1-[^{11}C]Methylpiperidin-4-yl propionate

[^{11}C]PMP

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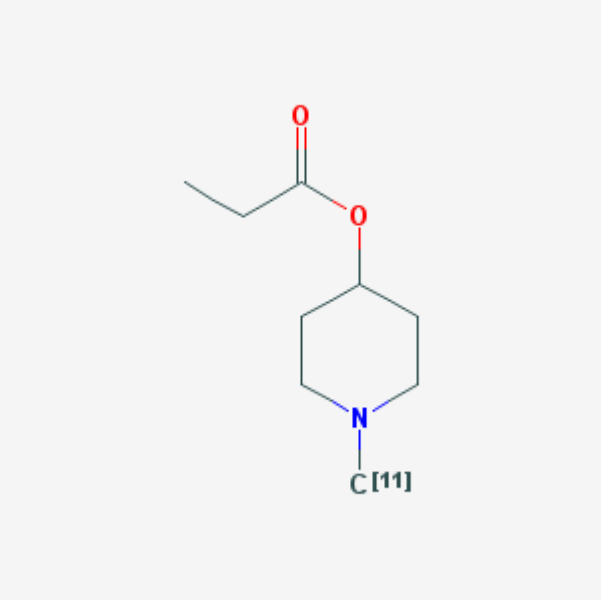
Chemical name:	1-[^{11}C]Methylpiperidin-4-yl propionate
Abbreviated name:	[^{11}C]PMP
Synonym:	[^{11}C]MP4P
Agent category:	Compound
Target:	Acetylcholinesterase (AChE)
Target category:	Enzyme
Method of detection:	PET
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Non-Human Primates • Humans



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Background

[PubMed]

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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, cognition, and consciousness. Degeneration of cholinergic neurons has been observed in several neurodegenerative disease, 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, followed by the cerebellum, thalamus, 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).

For measurements of AChE activity, various labeled esters of 1-methy-4-hydroxypiperidine have been designed and evaluated as acetylcholine substrate analogs (3). Two of them, *N*-[^{11}C]methylpiperidin-4-yl acetate ([^{11}C]MP4A) and 1-[^{11}C]methylpiperidin-4-yl propionate ([11C]PMP), were chosen for further development as radioligands for use in positron emission tomography (PET). Each has a tertiary amine structure that makes it lipophilic; thus, it readily crosses the blood-brain barrier (BBB). [^{11}C]PMP is specifically hydrolyzed by AChE (86-95% specificity) and yields a hydrophilic metabolite, *N*-[^{11}C]methylpiperidinol ([^{11}C]MP4OH), which is trapped in the brain because it cannot cross the BBB. The hydrolysis rate of MP4P is 3- to 4-fold slower than that of MP4A in rat and human brain homogenates (1), thus allowing more precise estimates of AChE activity in regions of moderate to high AChE levels. [^{11}C]PMP is being developed as a PET agent for the non-invasive study of brain AChE activity in patients with AD and PD.

Related Resource Links

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

Synthesis

[PubMed]

Snyder et al. (4) reported synthesis of [^{11}C]PMP by direct N-methylation of 4-piperidinyl propionate with [^{11}C]methyl trifluoromethanesulfonate at room temperature in dimethylformamide, with a radiochemical yield of 57% (end of synthesis) after high-performance liquid chromatography purification. Radiochemical purities were >99% with a specific activity of 41 GBq/mmol (1,500 Ci/mmol) and a total synthesis time of ~35 min.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Shinotoh et al. (1) reported that PMP was rapidly hydrolyzed to MP4OH and propanoic acid by rat and human brain homogenates with 95 and 86% specificity for AChE, respectively. The hydrolysis rate in human cerebral cortex (0.042 fraction/min/g/ml) is about 10% that in rat cerebral cortex (0.39 fraction/min/g/ml).

Animal Studies

Rodents

[PubMed]

Kilbourn et al. (5) reported that 2 min after injection in mice, [^{11}C]PMP showed rapid accumulation in the brain and a regional retention of radioactivity in the striatum (12.9 ± 0.86% of injected dose (ID)/g), cortex (10.9 ± 1.31% ID/g), hippocampus (10.5 ± 1.33% ID/g), thalamus (9.53 ± 1.1% ID/g), hypothalamus (8.67 ± 1.48% ID/g), and cerebellum (7.01 ± 0.97% ID/g), reflecting known levels of AChE activity in the rodent brain. More than 95% of radioactivity in the brain was the hydrolytic metabolite, [^{11}C]MP4OH. There was a gradual washout in all regions with time (up to 30 min). At 10 min after injection, the striatum/cerebellum, cortex/cerebellum, and striatum/cortex ratios were 3.06 ± 0.31, 1.1.79 ± 0.15, and 1.71 ± 0.19, respectively. On the other hand, for [^{11}C]MP4A, the striatum/cerebellum, cortex/cerebellum, and striatum/cortex ratios were 1.81 ± 0.20, 1.64 ± 0.12, and 1.09 ± 0.08, respectively. Therefore, [^{11}C]PMP seems to be better for discrimination among regions of high, intermediate, and low AChE activity. Retention of [^{11}C]PMP radioactivity in all regions was reduced by pretreatment with 3 mg/kg diisopropylfluorophosphate (DFP), a specific irreversible AChE inhibitor. DFP pretreatment also significantly increased the proportions of intact ester in both blood and brain. Using PET scans, Shao et al. (6) estimated [^{11}C]PMP hydrolysis rate constant (k_3) values for the striatum and cortex to be 0.1009/min and 0.0453/min, respectively.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

Kilbourn et al. (5) performed [^{11}C]PMP PET studies in one monkey and found rapid accumulation in the brain within minutes after injection. About 15% and 50% of the initial high uptake in the striatum and cortex, respectively, was washed out in the initial 15

min and then remained constant with a maximal striatum/cortex ratio of 2.25, compared with 1.8 with [^{11}C]MP4A.

Human Studies

[PubMed]

Kinetic analysis of [^{11}C]PMP for measurement of cerebral AChE activity has been performed with and without arterial blood sampling (7, 8). A three-compartment model with three parameters was used to measure AChE hydrolysis of the tracer (k_3), the transport rate constant of the tracer from the blood to the brain through the BBB (K_1), and the transport rate constant of the tracer from the brain to the blood through the BBB (k_2). Kuhl et al. (9) studied 26 healthy controls and 14 patients with AD who had no dementia; the authors used [^{11}C]PMP PET, 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG), and 5-[^{123}I]iodobenzovesamicol ([^{123}I]IBVM) for AChE activity, glucose metabolism, and vesicular acetylcholine transporter activity, respectively. The highest uptake was in the striatum, followed by the cerebellum, pons, thalamus, occipital cortex, temporal cortex, and frontal cortex. The estimated AChE distribution in the brain of the control subjects agreed with the AChE distribution at biopsies reported by others (10, 11). There was a 30% reduction of AChE activity in the cerebral cortex of the AD patients compared with the controls. Treatment with physostigmine (an AChE inhibitor) produced little effect on the [^{11}C]PMP K_1 in the controls. In contrast, there were significant decreases in the [^{11}C]PMP k_3 of all brain regions. There was a 15% decrease in cortical [^{11}C]PMP K_1 in elderly controls compared with young controls. However, there was no correlation of [^{11}C]PMP k_3 values with age and gender. In 11 AD patients, [^{11}C]PMP k_3 correlated significantly with [^{123}I]IBVM binding, but neither the [^{11}C]PMP k_3 nor [^{123}I]IBVM binding correlated with FDG uptake. After treatment with donepezil (an AChE inhibitor), cerebral cortical [^{11}C]PMP k_3 inhibition in AD brain averaged 27% in 6 patients (12).

Marshall et al. (13) studied the relationship between the severity of white matter hyperintensity (WMH) and cortical AChE activity in 11 patients with parkinsonian dementia (PDem) and 14 control subjects. [^{11}C]PMP k_3 values were significantly reduced (–20%; $P< 0.001$) in the cortex of PDem patients (0.0185 ± 0.0019/min) compared with the controls (0.0231 ± 0.0026/min). PDem subjects had higher mean severity of WMH (+20.1%) compared with control subjects ($P < 0.05$). However, there was no significant correlation of cortical [^{11}C]PMP AChE activity with WMH severity. Bohnen et al. (14) found that [^{11}C]PMP AChE activity was significantly reduced (–11%; $P < 0.05$) in the cortex in patients with mild to moderate AD (0.0201 ± 0.0018/min; $n = 15$) compared with 12 normal controls (0.0226 ± 0.0023/min). Cortical [^{11}C]PMP AChE activity was more robustly associated with functions of attention and working memory ($P = 0.01$) than with performance on primary memory tests in AD.

Internal dosimetry data for [^{11}C]PMP in humans are not yet available in the literature

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