N-[^{18}F]Fluoroethylpiperidin-4ylmethyl acetate

[^{18}F]FEP-4MA

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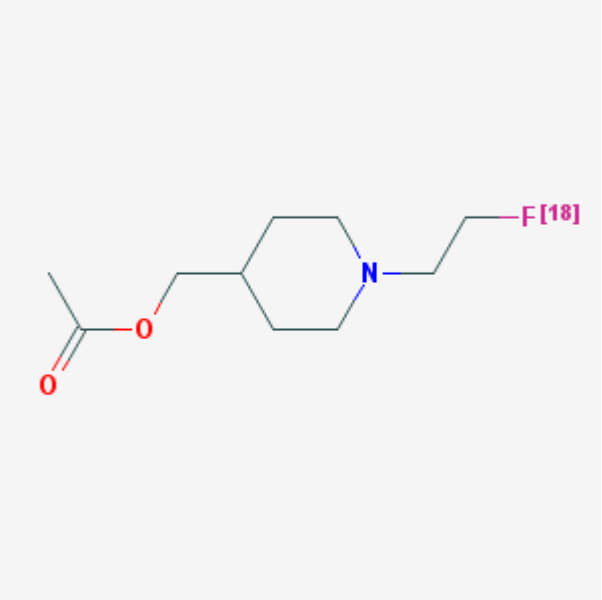
Chemical name:	*N*-[^{18}F]Fluoroethylpiperidin-4ylmethyl acetate
Abbreviated name:	[^{18}F]FEP-4MA
Synonym:	
Agent category:	Compound
Target:	Acetylcholinesterase (AChE)
Target category:	Enzyme
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



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Background

[PubMed]

Acetylcholine is an endogenous neurotransmitter at cholinergic synapses and neuroeffector junctions in the peripheral and central nervous systems. It acts on nicotinic and muscarinic receptors to mediate complex functions, such as attention, memory,

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cognition, and consciousness. Degeneration of cholinergic neurons has been observed in several neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), but not in vascular dementia. Acetylcholinesterase (AChE) is the enzyme that terminates cholinergic actions through the rapid hydrolysis of acetylcholine to choline and acetate. AChE is localized on both cholinergic and cholinoceptive neurons in the brain, with the highest activity in the striatum, thalamus, cerebellum, and cerebral cortex (1). AChE has been a target for radioligand development as well as drug development because its levels decrease in AD (1, 2). Radiolabeled AChE inhibitors and acetylcholine analog substrates are the two major approaches to mapping AChE *in vivo* in the human brain.

For measurements of AChE activity, various labeled esters of 1-methy-4-hydroxypiperidine have been designed and evaluated as acetylcholine substrate analogs (3). One of these analogs, *N*-[^{11}C]methylpiperidin-4-yl acetate ([^{11}C]MP4A), was chosen for further development as a positron emission tomography (PET) radioligand (4). [^{11}C]MP4A has a tertiary amine structure that makes it lipophilic, and thus it readily crosses the blood–brain barrier (BBB). [^{11}C]MP4A is specifically hydrolyzed by AChE (99% specificity) and yields a hydrophilic metabolite, *N*-[^{11}C]methylpiperidinol ([^{11}C]MP4OH), which is trapped in the brain because it is too polar to cross the BBB. [^{11}C]MP4A is being developed as a PET agent for the non-invasive study of brain AChE activity in patients with AD and PD. Because ^{18}F, with a longer physical half-life, has an advantage over ^{11}C, *N*-[^{18}F]fluoroethylpiperidin-4ylmethyl acetate ([^{18}F]FEP-4MA), an analog of [^{11}C]MP4A, has been evaluated as a potential PET agent for AChE activity in the brain (5).

Related Resource Links:

- Chapters in MICAD
- Gene information in NCBI (AChE).
- Articles in OMIM
- Clinical trials (AChE)
- Drug information in FDA

Synthesis

[PubMed]

Kikuchi et al. (6) reported the synthesis of [^{18}F]FEP-4MA by reacting piperidin-4-ylmethyl acetate with 1-bromo-2-[^{18}F]fluoroethane in dimethylformamide, with a radiochemical yield of ~70% (end of synthesis) after purification with high-performance liquid chromatography. The radiochemical purity was >98% with a total synthesis time of 92–96 min from the end of bombardment. The specific activity of [^{18}F]FEP-4MA was not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Kikuchi et al. (6) reported that [^{18}F]FEP-4MA was rapidly hydrolyzed to [^{18}F]FEP-MP4OH and acetic acid by rat cerebral cortical homogenate, with 86% specificity for AChE. The hydrolysis rate constant was 1.67 min^{-1}, which is similar to that of [^{11}C]MP4A.

Animal Studies

Rodents

[PubMed]

Kikuchi et al. (5) performed *ex vivo* biodistribution studies in rats, which showed rapid, high accumulation of radioactivity in various regions of the brain within minutes of injection with [^{18}F]FEP-4MA. The uptake values in striatum, hippocampus, cortex, and cerebellum were ~1.6–2.0% injected dose/g (ID/g) at 1 min, reflecting known levels of AChE activity in the brain, with >90% of radioactivity in the form of [^{18}F]FEP-4MOH. The retention fraction values were estimated from 1 min and 15 min after injection to be 0.65 and 0.45, respectively. The radioactivity levels in the blood and parietal bone were 0.4% ID/g and 0.3% ID/g at 30 min after injection, respectively. No blocking experiment was performed.

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

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