(*R*)-2-[^{11}C]Methoxy-*N*-*n*-propylnorapomorphine

[^{11}C]MNPA

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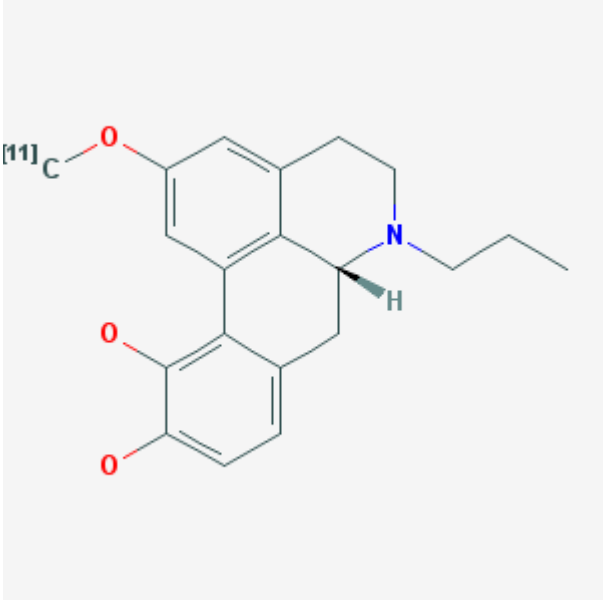
Chemical name:	(*R*)-2-[^{11}C]Methoxy-*N*-*n*-propylnorapomorphine
Abbreviated name:	[^{11}C]MNPA
Synonym:	
Agent Category:	Compound
Target:	Dopamine receptors (D_2 and D_3)
Target Category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates • Humans



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Background

[PubMed]

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Dopamine, a neurotransmitter, plays an important role in the mediation of movement, cognition, and emotion (1, 2). Dopamine receptors are involved in the pathophysiology of neuropsychiatric diseases, such as Parkinson's disease, Alzheimer's disease, Huntington's disease, and schizophrenia (3). Five subtypes of dopamine receptors, D_1 through D_5, have been well characterized pharmacologically and biochemically (4). These five subtypes are classified into two subfamilies: D_1-like (D_1 and D_5) and D_2-like (D_2, D_3, and D_4) dopamine receptors. D_1- and D_2-like receptors exert synergistic as well as opposite effects at both the biochemical and overall system level. A great majority of striatal D_1 and D_2 receptors are localized postsynaptically on caudate-putamen neurons and to a lesser extent presynaptically on nigrostriatal axons.

Dopamine receptors are G-protein-coupled receptors and exist in high- and low-affinity states with respect to agonist binding. The two states are interconvertible. In the high-affinity state, the receptor is coupled to G-proteins, whereas in the low-affinity state, it is not. Dopamine has a K_d of 7 nM for the high-affinity state (K_{high}) and a K_d of 1,720 nM for the low-affinity state (K_{low}) (5). Under physiologic conditions, dopamine is expected to bind predominately to receptors in the high-affinity state. The high-affinity state has been suggested to be the functional form of the dopamine receptors.

Substituted benzamides, such as sulpiride, raclopride, and iodobenzamide, are specific ligands with only moderate affinity for the D_2 receptors, making studies of extrastriatal D_2 receptors difficult (6-8). In binding studies, [^{123}I]-labeled epidepride, an analog of isoremoxipride, was found to have high potency and low nonspecific binding and to be selective for striatal and extrastriatal D_2 receptors (9). Epidepride has marginal binding to D_4 receptors, with little affinity for other known neurotransmitter receptors. (S)-*N*-((1-Allyl-2-pyrrolidinyl)methyl)-5-(3-[^{18}F]fluoropropyl)-2,3-dimethoxybenzamide ([^{18}F]fallypride), an analog of epidepride, was found to be a selective, high-affinity antagonist of $D_{2/3}$ receptors (10), and in positron emission tomography (PET) *in vivo* studies (11-13), it identified extrastriatal $D_{2/3}$ receptors. However, none of these antagonists distinguishes between the high- and low-affinity states of the D_2 receptors. (–)-*N*-Propyl-norapomorphine (NPA) was reported to have K_{high} and K_{low} values of 0.07-0.4 and 20-200 nM, respectively (5, 14-16). This provides a >50-fold selectivity for the high-affinity over the low-affinity receptors. NPA has good affinity (K_i = 0.3 nM) for D_3 receptors but not for other neurotransmitters (17). (*R*)-2-Methoxy-*N*-*n*-propylnorapomorphine (MNPA) is a methoxy analog of NPA and a selective D_2-like receptor agonist with a high affinity (K_i = 0.17 nM) and a D_2/D_1 potency ratio of 10,500 (18, 19). [^{11}C]MNPA is being developed as a PET agent for the non-invasive study of the high-affinity state of the $D_{2/3}$ receptors in the brain.

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Related Resource Links:

- Chapters in MICAD (Dopamine receptors)
- Gene information in NCBI (D_2 receptor,D_3 receptor)

- Articles in Online Mendelian Inheritance in Man (OMIM) (D_2 receptor, D_3 receptor)
- Clinical trials (Dopamine receptors)
- Drug information in Food and Drug Administration (Dopamine receptors)

Synthesis

[PubMed]

Finnema et al. (20) reported a synthesis of [^{11}C]MNPA that involved direct O-methylation of (*R*)-2-hydroxy-NPA with [^{11}C]methyl iodide and NaOH in dimethyl sulfoxide, with a radiochemical yield of 75% (based on [^{11}C]methyl iodide) at end of synthesis and an average specific activity of 13 GBq/μmol (350 Ci/mmol at end of synthesis) after high-performance liquid chromatography (HPLC) purification. Radiochemical purities were >98% with a total synthesis time of 30-35 min.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In competition binding to dopamine receptors in membranes of rat striatum, MNPA had K_i values of 1,780 and 0.17 nM for D_1 and D_2 receptors, respectively. The D_2/D_1 potency ratio was 10,500 for MNPA (19).

Animal Studies

Rodents

[PubMed]

Seneca et al. (21) performed [^{11}C]MNPA PET brain scans in normal male rats for 90 min. The striatal binding potential (BP_{ND}) values (n = 5) were 0.93 ± 0.12 and 0.83 ± 0.13 for kinetic and equilibrium reference tissue (cerebellum) methods, respectively. Depletion of endogenous dopamine with reserpine plus α-methyl-p-tyrosine increased the BP_{ND} values by ~100%. Thus, occupancy by D2/3 receptors by endogenous dopamine was calculated to be ~53%. Raclopride (2 mg/kg) displaced striatal activity by ~83% when injected during the steady state (50 min after injection of [^{11}C]MNPA), whereas BP 897 (a selective D_3 compound, 0.5 mg/kg) displaced the striatal activity by <10%. There were two less lipophilic radiometabolites and one more lipophilic radiometabolite than MNPA with 10% of total radioactivity in the brain at 30 min after injection. On the other hand, there was 8% of radiometabolites in the brain after dopamine depletion. Radiometabolites in the plasma were 71.4 ± 16.4% of total radioactivity at baseline and 61.3 ± 19.3% after dopamine depletion.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

[^{11}C]MNPA PET studies in non-human primates have provided useful assessment of the D_2 receptor in the brain, showing localization of [^{11}C]MNPA in the putamen and caudate. Finnema et al. (20) showed highest uptake in the striatum, moderate uptake in the thalamus, and low uptake in the cerebellum of 2 cynomolgus monkeys, with a striatum/cerebellum ratio of 2.23 ± 0.21 and thalamus/cerebellum ratio of 1.37 ± 0.06 at 72-78 min after injection of 56 MBq (1.5 mCi) of [^{11}C]MNPA. About 4.5% of the injected radioactivity was in the brain at 5 min. This uptake is higher than the 1-2% reported previously for [^{11}C]raclopride, a D_2 antagonist (22). The striatal accumulation of [^{11}C]MNPA was inhibited (79% reduction) by pretreatment with raclopride (1 mg/kg) with a striatum/cerebellum ratio of 1.26 at 78 min after injection. The fraction of unchanged [^{11}C]MNPA in plasma, as determined by HPLC, was 50 and 20% at 4 and 45 min after injection, respectively. All radiolabeled metabolites were more polar than the parent compound and would not be expected to cross the blood-brain barrier.

Seneca et al. (23) studied 4 cynomolgus monkeys with [^{11}C]raclopride (a D_2 antagonist) and [^{11}C]MNPA under baseline conditions and after administration of the potent dopamine releaser amphetamine. A two-parameter multilinear reference tissue model was used to derive the striatal binding potential (BP). The [^{11}C]raclopride BP was reduced by 2, 16, 15, and 23% after amphetamine doses of 0.1, 0.2, 0.5, and 1.0 mg/kg, respectively. [^{11}C]MNPA BP was reduced by 4, 23, 25, and 46% after amphetamine doses of 0.1, 0.2, 0.5, and 1.0 mg/kg, respectively. Thus, endogenous dopamine was 50% more effective at competing with [^{11}C]MNPA binding compared with [^{11}C]raclopride binding, which is consistent with the pharmacology of these tracers (agonist *versus* antagonist). These results also suggest that 61% of D_2 receptors are configured in a state of high affinity for agonists *in vivo*. [^{11}C]MNPA is able to detect the change in dopamine levels induced by D-amphetamine and is more vulnerable to competition by endogenous dopamine than by the antagonist radiotracer [^{11}C]raclopride. The large proportion of high-affinity sites might explain the vulnerability of D_2 radiotracers to competition by endogenous dopamine and is consistent with the reported *in vivo* binding of the agonist radiotracer [^{11}C]MNPA. Raclopride would be expected to bind to both high- and low-affinity sites with the same affinity and therefore would be present in proportion to the ratio of the sites. Dopamine competes only at high-affinity sites; therefore, the competition with MNPA, which also is bound only to high-affinity sites, will be more efficient.

Human Studies

[PubMed]

Otsuka et al. (24) performed 90-min dynamic PET scans in 10 healthy men (age = 27.7 ± 5.4 y) after an intravenous injection of 219 MBq (6 mCi) [^{11}C]MNPA. BP_{ND} was

calculated using the indirect kinetic method with a metabolite-corrected arterial input function, the simplified reference tissue model (SRTM) and transient equilibrium methods. BP_{ND} values obtained by kinetic analysis were 0.82 ± 0.09, 0.59 ± 0.11, and 0.28 ±0.06 in the putamen, caudate, and thalamus, respectively. BP_{ND} values obtained by the SRTM and transient equilibrium methods were in good agreement with those obtained by the indirect kinetic method (r = 0.98 and r = 0.93, respectively).

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Intramural Research Program

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