3-*N*-(2-[^{18}F]Fluoroethyl)spiperone

[^{18}F]FESP

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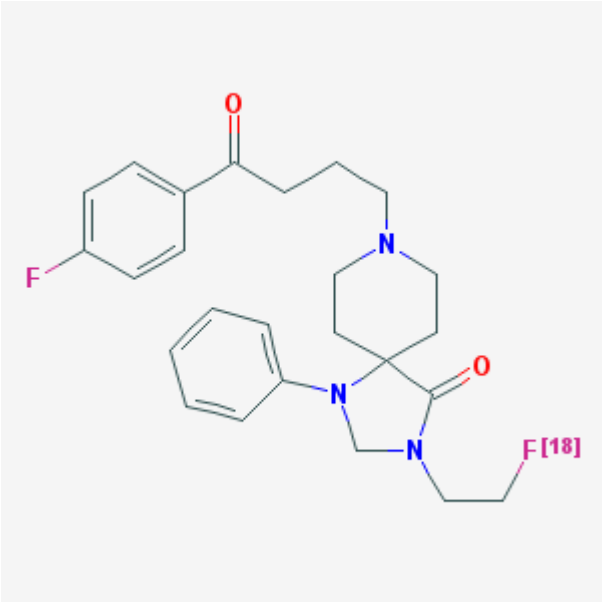
Chemical name:	3-*N*-(2-[^{18}F]Fluoroethyl)spiperone
Abbreviated name:	[^{18}F]FESP
Synonym:	
Agent Category:	Compound
Target:	D_2 dopamine receptor and 5-HT_2 serotonin receptor
Target Category:	Receptor
Method of detection:	PET
Source of signal / contrast:	^{18}F
Activation:	No
Studies:	• *In vitro* • 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 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, were well-characterized pharmacologically and biochemically (3). D_2 dopamine receptors have been implicated in the pathophysiology of PD, Alzheimer's disease, 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*-(2-fluoroethyl)spiperone (FESP) are high-affinity D_2 dopamine and 5-HT_2 serotonin receptor antagonists, showing a low affinity for α1-adrenergic receptors and marginal binding to other receptors (8). 3-*N*-(2-[^{18}F]Fluoroethyl)spiperone ([^{18}F]FESP) has been studied as a positron emission tomography (PET) tracer for imaging D_2 and 5HT_2 receptor densities. It has also used as a reporter probe for dopamine D_2 receptor in imaging transgene expression in rodents (9-11).

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]

[^{18}F]FESP can be synthesized by either N-alkylation or nucleophilic substitution (12-15). Alkylation of the amide nitrogen in spiperone by [^{18}F]fluorobromoethane in the presence of NaOH provided [^{18}F]FESP in 35-40% radiochemical yield (5-8% overall radiochemical yield). [^{18}F]Fluorobromoethane was easily prepared by the reaction of 1,2-bromoethane with potassium [^{18}F]fluoride Kryptofix complex in 15-20% radiochemical yield. The radiochemical purity of [^{18}F]FESP was found to be >99% by high-performance liquid chromatography (HPLC). The specific activity was 185-370 GBq/μmol (5-10 Ci/μmol) at the end of synthesis with a total synthesis time of 70 min.

A one-step, one-pot synthesis of [^{18}F]FESP using nucleophilic fluorination of 3-(2'-bromoethyl)spiperone or 3-(2'-methylsulfonyloxyethyl)spiperone with K[^{18}F]F/Kryptofix2.2.2 in acetonitrite in <60 min was performed (12). This method provided a 99% chemical purity and a specific activity of 74-370 GBq/μmol (2-10 Ci/μmol) at the end of synthesis (EOS). The radiochemical yield was 30-40% (EOS).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

FESP was reported to have selective binding affinity to D_2 (striatum) and 5-HT_2 (frontal cortex) receptor sites in homogenates of rat brain membranes (8). The K_i values for D_2 and 5-HT_2 were 0.44 nM and 0.57 nM, respectively. It has a K_i value of 23 nM for the α1-adrenergic receptor in rat forebrain membrane and negligible binding to other sites.

Animal Studies

Rodents

[PubMed]

Biodistribution studies in rats showed a high uptake of radioactivity in the lung (1.80% injected dose (ID)/g), kidney (1.00% ID/g), spleen (0.97% ID/g), and liver (0.82% ID/g) at 15 min after injection of [^{18}F]FESP (16). The brain had a low uptake of 0.18% ID/g. Low radioactivity was observed in bone tissue, indicating little defluorination. [^{18}F]FESP remained 90% intact in the brain striatum, 32% in the cerebellum, and 46% in the frontal cortex for up to 4 h after injection. In mice, [^{18}F]FESP remained 90% intact in the brain striatum, and 62% in the cerebellum for up to 3.5 h after injection (17). [^{18}F]FESP was metabolized peripherally with only 11% intact [^{18}F]FESP in rat plasma at 2 h after injection (16).

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

[^{18}F]FESP PET studies in non-human primates have provided useful assessment of the D_2 and 5-HT_2 receptor in the brain (16-21). Coenen et al. (18) showed a selective uptake in striatum (0.048% ID/cm^3) over the frontal cortex (0.0088% ID/cm^3) and in the cerebellum (0.0056% ID/cm^3) in baboon brains at 4 h after injection. The striatum D_2 receptor sites in the striatum were saturable. The striatum [^{18}F]FESP uptake was blocked by pretreatment with excess unlabeled FESP (0.5 mg/kg) and (+)-butaclamol (0.5 mg/kg),

a D_1/D_2 antagonist (22). Ritanserin and ketanserin, 5-HT_2 antagonists, had no effect on [^{18}F]FESP uptake in the striatum and blocked only 15-20% [^{18}F]FESP uptake in the frontal cortex. [^{18}F]FESP arterial plasma activity rapidly decreased to 25% at 1 h and 8% at 4 h after injection. D_2 receptor density (B_{max}) was estimated by two PET studies to be 25.9 ± 12.7 pmol/g (19) and 37.5 ± 11.5 pmol/g (21). Using serial PET scans, 5-HT_2 receptor density was estimated to be 35.6 ± 10.9 pmol/g in the baboon frontal cortex (20).

Human Studies

[[PubMed]

Human dosimetry was estimated based on human dynamic PET scans after injection of 37 MBq (1 mCi) [^{18}F]FESP (23). The gallbladder received the highest dose (0.207 mGy/MBq or 797 mrad/mCi). Other organs that received high doses were the urinary bladder (0.083 mGy/MBq or 308 mrad/mCi) and liver (0.065 mGy/MBq or 110 mrad/mCi). The total body dose was 0.0119 mGy/MBq (44 mrad/mCi).

[^{18}F]FESP PET studies of D_2 receptor distribution in human brain were reported, showing a localization of radioactivity in the striatum (16, 24, 25). Only about 1% of [^{18}F]PESP entered the brain. [^{18}F]FESP was metabolized peripherally with 54% intact [^{18}F]FESP in arterial plasma at 2 h after injection (16). Striatal-to-cerebellum ratio and kinetic constants are commonly used as analytical parameters in [^{18}F]FESP PET studies. Wienhard et al. (25) reported on [^{18}F]FESP PET studies in 30 patients with various disorders related to the dopaminergic system and in 6 normal subjects. PET brain scans of normal subjects showed that the highest uptake was in the caudate and pituitary, followed by the cortex and cerebellum at 3 h after injection of 185 MBq (5 mCi) [^{18}F]FESP. PET scans of patients showed decreases in the number of available D_2 receptors in the striatum and striatum-to-cerebellum ratio. Patients with brain damage also showed both low [^{18}F]FDG and [^{18}F]FESP uptake in the striatum.

5-HT_2 receptor distribution in human brain were studied by [^{18}F]FESP PET in 20 healthy volunteers and 34 patients with unipolar depression (26) There was a significant reduction of binding capacity in 19 non-drug-treated patients as compared with healthy controls in the cortical regions but not in the striatum. In paroxetine-treated patients (n = 15), there was no significant difference between the drug-treated patients and healthy volunteers. Paroxetine is a specific serotonin reuptake inhibitor. Paroxetine treatment led to remission in these patients. Chronic treatment with fluvoxamine (27), another specific serotonin reuptake inhibitor, significantly increased the *in vivo* binding of [^{18}F]FESP in the frontal and occipital cortex but not in the striatum of drug-naïve, unipolar, depressed patients (n = 9).

[^{18}F]FESP PET is useful for objective monitoring of D_2 and 5-HT_2 receptor sites in patients with serotonergic and dopaminergic disorders. It revealed stage-related changes in depression and dopaminergic disorders. [^{18}F]FESP has also demonstrated its usefulness as a PET tracer in the imaging of non-functioning pituitary adenomas from meningiomas and craniopharyngiomas (28).

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