[^{18}F]Norchloro-fluoro-homoepibatidine

[^{18}F]NCFHEB

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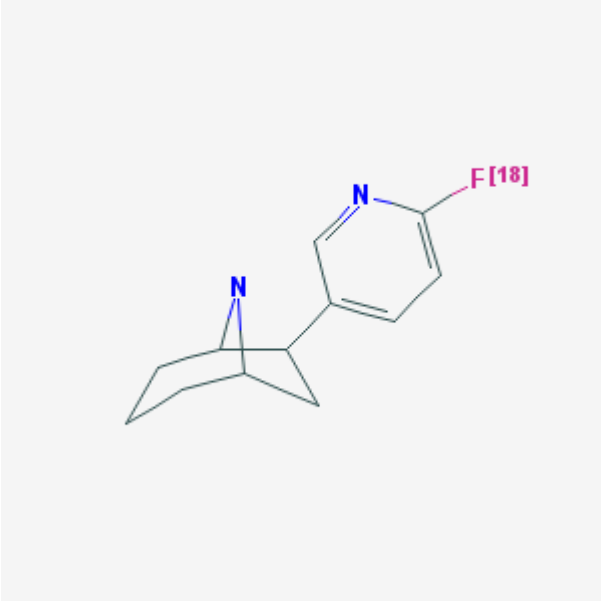
Chemical name:	[^{18}F]Norchloro-fluoro-homoepibatidine
Abbreviated name:	[^{18}F]NCFHEB
Synonym:	
Agent Category:	Compound
Target:	Neuronal α4β2 nicotinic acetylcholine receptor (nAChR)
Target Category:	Receptor-ligand binding
Method of detection:	PET
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Other Non-primate Mammals



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Background

[PubMed]

Neuronal α4β2 nicotinic cholinergic receptors (nAChRs) are part of a heterogeneous family of ligand-gated ion channels expressed in the central nervous system, where their activation by acetylcholine and nicotine 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 receptors (α2 to α10) and four subtypes of structural β receptors (β2 to β5). nAChRs have been found to be involved in cognitive processes such as learning memory and control of movement in normal subjects. nAChR dysfunction has been implicated in 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 and other health problems associated with tobacco smoking.

3-[2(S)-2-Azetidinylmethoxy]pyridine (A-85380) is a highly potent and selective α4β2 nAChR agonist with subnanomolar affinity (4, 5). 6-[^{18}F]Fluoro-A-85380 and 2-[^{18}F]fluoro-A-85380 have been studied in humans as positron emission tomography (PET) agents for α4β2 nAChR imaging in the brain. A-85380 has also been labeled as 5-[^{123}I]iodo-3-[2(S)-2-azetidinylmethoxy]pyridine (5-[^{123}I]iodo-A-85380 (5-[^{123}I]IA)), which has been developed as a single-photon emission computed tomography (SPECT) agent for the non-invasive study of nAChR in the brain. However, prolonged imaging times (2–4 h) are required for reliable quantification because of the slow kinetics of this agent. Norchloro-fluoro-homoepibatidine (NCFHEB), an analog of epibatidine, is a highly potent and selective α4β2 nAChR antagonist with subnanomolar affinity (6). NCFHEB has been shown to be a functional antagonist of α4β2 nAChR in mice. [^{18}F]NCFHEB is being developed as a PET agent for the noninvasive study of α4β2 nAChR in the brain.

Synthesis

[PubMed]

Deuther-Conrad et al. (7) reported synthesis of [^{18}F]NCFHEB by a two-step procedure, which consisted of standard ([^{18}F]KF/Kryptofix 2.2.2) ^{18}F-nucleophilic aromatic fluorination of *N*-ethoxycarbonyl-norchloro-bromo-homoepibatidine and deprotection of the product. Enantiomers ((+)[^{18}F]NCFHEB and (-)[^{18}F]NCFHEB) were separated with high-performance liquid chromatography. Average radiochemical yield was 2% (end of synthesis, based on [^{18}F]KF) for each enantiomer. Time of synthesis, radiochemical purity, and specific activity were not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Deuther-Conrad et al. (6) reported that (+)NCFHEB exhibited inhibition constant (K_i) values (obtained with the use of [^{3}H]epibatidine) of 0.064 ± 0.005, 3.81 ± 0.87, and 31.7 ± 21.7 nM in human α4β2, α3β4, and α7 receptors, respectively. (-)NCFHEB exhibited K_i values of 0.112 ± 0.035, 2.58 ± 0.89, and 119 ± 69 nM in human α4β2, α3β4, and α7 receptors, respectively. On the other hand, 2-fluoro-A-85380 exhibited K_i values of 0.069 ± 0.028, 86.4 ± 29.6, and 317 (n =1) nM in human α4β2, α3β4, and α7 receptors, respectively. Therefore, NCFHEB enantiomers exhibit binding affinities to these receptors that are similar to the binding affinities of 2-fluoro-A-85380, with a lower $K_{i,\alpha3\beta4}/K_{i,\alpha4\beta2}$ ratio than 2-fluoro-A-85380. (-)NCFHEB, (+)NCFHEB, and 2-fluoro-A-85380 had K_i values of 0.069, 0.512, and 0.475 nM for α4β2 in rat thalamic membranes, respectively.

Animal Studies

Rodents

[PubMed]

Deuther-Conrad et al. (7) reported biodistribution studies of (+)[^{18}F]NCFHEB and (-)[^{18}F]NCFHEB in mice, showing peak accumulation in the brain of 7.45% injected dose/gram (ID/g) and 5.60% ID/g at 20 min, respectively. Co-injection or pretreatment of 2-fluoro-A-85380, (-)NCFHEB, or (+)NCFHEB reduced the radioactivity in the brain by 50% to 76%. The urinary bladder had the highest accumulation (~50% ID/g), followed by the kidney (>10% ID/g) and the liver (~10% ID/g). Little radioactivity accumulation was observed in the femur. The total brain accumulation of 2-[^{18}F]fluoro-A-85380 was 3.20% ID/g at 20 min after injection.

Other Non-Primate Mammals

[PubMed]

Brust et al. (8) used PET imaging to compare the kinetics of the two enantiomers of [^{18}F]NCFHEB with 2-[^{18}F]fluoro-A85380 in the porcine brain. Juvenile female pigs (n = 24) were studied with PET using [^{18}F]NCFHEB; in a parallel experiment, nine animals received an injection (1 mg/kg) of the nAChR agonist A81418 before radiotracer administration followed by infusion (2 mg/kg per 7 h). Several compartment models were performed for quantification. (-)[^{18}F]NCFHEB and (+)[^{18}F]NCFHEB showed brain accumulation two to three times greater than 2-[^{18}F]fluoro-A-85380. All three radiotracers displayed spatially heterogeneous binding kinetics in brain regions with high (thalamus and hippocampus), moderate (striatum and cortex), or low (cerebellum) specific binding. The equilibrium of the specific binding of (-)[^{18}F]NCFHEB was reached in ~2 h, which was earlier than that of (+)[^{18}F]NCFHEB or 2-[^{18}F]fluoro-A85380. Continuous administration of A81418 significantly inhibited the specific binding of (-)[^{18}F]NCFHEB and (+)[^{18}F]NCFHEB ($P < 0.05$) by 51% to 72% in the thalamus and hippocampus. Moderate inhibition was observed in the striatum and cortex (24% to 50%) and marginal inhibition (11% to 36%) was observed in the cerebellum. The peripheral

metabolism of (-)NCFHEB and (+)[^{18}F]NCFHEB proceeded slowly with ~40% to 50% intact at 90 min after injection.

Non-Human Primates

[PubMed]

No publication is currently available.

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., Riganti L., Vailati S., Clementi F. 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. Abreo M.A., Lin N.H., Garvey D.S., Gunn D.E., Hettinger A.M., Wasicak J.T., Pavlik P.A., Martin Y.C., Donnelly-roberts D.L., Anderson D.J., Sullivan J.P., Williams M., Arneric S.P., Holladay M.W. Novel 3-Pyridyl ethers with subnanomolar affinity for central neuronal nicotinic acetylcholine receptors. J Med Chem. 1996;**39**(4):817–25. PubMed PMID: 8632405.
5. Sullivan J.P., Donnelly-Roberts D., Briggs C.A., Anderson D.J., Gopalakrishnan M., Piattoni-Kaplan M., Campbell J.E., McKenna D.G., Molinari E., Hettinger A.M., Garvey D.S., Wasicak J.T., Holladay M.W., Williams M., Arneric S.P. A-85380 [3-(2(S)-azetidinylmethoxy) pyridine]: in vitro pharmacological properties of a novel, high affinity alpha 4 beta 2 nicotinic acetylcholine receptor ligand. Neuropharmacology. 1996;**35**(6):725–34. PubMed PMID: 8887981.
6. Deuther-Conrad W., Patt J.T., Feuerbach D., Wegner F., Brust P., Steinbach J. Norchloro-fluoro-homoepibatidine: specificity to neuronal nicotinic acetylcholine receptor subtypes in vitro. Farmaco. 2004;**59**(10):785–92. PubMed PMID: 15474055.
7. Deuther-Conrad W., Patt J.T., Lockman P.R., Allen D.D., Patt M., Schildan A., Ganapathy V., Steinbach J., Sabri O., Brust P. Norchloro-fluoro-homoepibatidine (NCFHEB) - a promising radioligand for neuroimaging nicotinic acetylcholine receptors with PET. Eur Neuropsychopharmacol. 2008;**18**(3):222–9. PubMed PMID: 17728108.

8. Brust P., Patt J.T., Deuther-Conrad W., Becker G., Patt M., Schildan A., Sorger D., Kendziorra K., Meyer P., Steinbach J., Sabri O. In vivo measurement of nicotinic acetylcholine receptors with [18F]norchloro-fluoro-homoepibatidine. Synapse. 2008;**62**(3):205–18. PubMed PMID: 18088060.