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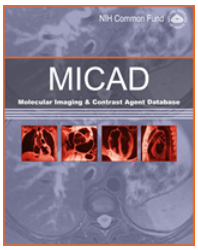


# *N*-[$^{11}$C]Methylpiperidin-4-yl acetate

## [$^{11}$C]MP4A

Kam Leung, PhD[1]

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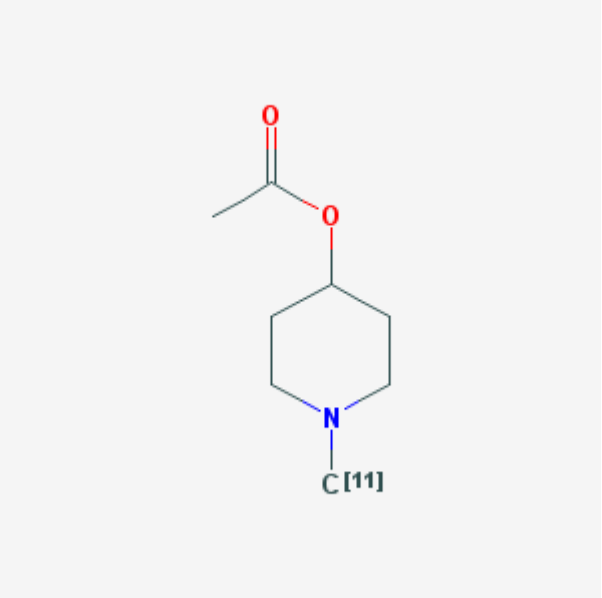
|---|---|
| **Chemical name:** | *N*-[$^{11}$C]Methylpiperidin-4-yl acetate |
| **Abbreviated name:** | [$^{11}$C]MP4A, [$^{11}$C]AMP |
| **Synonym:** | |
| **Agent category:** | Compound |
| **Target:** | Acetylcholinesterase (AChE) |
| **Target category:** | Enzyme |
| **Method of detection:** | PET |
| **Source of signal:** | $^{11}$C |
| **Activation:** | No |

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**Studies:**

- *In vitro*
- Rodents
- Non-Human Primates
- Humans

# 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, 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, thalamus,

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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. It 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.

### Related Resource Links

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

## Synthesis

[PubMed]

Irie et al. (3) reported the synthesis of [$^{14}$C]MP4A by direct N-methylation of piperidin-4-yl acetate with [$^{14}$C]methyl iodine in acetone, with a radiochemical yield of 80% (end of synthesis) after purification via high-performance liquid chromatography. Radiochemical purities were >97% with a total synthesis time of ~30 min. Iyo et al. (4) reported a specific activity of 18 GBq/μmol (0.49 Ci/μmol) when they used this same method to prepare [$^{11}$C]MP4A . Nguyen et al. (5) prepared [$^{11}$C]MP4A using [$^{11}$C]methyl triflate for N-methylation in dimethyl sulfoxide, with radiochemical yields of 10-40%. Carpinelli et al. (6) described a fully automated synthesis of [$^{11}$C]MP4A using [$^{11}$C]methyl iodine for N-methylation of piperidin-4-yl acetate hydrochloride in anhydrous dimethylformamide; the radiochemical purity of the product was >98%. The radiochemical yields were 20-60% within 40 min after end of bombardment, with an average specific activity of 37 GBq/μmol (1 Ci/μmol) ($n$ = 10).

## *In Vitro* Studies: Testing in Cells and Tissues

[PubMed]

Irie et al. (7) reported that MP4A was rapidly hydrolyzed to MP4OH and acetic acid by mouse, rat, and human brain homogenates, with 94-99% specificity for AChE. The hydrolysis rate in human cerebral cortex (0.16/fraction/min/g/ml) is about 10% of that in the cerebral cortex of the rat and mouse (1.54/fraction/min/g/ml).

## Animal Studies

### Rodents

[PubMed]

Biodistribution studies by Irie et al. (7) in mice showed rapid, high accumulation of radioactivity in the brain within minutes after injection of [$^{14}$C]MP4A. The uptakes in striatum, cortex, and cerebellum were about 10%

of injected dose/g at 1 min, and >95% of radioactivity was the hydrolytic metabolite, [$^{14}$C]MP4OH. There was little difference in regional blood flow measured by [$^{123}$I]isopropyliodoamphetamine ([$^{123}$I]IMP). In contrast, [$^{14}$C]MP4A showed heterogeneous distributions, with striatum/cerebellum and cortex/cerebellum ratios of 2.1-3.8 and 1.4-2.0, respectively.

Kilbourn et al. (8) reported that 30 min after injection in mice, [$^{11}$C]MP4A showed rapid accumulation in the brain and a regional retention of radioactivity (striatum > cortex, hippocampus > hypothalamus > cerebellum) reflecting known levels of AChE activity in the brain, with >95% of radioactivity in the form of [$^{11}$C]MP4OH. Striatum/cerebellum and striatum/cortex ratios were 1.94 ± 0.16 and 1.03 ± 0.14, respectively. Retention of radioactivity in all regions was reduced by pretreatment with 3 mg/kg diisopropylfluorophosphate (DFP), a specific irreversible AChE inhibitor. DFP treatment also significantly increased the proportions of intact ester in both the blood and brain.

## Other Non-Primate Mammals

[PubMed]

No publication is currently available.

## Non-Human Primates

[PubMed]

Tsukada et al. (9) performed PET studies with [$^{11}$C]MP4A in 5 young (5.2 ± 1.1 years old) and 5 aged (20.3 ± 2.6 years old) male rhesus monkeys and found rapid accumulation in the brain within minutes after injection. The highest uptake was in the striatum and thalamus, followed by the cerebellum, occipital cortex, temporal cortex, and frontal cortex. Quantitative analysis of [$^{11}$C]MP4A uptake was usually described by a three-compartment model with three parameters to measure AChE activity ($k_3$) with or without blood sampling. The striatum or cerebellum, used as a "reference region" because of their high AChE activity, reflected a biologic integrator of plasma input function during PET scanning. Donepezil (AChE inhibitor) at doses of 50 and 250 μg/kg suppressed the AChE activity ($k_3$) of [$^{11}$C]MP4A in all cortical regions in a dose-dependent manner in both age groups. However, the suppression was greater in young than in aged monkeys. AChE inhibition by donepezil led to a dose-dependent increase in acetylcholine levels in the prefrontal cortex of young animals as measured by microdialysis. Aged monkeys showed impaired working memory performance compared with young monkeys, and the impaired performance was partly improved by the administration of donepezil because of facilitation of the cholinergic neuronal system by AChE inhibition.

# Human Studies

[PubMed]

Kinetic analysis of [$^{11}$C]MP4A for measurement of cerebral AChE activity can be performed with or without arterial blood sampling (10-13). A three-compartment model with three parameters is used to measure AChE hydrolysis of the tracer ($k_3$), the transport rate constant of the tracer from blood to brain through the BBB ($K_1$), and the transport rate constant of the tracer from brain to blood through the BBB ($k_2$). Using [$^{11}$C]MP4A PET, Iyo et al. (4) studied eight elderly healthy controls and five patients with AD who had mild dementia. The estimated AChE distribution in the brain of the control subjects agreed with the AChE distribution at biopsy. The median $K_1$ and $k_2$ values for all regions in the controls were 0.54 ± 0.10 ml/g/min and 0.13 ± 0.02/min, respectively. The median $K_1$ and $k_2$ values in the AD patients were 0.42 ± 0.07ml/g/min and 0.11 ± 0.02/min, respectively. This reduction is attributable to the cortical reduction of regional blood flow in the AD patients as measured by [$^{123}$I]IMP. All patients with AD had multiple cortical regions with a reduced $k_3$ value compared with controls. The reduction in $k_3$ was heterogeneous both regionally and individually. The reduction was more

marked in the temporoparietal cortex, with an average reduction rate of 31% in the temporal and 38% in the parietal cortex, with less pronounced reductions in other cortical lesions (19% in the frontal, 24% in the occipital, and 20% in the sensorimotor cortex). Each patient was found to have at least two cortical regions with significantly reduced AChE activity.

Shinotoh et al. (14) subsequently confirmed a significant reduction in $k_3$ values in the neocortex, hippocampus, and amygdale in 15 early-onset AD patients, whereas $k_3$ values were significantly reduced only in the temporoparietal cortex and amygdale in late-onset AD patients. There was a significant correlation between the cortical $k_3$ values and the Mini-Mental State Examination scores. Herholz et al. (15) found that AChE activity was significantly reduced in the amygdale and cerebral cortex in patients with mild to moderate AD, whereas reduction of cerebral blood flow and glucose metabolism was more limited to temporoparietal regions. Rinne et al. (16) cautioned that the $k_3$ values in the hippocampus were only slightly reduced in mild cognitive impairment and early AD compared with AD, limiting their usefulness in detecting early AD.

Hilker et al. (17) performed combined PET with [$^{11}$C]MP4A and [$^{18}$F]fluorodopa (FDOPA) for evaluation of cholinergic and dopaminergic transmitter changes in 17 non-demented patients with PD and 10 PD patients with associated dementia (PDD) compared with 31 age-matched controls. The striatal FDOPA uptake was significantly decreased in PD and PDD without differences between the groups. The global cortical $k_3$ values for [$^{11}$C]MP4A were strongly reduced in PDD (29.7%; $P < 0.001$) and moderately decreased in PD (10.7%; $P < 0.01$) compared with controls. The PDD group had lower parietal $k_3$ values for [$^{11}$C]MP4A than did patients with PD. Frontal and temporoparietal cortices showed a significant correlation of striatal FDOPA reduction and decreased $k_3$ for [$^{11}$C]MP4A in patients with PDD.

Internal dosimetry data for [$^{11}$C]MP4A in humans have not yet been available in the literature.

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