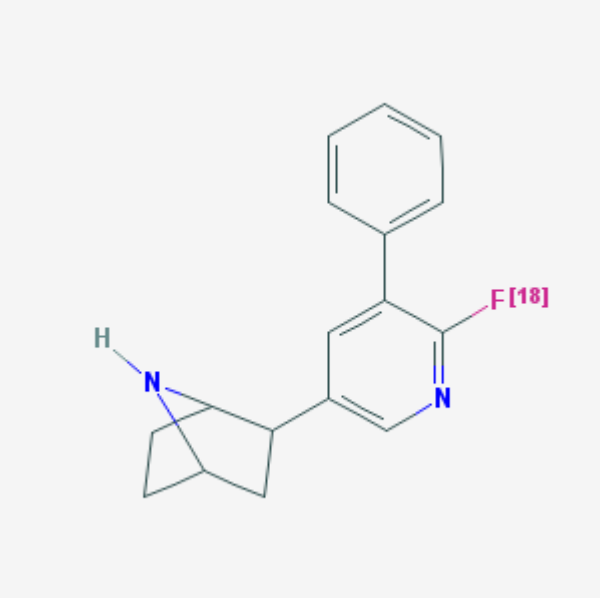
2-(+/-)-2-*exo*-(2'-[^{18}F]Fluoro-3'-phenyl-pyridin-5'-yl)-7-azabicyclo[2.2.1]heptane

[^{18}F]FPhEP

Kam Leung, PhD[1]

Created: October 6, 2006; Updated: December 4, 2006.

Chemical name:	2-(+/-)-2-*exo*-(2'-[^{18}F]Fluoro-3'-phenyl-pyridin-5'-yl)-7-azabicyclo[2.2.1]heptane
Abbreviated name:	[^{18}F]FPhEP
Synonym:	
Agent category:	Compound
Target:	Neuronal α4β2 nicotinic acetylcholine receptor (nAChR)
Target category:	Receptor
Method of detection:	PET
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates



Click on the above structure for additional information in PubChem.

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

Corresponding author.

NLM Citation: Leung K. 2-(+/-)-2-*exo*-(2'-[^{18}F]Fluoro-3'-phenyl-pyridin-5'-yl)-7-azabicyclo[2.2.1]heptane. 2006 Oct 6 [Updated 2006 Dec 4]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

Background

[PubMed]

Neuronal nicotinic cholinergic receptors (nAChRs) are a heterogeneous family of ligand-gated ion channels expressed in the central nervous system, where their activation by acetylcholine and nicotine always causes a rapid increase in cellular permeability to ions, such as Na^+ and Ca^{2+} (1-3). Nicotinic receptors exist as pentamers (homomeric or heteromeric) in various brain regions and ganglia. There are nine subtypes of ligand-binding α (α2-α10) and four subtypes of structural β (β2-β5). nAChRs have been demonstrated to be involved in cognitive processes such as learning and memory and control of movement in normal subjects. Dysfunction of nAChR has been implicated to a number of human diseases such as schizophrenia, Huntington's disease, Alzheimer's disease and Parkinson's disease. nAChRs also play a significant role in nicotine addiction.

6-[^{18}F]Fluoro-A-85380 (6-[^{18}F]FA) and 2-[^{18}F]FA have been evaluated as positron emission tomography (PET) agents for the non-invasive study of α4β2 nAChR in humans (4, 5). However, prolonged imaging times (2-4 h) are required for reliable quantification because of their slow kinetics. 2-(+/-)-2-*exo*-(2'-Fluoro-3'-phenyl-pyridin-5'-yl)-7-azabicyclo[2.2.1]heptane (FPhEP) is a highly potent and selective α4β2 nAChR antagonist with subnanomolar affinity (6, 7). FPhEP is an analogue of epibatidine, which was showed to be a functional antagonist of α4β2 nAChR in mice. [^{18}F]FPhEP is being developed as a PET agent with a faster kinetics than 2-[^{18}F]FA and 6-[^{18}F]FA for the non-invasive study of α4β2 nAChR in the brain.

Related Resource Links:

- Chapters in MICAD (nACHR)
- Gene information in NCBI (nAChR).
- Articles in Online Mendelian Inheritance in Man (OMIM) (nAChR)
- Clinical trials (nAChR)
- Drug information in FDA (nAChR)

Synthesis

[PubMed]

Roger et al. (7) reported synthesis of [^{18}F]FPhEP by a 2-step reaction, which consisted of standard ^{18}F-nucleophilic fluorination of the corresponding N-Boc-protected chloro- or bromo derivatives using microwave heating for 1.5 min and acidic deprotection of the product. An average radiochemical yield was 10-20% (non-decay corrected) with a total synthesis time of 75-80 min. Specific -activities were 2.22-3.33 GBq/μmol (60-90 mCi/μmol at end of synthesis) with a radiochemical purity of >99%.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Roger et al. (7) reported [^{18}F]FPhEP had a K_d value of 660 ± 75 pM and a B_{max} value of 65 ± 2 fmol/mg protein in saturation binding assays using rat brain membranes. Cytisine and nicotine (α4β2-specific ligands) exhibited good inhibition on the [^{18}F]FPhEP binding with K_i values of 1.09 and 5.83 nM, respectively. *In vitro* autoradiography studies of rat brain slices indicated the highest binding of [^{18}F]FPhEP in the thalamus and the lowest in the corpus callosum, consistent with α4β2 receptor distribution. Nicotine (300 μM) and FPhEP (300 μM) blocked [^{18}F]FPhEP specific binding across the brain regions.

Animal Studies

Rodents

[PubMed]

No publication is currently available.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

Biodistribution PET study in one anesthetized baboon injected with 163 MBq (4.4 mCi, 2.1 nmol) [^{18}F]FPhEP was performed by Roger et al. (7) showing a rapid accumulation of radioactivity in the brain. PET study showed selective maximal uptake in the thalamus. The cerebellum showed lower binding than the other brain regions. The peak level of 4.86% injected dose(ID)/100 ml was reached in the thalamus at 20 min. [^{18}F]FPhEP radioactivity was washed out slowly in the thalamus to ~2.0% ID/100 ml at 180 min. On the other hand, injection of 430 MBq (11.6 mCi, 1.2 nmol) 2-[^{18}F]FA slowly reached a peak value of 3.94% ID/100 ml at 80-90 min after injection with also a slow clearance to 3.75% ID/100 ml at 180 min. Therefore, [^{18}F]FPhEP exhibited a faster kinetics than 2-[^{18}F]FA.

Valette et al. (8) performed PET studies in three baboons after injection of 215 MBq (5.8 mCi, 3.3 nmol) [^{18}F]FPhEP. The peak radioactivity level of 4.9 ± 0.2% ID/100 ml was reached in the thalamus at 20 min. [^{18}F]FPhEP radioactivity was washed out slowly in the thalamus to 2.0 ± 0.1% ID/100 ml at 180 min. The accumulation was the lowest in the cortex. The thalamus/cerebellum ratio was 1.4 at 30 min after injection and did not increase with time. Pretreatment with nicotine, cytisine or FPhEP reduced the

distribution volume (DV) values by 35% in the thalamus and 20% in the cortices, hippocampus, and putamen. The investigators concluded that [^{18}F]FPhEP is not a suitable PET tracer for imaging α4β2 nAChR in the brain because nicotine failed to show substantial inhibition of [^{18}F]FPhEP binding.

Human Studies

[PubMed]

No publication is currently available.

References

1. Alkondon M., Albuquerque E.X. *The nicotinic acetylcholine receptor subtypes and their function in the hippocampus and cerebral cortex.* Prog Brain Res. 2004;145:109–20. PubMed PMID: 14650910.
2. Gotti C.et al. *Brain neuronal nicotinic receptors as new targets for drug discovery.* Curr Pharm Des. 2006;12(4):407–28. PubMed PMID: 16472136.
3. Hogg R.C., Raggenbass M., Bertrand D. *Nicotinic acetylcholine receptors: from structure to brain function.* Rev Physiol Biochem Pharmacol. 2003;147:1–46. PubMed PMID: 12783266.
4. Ding Y.S.et al. *6-[18F]Fluoro-A-85380, a new PET tracer for the nicotinic acetylcholine receptor: studies in the human brain and in vivo demonstration of specific binding in white matter.* Synapse. 2004;53(3):184–9. PubMed PMID: 15236351.
5. Kimes A.S.et al. *2-[18F]F-A-85380: PET imaging of brain nicotinic acetylcholine receptors and whole body distribution in humans.* Faseb J. 2003;17(10):1331–3. PubMed PMID: 12759330.
6. Huang Y.et al. *Epibatidine analogues as selective ligands for the alpha(x)beta2-containing subtypes of nicotinic acetylcholine receptors.* Bioorg Med Chem Lett. 2005;15(19):4385–8. PubMed PMID: 16039849.
7. Roger G.et al. *Synthesis and radiosynthesis of [(18)F]FPhEP, a novel alpha(4)beta(2)-selective, epibatidine-based antagonist for PET imaging of nicotinic acetylcholine receptors.* Bioorg Med Chem. 2006;14(11):3848–58. PubMed PMID: 16455259.
8. Valette H.et al. *[18F]FPhEP and [18F]F2PhEP, two new epibatidine-based radioligands: evaluation for imaging nicotinic acetylcholine receptors in baboon brain.* Synapse. 2007;61(9):764–70. PubMed PMID: 17568410.