

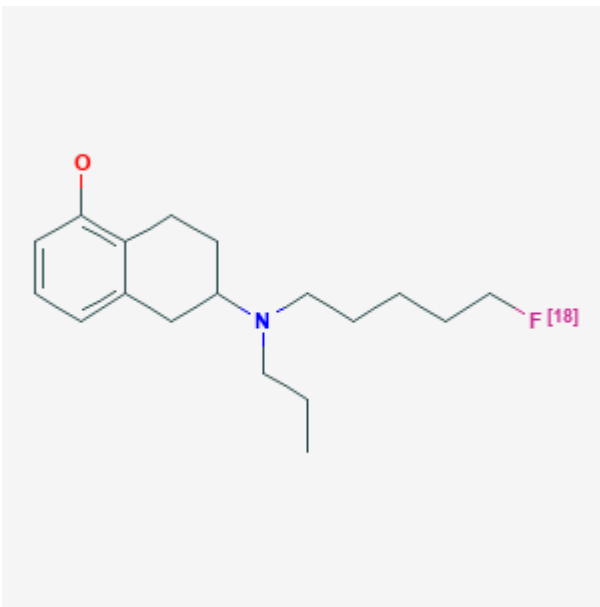


(R,S)-2-(N-Propyl-N-5'-[¹⁸F]fluoropentyl)amino-5-hydroxytetralin

[¹⁸F]-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:	<ul style="list-style-type: none"> <i>In vitro</i> 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, D₁ through D₅, have been well characterized pharmacologically and biochemically (4). These five dopamine receptor subtypes are classified into two subfamilies: D₁-like (D₁ and D₅) and D₂-like (D₂, D₃, and D₄). D₁-like and D₂-like receptors exert synergistic as well as opposite effects at both the biochemical and overall system

levels. Most striatal D₁ and D₂ 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, [¹²³I]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 D₄ receptors, with little affinity for other known neurotransmitter receptors. (S)-N-((1-Allyl-2-pyrrolidinyl)methyl)-5-(3-[¹⁸F]fluoropropyl)-2,3-dimethoxybenzamide ([¹⁸F]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 D₂ 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-[¹¹C]Propyl-norapomorphine ([¹¹C]NPA) and [¹¹C](+)-4-N-propyl-,3,4a,5,6,10b-hexahydro-2H-naphth[1,2-b][1,4]oxazin-9-ol ([¹¹C]PHNO) have been studied as radiolabeled dopamine agonists.

Various hydroxytetralin analogs with different binding affinities for the D₂ receptors have been developed as ¹¹C-labeled agonist radiotracers (16). (R,S)-2-(N-propyl-N-5'-[¹⁸F]fluoropentyl)amino-5-hydroxytetralin ([¹⁸F]-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 [¹⁸F]-5-OH-FPPAT. 2-(N-propyl-N-5'-bromovaleryl)amino-5-tetrahydropyranilyltetralin was reacted first with [¹⁸F]KF/Kryptofix 2.2.2, followed by LiAlH₄ 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 [¹⁸F]fallypride, 5-OH-FPPAT had an inhibitory concentration (IC₅₀) of 6.95 nM (17). *In vitro* autoradiography studies of rat brain slices indicated selective binding of [¹⁸F]-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 [¹⁸F]-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 [¹⁸F]-5-OH-FPPAT to the striata by 40%. [¹⁸F]-5-OH-FPPAT showed higher striata/cerebellum ratio than the ¹¹C-labeled hydroxytetralin analogs, such as [¹¹C]PPHT and [¹¹C]ZYY-339. Uptake of [¹⁸F]-5-OH-FPPAT is comparable to [¹¹C]-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 [¹⁸F]-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. [¹⁸F]-5-OH-FPPAT showed higher striata/cerebellum ratios than ¹¹C-labeled hydroxytetralin analogs, such as [¹¹C]PPHT and [¹¹C]ZYY-339.

Human Studies

[PubMed]

No publication is currently available.

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