(*R*,*S*)-2-(*N*-Propyl-*N*-5'-[^{18}F]fluoropentyl)amino-5-hydroxytetralin

[^{18}F]-5-OH-FPPAT

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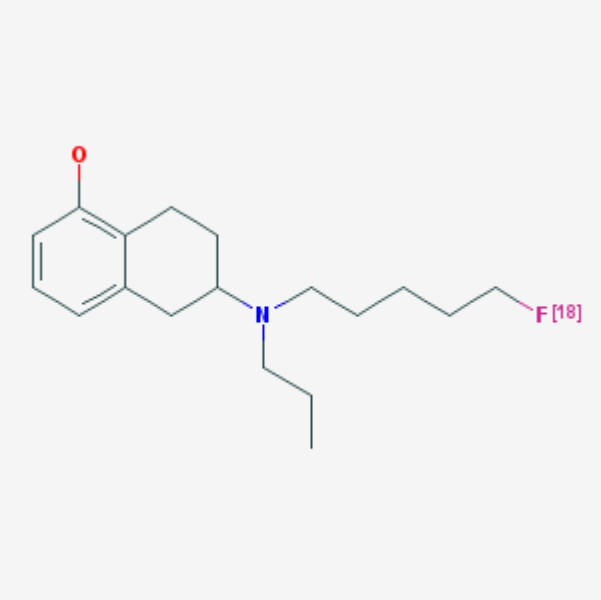
Chemical name:	(*R*,*S*)-2-(*N*-Propyl-*N*-5'-[^{18}F]fluoropentyl)amino-5-hydroxytetralin
Abbreviated name:	[^{18}F]-5-OH-FPPAT
Synonym:	(*R*,*S*)-5-Hydroxy-2-(*N*-propyl-*N*-(5'-[^{18}F]fluoropentyl)aminotetralin
Agent Category:	Compound
Target:	D_2 and D_3 dopamine receptors
Target Category:	Receptor binding
Method of detection:	PET
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates



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Background

[PubMed]

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 dopamine receptor 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). D_1-like and D_2-like receptors exert synergistic as well as opposite effects at both the biochemical and overall system levels. Most 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, dopamine receptors are coupled to G-proteins, whereas in the low-affinity state they are not. Dopamine has a dissociation constant (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 was suggested to be the functional form of the dopamine receptors (6).

Substituted benzamides, such as sulpiride, raclopride, and iodobenzamide, are specific ligands with only moderate affinity for the $D_{2/3}$ receptors, making studies of extrastriatal $D_{2/3}$ receptors difficult (7-9). In binding studies, [^{123}I]epidepride was found to have high potency and low nonspecific binding, and to be selective for striatal and extrastriatal $D_{2/3}$ receptors (10). Epidepride exhibits 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 (11), and in positron emission tomography (PET) *in vivo* studies (12-15) 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. Many effects have been pursued to develop radiolabeled agonists for the non-invasive study of the high-affinity state of the $D_{2/3}$ receptors in the brain. (–)-*N*-[^{11}C]Propyl-norapomorphine ([^{11}C]NPA) and [^{11}C](+)-4-*N*-propyl-,3,4a,5,6,10b-hexahydro-2*H*-naphth[1,2-*b*][1,4]oxazin-9-ol ([^{11}C]PHNO) have been studied as radiolabeled dopamine agonists.

Various hydroxytetralin analogs with different binding affinities for the D_2 receptors have been developed as ^{11}C-labeled agonist radiotracers (16). (*R,S*)-2-(*N*-propyl-*N*-5'-[^{18}F]fluoropentyl)amino-5-hydroxytetralin ([^{18}F]-5-OH-FPPAT) is being evaluated as a PET agent for the high-affinity state of $D_{2/3}$ receptors.

Synthesis

[PubMed]

Shi et al. (17) reported a three-step synthesis of [^{18}F]-5-OH-FPPAT. 2-(*N*-propyl-*N*-5'-bromovaleryl)amino-5-tetrahydropyranyltetralin was reacted first with [^{18}F]KF/Kryptofix 2.2.2, followed by $LiAlH_4$ reduction and acidic deprotection, with a radiochemical yield of 10–15% (decay-corrected) at the end of bombardment and an average specific activity of 56–74 GBq/μmol (1.5–2.0 Ci/μmol) at end of synthesis after purification by high-performance liquid chromatography.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In a binding study of dopamine receptors in membranes of the rat striata with [^{18}F]fallypride, 5-OH-FPPAT had an inhibitory concentration (IC_{50}) of 6.95 nM (17). *In vitro* autoradiography studies of rat brain slices indicated selective binding of [^{18}F]-5-OH-FPPAT to the striata, which was almost completely inhibited by co-incubation with 10 μM sulpiride (a $D_{2/3}$ antagonist) and Gpp(NH)p (conversion of the high-affinity states to the low-affinity states). There was little specific binding in the cortex and cerebellum, with a striata/cerebellum ratio of 17.4, a striata/cortex ratio of 12.8, and a cortex/cerebellum ratio of 1.35.

Animal Studies

Rodents

[PubMed]

Biodistribution studies in rats showed a marked accumulation of the tracer in the striata with 1.65% injected dose per gram (%ID/g) at 15 min after injection of [^{18}F]-5-OH-FPPAT (17). The striata/cerebellum ratio was 1.9 at 30 min and 2.0 at 60 min. Significant nonspecific binding was observed in the cortical regions and cerebellum. The cortex/cerebellum ratio was 1.28 at 30 min and 1.35 at 60 min. Pretreatment with risperidone (0.05 mg/kg) and PPHT (0.1 mg/kg), both $D_{2/3}$ antagonists, reduced specific binding of [^{18}F]-5-OH-FPPAT to the striata by 40%. [^{18}F]-5-OH-FPPAT showed higher striata/cerebellum ratio than the ^{11}C-labeled hydroxytetralin analogs, such as [^{11}C]PPHT and [^{11}C]ZYY-339. Uptake of [^{18}F]-5-OH-FPPAT is comparable to [^{11}C]-5-OH-DPAT.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

Shi et al. (17) showed uptake in the brain (0.05% ID/ml) of rhesus monkeys with striata/cerebellum ratios of 1.5 at 10 min and 2.0 at 40 min after injection of 111 MBq (3 mCi) of [^{18}F]-5-OH-FPPAT. The thalamus/cerebellum ratio was 1.4 at 40 min. The striata showed slower clearance than the cortex and cerebellum. The authors suggested that use of the more active *S*-isomer may provide a higher striata/cerebellum and thalamus/cerebellum ratios. [^{18}F]-5-OH-FPPAT showed higher striata/cerebellum ratios than ^{11}C-labeled hydroxytetralin analogs, such as [^{11}C]PPHT and [^{11}C]ZYY-339.

Human Studies

[PubMed]

No publication is currently available.

References

1. Carbon M., Ghilardi M.F., Feigin A., Fukuda M., Silvestri G., Mentis M.J., Ghez C., Moeller J.R., Eidelberg D. Learning networks in health and Parkinson's disease: reproducibility and treatment effects. Hum Brain Mapp. 2003;**19**(3):197–211. PubMed PMID: 12811735.
2. Chesselet M.F., Delfs J.M. Basal ganglia and movement disorders: an update. Trends Neurosci. 1996;**19**(10):417–22. PubMed PMID: 8888518.
3. Seeman P., Bzowej N.H., Guan H.C., Bergeron C., Reynolds G.P., Bird E.D., Riederer P., Jellinger K., Tourtellotte W.W. Human brain D1 and D2 dopamine receptors in schizophrenia, Alzheimer's, Parkinson's, and Huntington's diseases. Neuropsychopharmacology. 1987;**1**(1):5–15. PubMed PMID: 2908095.
4. Stoof J.C., Kebabian J.W. Two dopamine receptors: biochemistry, physiology and pharmacology. Life Sci. 1984;**35**(23):2281–96. PubMed PMID: 6390056.
5. Sunahara R.K., Guan H.C., O'Dowd B.F., Seeman P., Laurier L.G., Ng G., George S.R., Torchia J., Van Tol H.H., Niznik H.B. Cloning of the gene for a human dopamine D5 receptor with higher affinity for dopamine than D1. Nature. 1991;**350**(6319):614–9. PubMed PMID: 1826762.
6. Sibley D.R., De Lean A., Creese I. Anterior pituitary dopamine receptors. Demonstration of interconvertible high and low affinity states of the D-2 dopamine receptor. J Biol Chem. 1982;**257**(11):6351–61. PubMed PMID: 6176582.
7. Gehlert D.R., Wamsley J.K. Autoradiographic localization of [3H]sulpiride binding sites in the rat brain. Eur J Pharmacol. 1984;**98**(2):311–2. PubMed PMID: 6714315.
8. Lidow M.S., Goldman-Rakic P.S., Rakic P., Innis R.B. Dopamine D2 receptors in the cerebral cortex: distribution and pharmacological characterization with [3H]raclopride. Proc Natl Acad Sci U S A. 1989;**86**(16):6412–6. PubMed PMID: 2548214.

9. Brucke T., Tsai Y.F., McLellan C., Singhanyom W., Kung H.F., Cohen R.M., Chiueh C.C. In vitro binding properties and autoradiographic imaging of 3-iodobenzamide ([125I]-IBZM): a potential imaging ligand for D-2 dopamine receptors in SPECT. Life Sci. 1988;**42**(21):2097–104. PubMed PMID: 3260318.
10. Kessler R.M., Ansari M.S., Schmidt D.E., de Paulis T., Clanton J.A., Innis R., al-Tikriti M., Manning R.G., Gillespie D. High affinity dopamine D2 receptor radioligands. 2. [125I]epidepride, a potent and specific radioligand for the characterization of striatal and extrastriatal dopamine D2 receptors. Life Sci. 1991;**49**(8):617–28. PubMed PMID: 1830917.
11. Mukherjee J., Yang Z.Y., Das M.K., Brown T. Fluorinated benzamide neuroleptics--III. Development of (S)-N-[(1-allyl-2-pyrrolidinyl)methyl]-5-(3-[18F]fluoropropyl)-2, 3-dimethoxybenzamide as an improved dopamine D-2 receptor tracer. Nucl Med Biol. 1995;**22**(3):283–96. PubMed PMID: 7627142.
12. Grunder G., Landvogt C., Vernaleken I., Buchholz H.G., Ondracek J., Siessmeier T., Hartter S., Schreckenberger M., Stoeter P., Hiemke C., Rosch F., Wong D.F., Bartenstein P. The striatal and extrastriatal d2/d3 receptor-binding profile of clozapine in patients with schizophrenia. Neuropsychopharmacology. 2006;**31**(5): 1027–35. PubMed PMID: 16237387.
13. Kessler R.M., Ansari M.S., Riccardi P., Li R., Jayathilake K., Dawant B., Meltzer H.Y. Occupancy of striatal and extrastriatal dopamine d(2)/d(3) receptors by olanzapine and haloperidol. Neuropsychopharmacology. 2005;**30**(12):2283–9. PubMed PMID: 16123775.
14. Mukherjee J., Christian B.T., Narayanan T.K., Shi B., Collins D. Measurement of d-amphetamine-induced effects on the binding of dopamine D-2/D-3 receptor radioligand, 18F-fallypride in extrastriatal brain regions in non-human primates using PET. Brain Res. 2005;**1032**(1-2):77–84. PubMed PMID: 15680944.
15. Riccardi P., Li R., Ansari M.S., Zald D., Park S., Dawant B., Anderson S., Doop M., Woodward N., Schoenberg E., Schmidt D., Baldwin R., Kessler R. Amphetamine-induced displacement of [(18)f] fallypride in striatum and extrastriatal regions in humans. Neuropsychopharmacology. 2006;**31**(5):1016–26. PubMed PMID: 16237395.
16. Shi B., Narayanan T.K., Yang Z.Y., Christian B.T., Mukherjee J. Radiosynthesis and in vitro evaluation of 2-(N-alkyl-N-1'-11C-propyl)amino-5-hydroxytetralin analogs as high affinity agonists for dopamine D-2 receptors. Nucl Med Biol. 1999;**26**(7):725–35. PubMed PMID: 10628551.
17. Shi B., Narayanan T.K., Christian B.T., Chattopadhyay S., Mukherjee J. Synthesis and biological evaluation of the binding of dopamine D2/D3 receptor agonist, (R,S)-5-hydroxy-2-(N-propyl-N-(5'-(18)F-fluoropentyl)aminotetralin ((18)F-5-OH-FPPAT) in rodents and nonhuman primates. Nucl Med Biol. 2004;**31**(3):303–11. PubMed PMID: 15028242.