(*R*)-(-)-2-Chloro-*N*-[1-^{11}C-propyl]*n*-propylnorapomorphine

2-Cl-[^{11}C]-(-)-NPA

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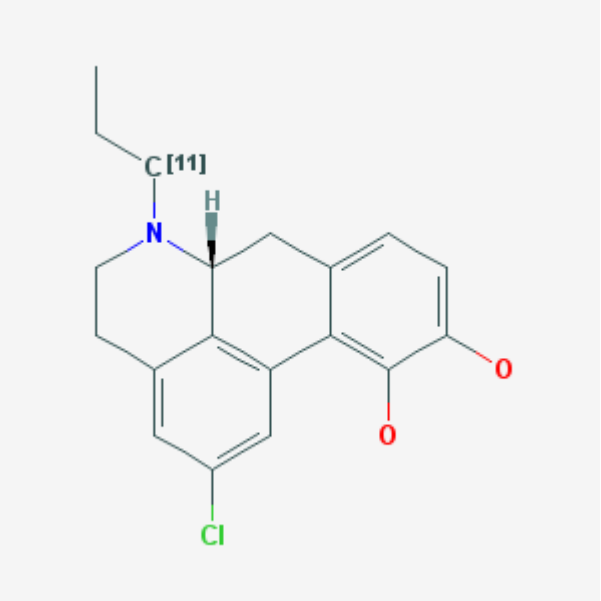
Created: October 24, 2010; Updated: December 11, 2010.

Chemical name:	(*R*)-(-)-2-Chloro-*N*-[1-^{11}C-propyl]*n*-propylnorapomorphine
Abbreviated name:	2-Cl-[^{11}C]-(-)-NPA
Synonym:	
Agent category:	Compound
Target:	D_3 dopamine receptors
Target category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents



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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

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NLM Citation: Leung K. (*R*)-(-)-2-Chloro-*N*-[1-^{11}C-propyl]*n*-propylnorapomorphine. 2010 Oct 24 [Updated 2010 Dec 11]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

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-Like and D_2-like receptors exert synergistic as well as opposite effects at both the biochemical and overall system levels. 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. The high-affinity state is coupled to G-proteins, whereas the low-affinity state is 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 physiological conditions, dopamine is expected to bind predominantly to the high-affinity state, which is ~50% occupied by 10 nM dopamine. The high-affinity state was 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-like 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) in positron emission tomography (PET) *in vivo* studies (11-13). [^{18}F]fallypride identified extrastriatal $D_{2/3}$ receptors. However, none of these antagonists distinguish 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 other neurotransmitters (17). [^{11}C]NPA is being developed as a PET agent for the noninvasive study of the high-affinity state of the D_2 receptors in the brain. (*R*)-(-)-2-Chloro-*N*-[1-^{11}C-propyl]*n*-propylnorapomorphine (2-Cl-[^{11}C]-(-)-NPA) has been evaluated as a D_3-selective probe because 2-Cl-(-)-NPA showed a higher selectivity for D_3 than for D_2 (D_3/D_2, 3.85) than did (-)-NPA (D_3/D_2, 1.75) (18).

Related Resource Links:

- Chapters in MICAD
- Gene information in NCBI (D_2 receptor,D_3 receptor)
- Articles in OMIM (D_2 receptor, D_3 receptor)
- Clinical trials (Dopamine receptors)

Synthesis

[PubMed]

Palner et al. (18) reported a one-pot synthesis of 2-Cl-[^{11}C]-(-)-NPA by reacting [^{11}C]propionyl chloride with (-)-chloronorapomorphine hydrobromide and a $LiAlH_4$ reduction, with a radiochemical yield of ~9% (based on [^{11}C]CO_2, end of bombardment) and specific activities of 28–45 GBq/μmol (757–1,220 mCi/μmol) at the end of synthesis after C-18 Sep-Pak and purification with high-performance liquid chromatography. Radiochemical purities were >97%. [^{11}C]Propionyl chloride was prepared by reacting [^{11}C]CO_2 with ethylmagnesium bromide, followed by reaction with phthaloyl chloride. The total synthesis time was ~40 min.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In binding to dopamine receptors in membranes of porcine anterior pituitary, [^{3}H]NPA had an average K_d of 0.26 ± 0.01 nM and a B_{max} of 2.3 ± 0.1 pmol/g tissue (19). 2-Cl-[^{11}C]-(-)-NPA exhibited K_i values of 4.52 ± 0.98 and 17.26 ± 2.88 nM for D_2 and D_3, respectively (18). [^{11}C]-(-)-NPA had K_i values of 0.12 ± 0.04 and 0.21 ± 0.09 nM for D_2 and D_3, respectively. The cLog D values were calculated to be 2.25 and 0.79 for 2-Cl-[^{11}C]-(-)-NPA and [^{11}C]-(-)-NPA, respectively.

Animal Studies

Rodents

[PubMed]

Palner et al. (18) performed *ex vivo* brain biodistribution studies of 37 MBq (1 mCi) 2-Cl-[^{11}C]-(-)-NPA in rats. 2-Cl-[^{11}C]-(-)-NPA accumulated more slowly in the striatum than did [^{11}C]-(-)-NPA, reaching maximum concentrations after 30 min. The maximal striatal uptake of 2-Cl-[^{11}C]-(-)-NPA (standard uptake value (SUV) = 0.72 ± 0.24) was approximately half that of [^{11}C]-(-)-NPA (SUV = 1.37 ± 0.18). Nonspecific uptake was similar for the two tracers in the cerebellum (SUV = 0.32–0.33). The striatum/cerebellum ratios were 1.18 and 3.31 for 2-Cl-[^{11}C]-(-)-NPA and [^{11}C]-(-)-NPA, respectively, at 60 min after injection. 2-Cl-[^{11}C]-(-)-NPA was metabolized quickly to one major and two minor less lipophilic metabolites, leaving only 17% of 2-Cl-[^{11}C]-(-)-NPA in the plasma after 30 min. The specific binding of 2-Cl-[^{11}C]-(-)-NPA was completely blocked by pretreatment with haloperidol (5 mg/kg, 30 min). The authors concluded that 2-Cl-[^{11}C]-(-)-NPA is less likely to be more useful as a PET agent than [^{11}C]-(-)-NPA because of slower brain uptake and a lower striatum/cerebellum ratio.

Other Non-Primate Mammals

[PubMed]

No publications are currently available.

Non-Human Primates

[PubMed]

No publications are currently available.

Human Studies

[PubMed]

No publications are currently available.

NIH Support

N01MH32004

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