxen A., Reznik M. *Preoperative evaluation of 54 gliomas by PET with fluorine-18-fluorodeoxyglucose and/or carbon-11-methionine.* . J Nucl Med. 1998;39(5):778–85. PubMed PMID: 9591574.
3. Herholz K., Heiss W.D. *Positron emission tomography in clinical neurology.* . Mol Imaging Biol. 2004;6(4):239–69. PubMed PMID: 15262239.
4. 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.
5. 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.
6. 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.
7. Palacin M., Estevez R., Bertran J., Zorzano A. *Molecular biology of mammalian plasma membrane amino acid transporters.* . Physiol Rev. 1998;78(4):969–1054. PubMed PMID: 9790568.
8. Shoup T.M., Olson J., Hoffman J.M., Votaw J., Eshima D., Eshima L., Camp V.M., Stabin M., Votaw D., Goodman M.M. *Synthesis and evaluation of [18F]1-amino-3-fluorocyclobutane-1-carboxylic acid to image brain tumors.* . J Nucl Med. 1999;40(2):331–8. PubMed PMID: 10025843.
9. McConathy J., Voll R.J., Yu W., Crowe R.J., Goodman M.M. *Improved synthesis of anti-[18F]FACBC: improved preparation of labeling precursor and automated radiosynthesis.* . Appl Radiat Isot. 2003;58(6):657–66. PubMed PMID: 12798374.
10. Oka S., Hattori R., Kurosaki F., Toyama M., Williams L.A., Yu W., Votaw J.R., Yoshida Y., Goodman M.M., Ito O. *A preliminary study of anti-1-amino-3-18F-fluorocyclobutyl-1-carboxylic acid for the detection of prostate cancer.* . J Nucl Med. 2007;48(1):46–55. PubMed PMID: 17204698.
11. Yu W., Williams L., Camp V.M., Malveaux E., Olson J.J., Goodman M.M. *Stereoselective synthesis and biological evaluation of syn-1-amino-3-[18F]fluorocyclobutyl-1-carboxylic acid as a potential positron emission tomography brain tumor imaging agent.* . Bioorg Med Chem. 2009;17(5):1982–90. PubMed PMID: 19216081.
12. Nye J.A., Schuster D.M., Yu W., Camp V.M., Goodman M.M., Votaw J.R. *Biodistribution and radiation dosimetry of the synthetic nonmetabolized amino acid analogue anti-18F-FACBC in humans.* . J Nucl Med. 2007;48(6):1017–20. PubMed PMID: 17504867.
13. Schuster D.M., Votaw J.R., Nieh P.T., Yu W., Nye J.A., Master V., Bowman F.D., Issa M.M., Goodman M.M. *Initial experience with the radiotracer anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid with PET/CT in prostate carcinoma.* . J Nucl Med. 2007;48(1):56–63. PubMed PMID: 17204699.
14. Savir-Baruch, B., D.M. Schuster, N. Jarkas, V.A. Master, P.T. Nieh, R.K. Halkar, J.A. Nye, M.M. Lewis, R.J. Crowe, R.J. Voll, V.M. Camp, L.M. Bellamy, D.L. Roberts, and M.M. Goodman, *Pilot Evaluation of Anti-1-amino-2-[(18)F] fluorocyclopentane-1-carboxylic acid (anti-2-[(18)F] FACPC) PET-CT in Recurrent Prostate Carcinoma.* Mol Imaging Biol, 2010