(+)-*p*-[^{11}C]Methylvesamicolphenoxy)

(+)-[^{11}C]PMV

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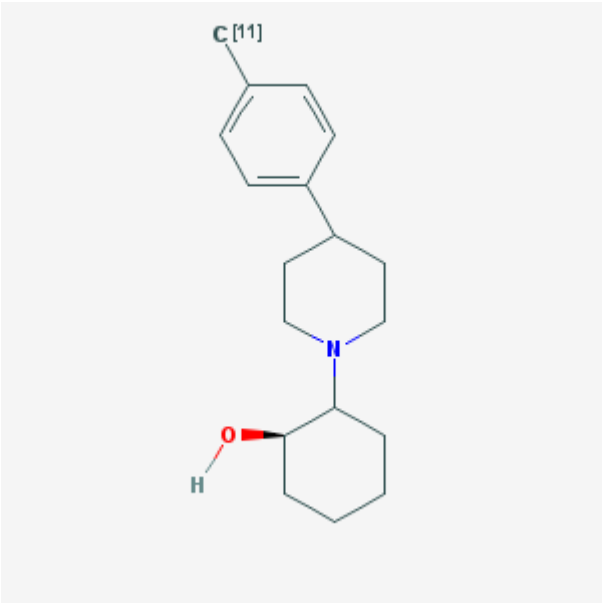
Chemical name:	(+)-*p*-[^{11}C]Methylvesamicol
Abbreviated name:	(+)-[^{11}C]PMV
Synonym:	(+)-2-[4-(4-[^{11}C]Methyl)phenylpiperidino]cyclohexanol
Agent Category:	Compound
Target:	Sigma (σ) receptor
Target Category:	Receptor binding
Method of detection:	Positron Emission Tomography (PET)
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents



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Background

[PubMed]

(+)-*p*-[^{11}C]Methylvesamicol ((+)-[^{11}C]PMV) is a radioligand developed for positron emission tomography (PET) imaging of the sigma (σ) receptors. It is a sigma (σ) receptor ligand labeled with ^{11}C, a positron emitter with a physical half-life ($t_{½}$) of 20.4 min (1).

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σ receptors are functional, membrane-bound proteins distributed in the central nervous system (CNS) and peripheral organs (2). The CNS σ receptors are unique binding sites related to higher brain functions (3). They are distinct from opiate and phencyclidine (PCP) binding sites. There are at least two subtypes of σ receptors, σ_1 and σ_2 receptors. The precise mechanism of the functional response of these receptors is not entirely known. These receptors appear to be involved in numerous pharmacologic and physiologic functions, and they also modulate a number of central neurotransmitter systems, including noradrenergic, glutamatergic, and dopaminergic systems. PCP and derivatives, cocaine and derivatives, some neuroleptics, atyptical antipsychotic agents, and other chemically unrelated compounds can bind to the σ receptor sites. Studies have shown that these receptors may play a role in the pathogenesis of psychiatric disorders (4, 5).

The σ_1 receptor subtypes appear to play a role in motor functions and potassium channels (2). The σ_2 receptor subtypes are implicated in CNS disorders and malignant neoplastic diseases. Because of these effects, σ receptor ligands may be useful for detection and treatment in neurology and oncology. Matsuno et al. (6) developed a potent σ agonist, 1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl)-piperazine dihydrochloride (SA4503), which is highly selective for σ_1 receptors compared to σ_2 receptors (6). SA4503 can be labeled with ^{11}C or ^{18}F for PET studies of σ receptors (1, 7, 8). Another potential PET ligand is methylvesamicol, an analog of vesamicol. Vesamicol has been found to block the release of acetylcholine from cholinergic nerve terminals, and a number of radioiodine-, ^{18}F-, and ^{11}C-labeled vesamicol derivatives have been synthesized as PET or single-photon emission computed tomography (SPECT) radioligands to map vesicular cholinergic transporter (VAChT) sites (9, 10). Some of these vesamicol analogs have been shown to have moderate to high affinity for σ receptors (11, 12). Shiba et al. (13) showed that radiodinated (+)-*p*-iodovesamicol bound to σ_1 receptors with high affinity and selectivity. In addition, Shiba et al. (12) reported that the (+)-enantiomer of methylvesamicol, (+)-PMV, had high affinity for the σ_1 receptor and very low affinity for VAChT.

Synthesis

[PubMed]

Shiba et al. (14) reported the synthesis of (+)-PMV from 4-(4-methylphenyl)piperidine. The 10-step reactions produced an overall yield of 1.3-4.1%. (+)-*p*-Tributylstannylvesamicol was used as the precursor of (+)-[^{11}C]PMV prepared by a palladium-catalyzed reaction of the corresponding iodovesamicol. Radiosynthesis of (+)-[^{11}C]PMV was performed by substituting the tributylstannyl group with [^{11}C]methyl iodide in a palladium-promoted cross-coupling reaction (15). Briefly, [^{11}C]methyl iodide was produced from [^{11}C]CO_2 and trapped in an N,N-dimethylformamide solution containing the precursor, tris(dibenzylideneacetone)dipalladium, tri(*o*-tolyl)phosphine, copper chloride, and potassium carbonate and then cooled by air. The reaction mixture was heated at 80°C for 3 min. After the addition of ammonium acetate, the reaction mixture was filtered and purified by high-performance liquid chromatography (HPLC).

The radiochemical yield was 7.7-19% based on [^{11}C]methyl iodide, and the radiochemical purity was >97%. The specific activity of (+)-[^{11}C]PMV was 41-162 TBq/mmol (1,107-4,374 Ci/mmol).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Shiba et al. (14) reported the *in vitro* binding affinities of (+)-PMV to the σ receptors and VAChT. *In vitro* competitive binding studies were conducted with (−)-[^{3}H]vesamicol, (+)-[^{3}H]pentazocine, or [^{3}H]DTG in rat cerebral or liver membrane preparations. The K_i values (nM) were 3.0 ± 0.2, 40.7 ± 2.9, and 199 ± 32 for the σ_1 receptor, the σ_2 receptor, and VAChT, respectively. In comparison, SA4503 had K_i values of 4.4 ± 1.0, 242 ± 17, and 50.2 ± 7.2 for the σ_1 receptor, the σ_2 receptor, and VAChT, respectively.

Animal Studies

Rodents

[PubMed]

In a rat distribution study, an i.v. dose of 10 MBq/0.13 nmol (0.27 mCi/0.13 nmol) (+)-[^{11}C]PMV was administered to each rat (15). The radioactivity levels (n = 4) in the brain were 0.97 ± 0.11, 0.96 ± 0.17, 1.00 ± 0.07, and 0.85 ± 0.08% injected dose (ID)/g at 5, 15, 30, and 60 min, respectively. The relative regional brain distribution was: cerebral cortex > cerebellum ≈ striatum > hippocampus. The striatum/cerebellum ratio decreased slightly from 1.01 ± 0.04 to 0.94 ± 0.05 at 60 min. In comparison, the ratio of [^{11}C]SA4503 remained constant with 0.99 ± 0.05 at 5 min and 1.03 ± 0.02 at 60 min. Pretreatment with 50 µmol/kg of (±)-pentazocine reduced the radioactivity levels of (+)-[^{11}C]PMV in all brain regions by 50%. Co-injections with SA4503, haloperidol, (±)-PMV, and (−)-vesamicol also reduced the whole-brain radioactivity levels by 39-57%. Blood radioactivity cleared rapidly. At 5 min after injection, the levels of radioactivity in various organs were 4.66 ± 1.04 (lung), 1.39 ± 0.37 (pancreas), 1.32 ± 0.19 (kidney), 0.93 ± 0.09 (heart), 0.36 ± 0.10 (liver) and 0.11 ± 0.03% ID/g (blood). After 60 min, these levels changed to 2.37 ± 0.42 (lung), 2.00 ± 0.48 (pancreas), 0.81 ± 0.12 (kidney), 0.50 ± 0.05 (heart), 0.65 ± 0.06 (liver) and 0.045 ± 0.005% ID/g (blood). Analysis of (+)-[^{11}C]PMV metabolites by HPLC in the plasma and brain samples obtained at 30 min after injection showed that 95% and 21% of (+)-[^{11}C]PMV remained in the brain and plasma, respectively.

Ex vivo autoradiography of (+)-[^{11}C]PMV (110 MBq/1.4-1.8 nmol (2.97 mCi/1.4-1.8 nmol) in rats showed brain distribution similar to [^{11}C]SA4503 at 15 or 30 min after injection (15).

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.

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