3-*N*-[^{11}C]Methylspiperone

[^{11}C]NMSP

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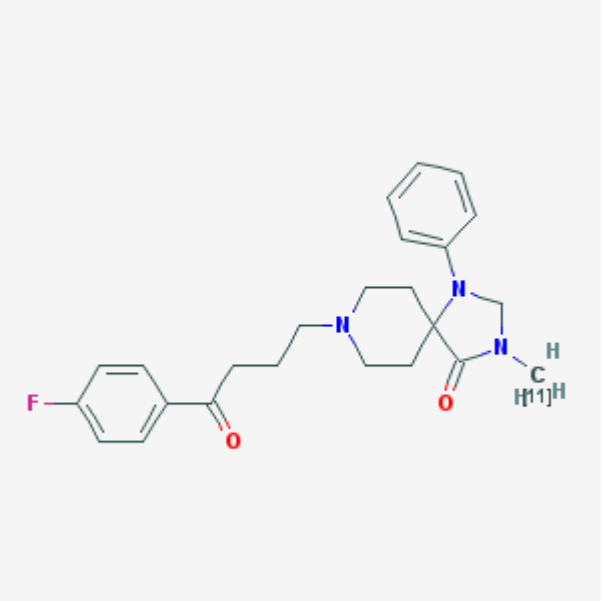
Chemical name:	3-*N*-[^{11}C]Methylspiperone
Abbreviated name:	[^{11}C]NMSP
Synonym:	
Agent Category:	Compound
Target:	5-HT$_{2A}$ serotonin receptor, dopamine D$_{2/3}$ receptors
Target Category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals • Non-human primates • Humans



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Background

[PubMed]

Dopamine, a neurotransmitter, plays an important role in the mediation of movement, cognition, and emotion (1, 2). Dopamine shortage plays a role in various neuropsychiatric disorders, such as Parkinson's disease (PD), schizophrenia, autism, attention deficit hyperactivity disorder, and drug abuse. Two subtypes of dopamine receptors, D_1 and $D_{2/3}$, were well characterized pharmacologically and biochemically (3). $D_{2/3}$ dopamine receptors have been implicated in the pathophysiology of PD, Alzheimer's disease, Huntington's disease (HD), and schizophrenia (4).

Serotonin (5-hydroxytryptamine, 5-HT) has diverse physiological roles as a neurotransmitter in the central nervous system (5). It also is a regulator of smooth muscle function and platelet aggregation. The brain cortical 5-HT system has been implicated in several neuropsychiatric disorders, including major depression, anxiety, obsessive-compulsive disorder, and schizophrenia (6, 7).

Spiperone and its analog, 3-*N*-methylspiperone (NMSP), are high-affinity $D_{2/3}$ dopamine and 5-HT_{2A} serotonin receptor antagonists, showing a low affinity for α_1-adrenergic receptors (8, 9). 3-*N*-[^{11}C]Methylspiperone ([^{11}C]NMSP) has been studied as a positron emission tomography (PET) tracer for imaging $D_{2/3}$ and $5HT_{2A}$ receptor densities.

Related Resource Links:

- Chapters in MICAD (5-HT_{2A}, Dopamine receptors)
- Gene information in NCBI (5-HT_{2A}, D_2 receptor,D_3 receptor)
- Articles in Online Mendelian Inheritance in Man (OMIM) (5-HT_{2A}, D_2 receptor, D_3 receptor)
- Clinical trials (5-HT_{2A}, Dopamine receptors)
- Drug information in Food and Drug Administration (5-HT_{2A}, Dopamine receptors)

Synthesis

[PubMed]

A continuous flow procedure was used for the synthesis of [^{11}C]methyl iodide from [^{11}C]CO_2. Alkylation of the amide nitrogen in spiperone in tetrabutylammonium hydroxide solution by [^{11}C]methyl iodide provided [^{11}C]NMSP in 20-40% radiochemical yield against [^{11}C]CO_2 in 40 min (10). [^{11}C]NMSP was purified by high-performance liquid chromatography (HPLC). The specific activity was 10 GBq/μmol (270 mCi/μmol) at the end of synthesis (EOS). Omokawa et al. (11) and Dannals et al. (12) reported the time required for the synthesis and purification of [^{11}C]NMSP from [^{11}C] CO_2 and spiperone to be 20-21 min with radiochemical yields of 21-35%. [^{11}C]NMSP has been

prepared automatically with a high specific activity (37 ± 18 GBq/μmol or 1 Ci/μmol at EOS) at 98.3 ± 1.0% radiochemical purity in 29 min of total synthesis time (13).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

NMSP was reported to have selective binding affinity to D_2 (striatum) and 5-HT_{2A} (frontal cortex) receptor sites in homogenates of rat brain membranes (14). The K_d value of [^{3}H]NMSP was 0.28 nM when the 5-HT_{2A} binding sites in the striatum were blocked by 40 nM ketanserin and 0.32 nM without blocking. The K_d value of [^{3}H]raclopride was 2.08 nM. The D_2 receptor binding density (B_{max}) was almost identical for both radioligands (20 fmol/mg tissue). The B_{max} of [^{3}H]NMSP for 5-HT_{2A} in the frontal cortex was 6.8 fmol/mg (35% of the total binding).

Using human putamen homogenates, the K_d values of [^{3}H]NMSP and [^{3}H]raclopride were 0.16 nM (0.22 nM in the presence of ketanserin) and 3.89 nM, respectively (14). The D_2 receptor binding density (B_{max}) was almost identical for both radioligands (10 fmol/mg tissue). The B_{max} of [^{3}H]NMSP for 5-HT_{2A} was 3.3 fmol/mg tissue (30% of the total binding). The dissociation half-life values as measured by the addition of (+)-butaclamol were 14.8 and 1.19 min with [^{3}H]NMSP and [^{3}H]raclopride, respectively. NMSP was found to block the binding of [^{3}H]raclopride competitively, whereas raclopride blocked the binding of [^{3}H]NMSP both competitively and noncompetitively. Dopamine was found to be more potent in inhibiting [^{3}H]raclopride than inhibiting [^{3}H]NMSP binding to D_2 receptors, partly because of the lower affinity of raclopride.

Animal Studies

Rodents

[PubMed]

Biodistribution studies in mice showed a high accumulation of radioactivity in the liver (9.98% injected dose (ID)/g) and kidneys (3.94% ID/g) at 30 min after injection of [^{11}C]NMSP (15). The brain had a moderate uptake of 1.13% ID/g. The striatum had an uptake of 4.89% ID/g at 60 min with a striatum-to-cerebellum ratio of 20:1.

In the biodistribution studies in rats, there was a high accumulation of radioactivity in the liver, lung, and kidneys, whereas the brain radioactivity was not as high (16). The radioactivity in the striatum increased from 0.98% ID/g at 10 min to 1.9% at 60 min. On the other hand, the radioactivity in the cerebellum, which contains few or no D_2 receptors, decreased from 0.29% at 10 min to 0.19% at 60 min. In the striatum, *in vivo* saturation and displacement studies estimated a B_{max} of 10-14 fmol/mg of tissue for [^{11}C]NMSP and a K_d of 10-20 nmol/kg of body weight. Pretreatment of 5 mg/kg of spiperone 15 min before [^{11}C]NMSP injection caused more inhibition than 15 min after

[^{11}C]NMSP injection. This indicated that [^{11}C]NMSP bound tightly to its receptor sites in the striatum.

Other Non-Primate Mammals

[PubMed]

Using PET, Rosa-Neto et al. (17) reported the binding potentials (PBs, ratios of B_{max} to K_d) of [^{11}C]raclopride and [^{11}C]NMSP in brain of living pigs, first in a baseline condition and then at 45 and 165 min after intravenous infusion of methylenedioxymethamphetamine (MDMA, "Ecstasy") (1 mg/kg). Concomitant studies of cerebral blood flow did not reveal significant perfusion changes in the cerebellum reference region or in striatum. Relative to the baseline PB of [^{11}C]raclopride for dopamine D_2 receptors in striatum (PB = 1.5-2.2), MDMA treatment reduced PB by 35% in the first post-treatment scan and by 22% in the second post-treatment scan. However, the baseline PB of [^{11}C]NMSP for dopamine D_2 and 5-HT_{2A} receptors in striatum (PB = 4-5) was decreased by 30% in the first scan and by 50% in the second scan. Therefore, a simultaneous release of dopamine and serotonin induced by MDMA in brain may account for the progressive decline in the availability of [^{11}C]NMSP binding sites in striatum.

Non-Human Primates

[PubMed]

[^{11}C]NMSP PET studies in non-human primates have provided useful assessments of the D_2 and 5-HT_{2A} receptors in the brain [PubMed]. Eckernas et al. (18) showed a selective uptake in putamen (7.16% ID/cm^3) over the frontal cortex (1.68% ID/cm^3) and in the cerebellum (0.94% ID/cm^3) in baboon brains at 60 min after injection. The striatum [^{11}C]NMSP retention was blocked by pretreatment with excess unlabeled NMSP (0.075 mg/kg).

Clozapine, a neuroleptic drug in the treatment of schizophrenia by dopamine receptor blockade, blocked [^{11}C]NMSP accumulation in the striatum of a monkey pretreated with 0.3 and 3 mg/kg of clozapine (19). D-Amphetamine is known to induce a marked release of dopamine to the synaptic cleft (20). D-Amphetamine administration to monkeys decreased [^{11}C]raclopride binding by 31.2 ± 8.1% but only by 6.0 ± 17.5% in [^{11}C]NMSP binding in the striatum (21). [^{11}C]NMSP was not sensitive enough to detect the change in dopamine levels induced by D-amphetamine in this study.

Using a system to study conscious monkeys, a significant increase in accumulation of [^{11}C]NMSP was observed in the striatum of monkeys administered with ketamine (5 mg/kg) compared with the level in the conscious state, whereas no significant change was observed in the frontal cortex and cerebellum (22). This dose of ketamine caused sedation accompanied by psychotic symptoms, such as nystagmus and stereotyped movements of extremities. Kinetic analysis revealed that the value of the association constant for [^{11}C]NMSP binding in the striatum was increased to approximately 130% by ketamine

compared with the control values. Furthermore, the release of dopamine from the striatum measured by microdialysis was not affected by ketamine anesthesia. It was concluded that ketamine facilitates striatal dopaminergic neurotransmission through increasing the binding activity of dopamine D_2 receptors in the striatum, suggesting that these changes may be related to the psychotomimetic behavioral symptoms of this drug. In a later study in monkeys, it was found that [^{11}C]NMSP binding was increased, whereas [^{11}C]raclopride binding was decreased with ketamine (23).

Human Studies

[PubMed]

[^{11}C]NMSP studies of D_2 receptor distribution in human brain were reported, showing a localization of radioactivity in the striatum. Gjedde and Wong (24) reported on [^{11}C]NMSP PET studies in 14 patients with schizophrenia, 5 patients with manic depression, and 15 normal subjects (3 old men and 12 young men). In the young normal volunteers, a B_{max} of 17 pmol/g tissue was estimated in the caudate, with a K_i of 3 nM for haloperidol. The B_{max} values for the older normal men, manic-depressive men, drug-naïve schizophrenic patients, and drug-treated schizophrenic patients were 6, 21, 39, and 41 pmol/g, respectively. Other [^{11}C]NMSP PET studies also confirmed the age-related decrease of D_2 receptor density in the caudate nucleus and putamen (25, 26) and the elevated level of striatal D_2 receptor density in patients with chronic schizophrenia as compared with controls (27). However, Farde et al. (28) found that there was little difference in D_2 receptor density in schizophrenic patients and normal subjects using [^{11}C]raclopride, indicating that there may be some important differences in the binding properties and selectivity of the two tracers. In 21 patients with HD, there was a significant reduction in relative binding of [^{11}C]NMSP to D_2 receptor sites in the caudate nucleus and putamen of HD patients as compared with 8 normal subjects at risk for HD (29). There was a correlation of [^{11}C]NMSP binding in the caudate with motor functions. The [^{11}C]NMSP binding in the putamen correlated with the duration of the illness.

Effect of risperidone (a high-affinity 5-HT_{2A} and D_2 antagonist) on 5-HT_{2A} receptor occupancy was studied in 3 normal healthy volunteers by [^{11}C]NMSP PET (30). There was 60% 5-HT_{2A} receptor occupancy ([^{11}C]NMSP) in the neocortical regions and 50% D_2 receptor occupancy ([^{11}C]raclopride) in the putamen after oral administration of 1 mg of risperidone. In a later study with 6 schizophrenic patients, D_2 receptor occupancy was 82% and 5-HT_{2A} receptor occupancy was 95% at 6-mg/day doses for 4 weeks (31). All six patients had extrapyramidal side effects. Subsequently, when the dose was reduced to 3 mg/day for 2 weeks, D_2 receptor occupancy was 72% and 5-HT_{2A} receptor occupancy was 83%. Three patients had extrapyramidal side effects.

[^{11}C]NMSP PET is useful for objective monitoring of D_2 and 5-HT_{2A} receptor occupancy and density in patients being treated with antipsychotic drugs. Internal dosimetry data for [^{11}C]NMSP in humans are not available in the literature.

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