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NLM Citation: Leung K. 4-[^{18}F]Fluorobenzoyl-Phe-Ala-Leu-Gly-Glu-Ala-NH_2. 2011 Aug 26 [Updated 2011 Dec 8]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.
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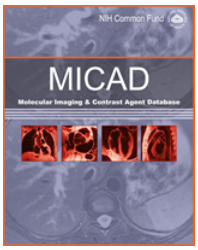

4-[^{18}F]Fluorobenzoyl-Phe-Ala-Leu-Gly-Glu-Ala-NH_2

[^{18}F]FBA-FALGEA-NH_2

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Created: August 26, 2011; Updated: December 8, 2011.

Chemical name:	4-[^{18}F]Fluorobenzoyl-Phe-Ala-Leu-Gly-Glu-Ala-NH_2	
Abbreviated name:	[^{18}F]FBA-FALGEA-NH_2	
Synonym:	[^{18}F]FB-FALGEA-NH_2	
Agent Category:	Peptide	
Target:	Epidermal growth factor receptor variant III (EGFRvIII)	
Target Category:	Receptor	
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]

Epidermal growth factor (EGF) is a 53-amino-acid cytokine (6.2 kDa) secreted by ectodermic cells, monocytes, kidneys, and duodenal glands (1). EGF stimulates growth of epidermal and epithelial cells. EGF and at least seven other growth factors and their transmembrane receptor kinases play important roles in cell proliferation, survival, adhesion, migration, and differentiation. The EGF receptor (EGFR) family consists of four transmembrane receptors, including EGFR (HER1/erbB-1), HER2 (erbB-2/neu), HER3 (erbB-3), and HER4 (erbB-4) (2). HER1, HER3, and HER4 comprise three major functional domains: an extracellular ligand-binding domain, a hydrophobic transmembrane domain, and a cytoplasmic tyrosine kinase domain (2, 3). EGFR, which is overexpressed in many malignant epithelial tumors, contributes to gene amplification, which is believed to introduce mutations in the receptor (4). The overexpression, amplification, and/or mutation of EGFR can lead to the development of cancer. The most common mutation observed in the receptor is the deletion of a segment (amino acid residues 6–273 of the EGFR extracellular domain), including the ligand-binding region, which results in the generation of a variant known as constitutively activated variant III EGFR (EGFRvIII) (5). Although EGFRvIII is nonresponsive to EGF, it remains a constantly operating downstream tyrosine kinase signaling pathway that appears to promote the development of a neoplastic phenotype, particularly for

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glioblastoma and to some extent for other cancers such as those of the prostate and the breast (6). EGFRvIII has not been identified in normal tissues.

Monoclonal antibody (mAb) 806 and chimeric antibody ch806 (7, 8), which specifically target EGFRvIII, were radiolabeled for imaging EGFRvIII expression in tumors. However, the pharmacokinetics of the intact radiolabeled mAb, with high liver uptake and slow blood elimination, are generally not ideal for imaging because of poor tissue and tumor penetration (9). Smaller antibody fragments and peptides have better imaging pharmacokinetics because they are rapidly excreted by the kidneys. Denholt et al. (10) identified an EGFRvIII-targeting peptide, H-Phe-Ala-Leu-Gly-Glu-Ala-NH_2 (H-FALGEA-NH_2) using a Positional Scanning Synthetic Combinatorial Library. H-FALGEA-NH_2 was labeled with 4-[^{18}F]fluorobenzoic acid ([^{18}F]FBA) to form [^{18}F]FBA-FALGEA-NH_2 (11). [^{18}F]FBA-FALGEA-NH_2 has been evaluated for imaging of EGFRvIII expression in human glioblastoma multiforme (GBM) tumors in nude mice using positron emission tomography (PET).

Related Resource Links:

- Chapters in MICAD (EGFR, EGFRvIII)
- Gene information in NCBI (EGFR)
- Articles in Online Mendelian Inheritance in Man (OMIM) (EGFR)
- Clinical trials (EGFRvIII)
- Drug information in FDA (EGFRvIII)

Synthesis

[PubMed]

[^{18}F]FBA was synthesized in two steps from [^{18}F]KF (Kryptofix 2.2.2./K_2CO_3) (11). The decay-corrected yields of [^{18}F]FBA were 22%–54%, based on starting with [^{18}F]KF. H-FALGEA-XAL-resin and 250–500 MBq (6.8–13.5 mCi) [^{18}F]FBA were incubated for 30 min at room temperature. [^{18}F]FBA-FALGEA-NH_2 was cleaved from the resin by heating with trifluoroacetic acid for 20 min at 35°C. Total synthesis time was ~180 min, including the final high-performance liquid chromatography (HPLC) purification. The decay-corrected radiochemical yields, radiochemical purity, and specific activity of [^{18}F]FBA-FALGEA-NH_2 were 7.3 ± 1.1%, 95 ± 3%, and 6.4 ± 1.1 GBq/μmol (170 ± 30 mCi/μmol) (n = 6), respectively, at the end of HPLC purification.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The binding affinity (K_d) values of [^{18}F]FBA-FALGEA-NH_2 to NR6M cells (expressing EGFRvIII) and NR6W-A cells (expressing EGFR) were reported to be 23 nM and 691 nM (11), respectively. The B_{max} (receptor density) values for EGFRvIII and EGFR were reported to be 77 pmol × 10^3 cells and 596 nmol × 10^3 cells, respectively. The *in vitro* stability of [^{18}F]FBA-FALGEA-NH_2 in nude mouse plasma was 85% and 53% intact after 30 min and 60 min of incubation, respectively.

Animal Studies

Rodents

[PubMed]

Denholt et al. (11) performed PET imaging studies in nude mice bearing EGFRvIII-expressing human GBM tumors (7 mice, 11 tumors) and nude mice bearing EGFRvIII non-expressing human GBM tumors (5 mice, 10 tumors) at 60 min after injection of 5.7 ± 2.5 MBq (0.15 ± 0.7 mCi) [^{18}F]FBA-FALGEA-NH_2. The EGFRvIII-

positive tumors were clearly visualized compared to the control tumors. The tumor/muscle ratios for EGFRvIII-positive tumors and control tumors were 7.8 ± 3.2 and 3.4 ± 1.0, respectively. The average standard uptake value (SUV = Tissue concentration/(injected dose/body weight)) of 0.11 was low for the EGFRvIII-positive tumors. The liver and kidneys were also visualized in both groups of tumor-bearing mice with higher radioactivity in the kidneys. There was a linear correlation between tumor/muscle ratios and EGFRvIII mRNA expression on the tumors ($R = 0.86$, $P < 0.007$). No blocking studies were performed. Furthermore, no intact [^{18}F]FBA-FALGEA-NH_2 was detected in the plasma at 5 min after injection, indicating rapid metabolism by blood peptidases. In comparison, [^{18}F]FDG PET studies were performed one day before [^{18}F]FBA-FALGEA-NH_2 PET studies in the same nude mice bearing EGFRvIII tumors. The tumor/muscle ratio was 2.6 with an average SUV of 0.54 at 60 min after injection. The investigators concluded that a more stable peptide with higher affinity for EGFRvIII is needed to decrease the large variation in binding of [^{18}F]FBA-FALGEA-NH_2 to EGFRvIII-positive tumors.

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.

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