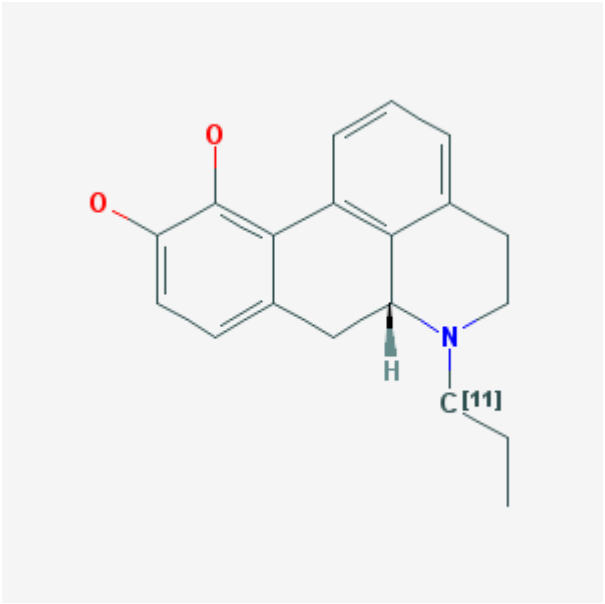
(-)-*N*-[^{11}C]Propyl-norapomorphine

[^{11}C]NPA

Kam Leung, PhD[1]

Created: April 6, 2006; Updated: June 30, 2011.

Chemical name:	(-)-*N*-[^{11}C]Propyl-norapomorphine
Abbreviated name:	[^{11}C]NPA
Synonym:	
Agent category:	Compound
Target:	D_2 dopamine receptors
Target category:	Receptor
Method of detection:	PET
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates • Humans



Click on the above structure for additional information in PubChem.

Background

[PubMed]

[1] National Center for Biotechnology Information, NLM, NIH, Bethesda, MD; Email: MICAD@ncbi.nlm.nih.gov.

NLM Citation: Leung K. (-)-*N*-[^{11}C]Propyl-norapomorphine. 2006 Apr 6 [Updated 2011 Jun 30]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

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 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 level. 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 nigrostiatal 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 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 predominately 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 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), and in positron emission tomography (PET) *in vivo* studies (11-13), it identified extrastriatal $D_{2/3}$ receptors. However, all these antagonists do not distinguish between the high- and low- affinity states of the D_2 receptors. (-)-*N*-Propyl-norapomorphine (NPA), a full dopamine $D_{2/3}$ receptor agonist, was reported to have the K_{high} and K_{low} values of 0.07-0.4 and 20-200 nM for D_2 receptors, respectively (5, 14-16). This provides a >50-fold selectivity for the high-affinity over the low affinity receptors. It 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 positron emission tomography (PET) agent for the non-invasive study of the high-affinity state of the D_2 receptors in the brain.

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]

Hwang et al (18) reported an one-pot synthesis of [^{11}C]NPA by reacting [^{11}C]propionyl chloride with norapomorphine and a $LiAlH_4$ reduction, with a radiochemical yield of 16% (based on [^{11}C]CO_2, end of bombardment) and an average specific activity of 63 GBq/μmol (1700 mCi/μmol at end of synthesis) after C-18 Sep-Pak and high-performance liquid chromatography (HPLC) purification. Radiochemical purities were >99%. [^{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 60 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 dissociation constant (K_d) of 0.26 ± 0.01 nM and a B_{max} of 2.3 ± 0.1 pmol/g tissue (19). Guanilylimidodiphosphate completely inhibited [^{3}H]NPA binding, suggesting that [^{3}H]NPA was binding primarily to the high-affinity state of dopamine D_2 receptors. Using [^{3}H]spiroperidol, NPA had the K_{high} and K_{low} values of 0.27 ± 0.04 and 26 ± 2.6 nM, respectively, About 54% of D_2 receptors were in the high-affinity state. Therefore, NPA has good selectivity and affinity for the high-affinity state of D_2. George et al. (5) reported that NPA had the K_{high} and K_{low} values of 0.31 and 207 nM, respectively.

Animal Studies

Rodents

[PubMed]

Ex vivo biodistribution studies in rats showed a high accumulation of radioactivity in the kidney [1.00% injected dose (ID)/g], followed by liver (0.72% ID/g), adrenal (0.66% ID/g), lung (0.31% ID/g), and spleen (0.25% ID/g) at 5 min after injection of [^{11}C]NPA (18). There was a marked accumulation of the tracer in the striatum within the first 30 min (0.88% ID/g), followed by a decrease of radioactivity to 0.56% ID/g at 60 min. The striatum/ cerebellum and frontal cortex/cerebellum ratios were 3.47 and 1.44 at 30 min after injection, respectively. Haloperidol pretreatment (1 mg/kg) effectively blocked specific binding of [^{11}C]NPA to the striatum (from 0.88 to 0.28% ID/g) and frontal cortex (from 0.36 to 0.21% ID/g) at 30 min. Little inhibition was seen in the cerebellum (from 0.25 to 0.22% ID/g). [^{11}C]NPA thus displays uptake and washout kinetics characteristic of reversible radiotracers.

Other Non-Primate Mammals

[PubMed]

No publications are currently available.

Non-Human Primates

[PubMed]

[^{11}C]NPA PET studies in non-human primates have provided useful assessment of the D_2 receptor in the brain, showing localization of [^{11}C]NPA in striatal regions. Hwang et al. (18) showed selective uptake in the striatum (0.031%ID/g) of a baboon monkey brain with striatum-to-cerebellum ratios of 2.33 at 15 min and 2.86 at 45 min after injection of 231 MBq (6.25 mCi) [^{11}C]NPA. The striatal accumulation of [^{11}C]NPA was inhibited by pretreatment with haloperidol (1 mg/kg) with the striatum-to-cerebellum ratio of 1.29 at 45 min after injection.

Hwang et al (20) performed quantitative measurements of [^{11}C]NPA binding with kinetic and graphical analyses, using arterial input function to derive potential (BP) and specific-to-nonspecific equilibrium partition coefficient (V_3") in 2 baboons. In kinetic analyses, BP estimates were 4.04 ± 1.05 ml/g in the striatum, whereas BP estimates were 3.90 ± 1.03 ml/g using graphical analysis with arterial input. At 40 min post injection, 31% of [^{11}C]NPA radioactivity remained intact in arterial plasma. It was concluded that data from 30 min of scanning were sufficient to derive V_3" values by kinetic, graphical and simplified reference-tissue model analyses.

Narendran et al. (21) studied 3 male baboons with [^{11}C]raclopride (a D_2 antagonist) and [^{11}C]NPA under baseline conditions and following administration of the potent DA releaser amphetamine . Kinetic modeling with an arterial input function was used to derive the striatal V_3". [^{11}C]Raclopride V_3" was reduced by 24 ± 10%, 32 ± 6%, and 44 ± 9% following amphetamine doses of 0.3, 0.5, and 1.0 mg/kg, respectively. [^{11}C]NPA V_3" was reduced by 32 ± 2%, 45 ± 3%, and 53 ± 9% following amphetamine doses of 0.3, 0.5, and 1.0 mg/kg, respectively. Thus, endogenous DA was 42% more effective at competing with [^{11}C]NPA binding compared to [^{11}C]raclopride binding, which is consistent with the pharmacology of these tracers (agonist vs. antagonist). These results also suggest that 71% of D_2 receptors are configured in a state of high affinity for agonists *in vivo*. [^{11}C]NPA is able to detect the change in dopamine levels induced by D-amphetamine and is more vulnerable to competition by endogenous dopamine than that of antagonist radiotracer [^{11}C]raclopride.

Narendran et al. (22) performed further PET studies in 3 baboons under noncarrier- and carrier-added conditions, to compare the B_{max} of [^{11}C]NPA and [^{11}C]raclopride in the same baboons. [^{11}C]raclopride K_d and B_{max} were 1.59 ± 0.28 nM and 27.3 ± 3.9 nM, respectively. The in vivo K_d of [^{11}C]NPA was 0.16 ± 0.01 nM, consistent with its affinity for D_{2high} reported *in vitro* binding. The B_{max} for [^{11}C]NPA was 21.6 ± 2.8 nM and 79% of the [^{11}C]raclopride B_{max}. This result suggested that 79% of D_2 receptors are configured

as high-affinity state in vivo. This large proportion of high-affinity sites might explain the vulnerability of D_2 radiotracers to competition by endogenous dopamine, and is consistent with the reported *in vivo* binding of agonist radiotracer [^{11}C]NPA (21).

Human Studies

[PubMed]

Narendran et al. (23) studied the vulnerability of the *in vivo* binding of [^{11}C]NPA to acute fluctuation in synaptic dopamine was assessed with PET imaging in ten healthy humans (eight females and two males) and compared with that of the reference $D_{2/3}$ receptor antagonist radiotracer [^{11}C]raclopride before and after the administration of 0.5 mg/kg oral d-amphetamine. The binding potential relative to nonspecific uptake (BP_{ND}) values in the ventral striatum (VST), caudate (CAD), and putamen (PUT) were determined using kinetic modeling with an arterial input function. [^{11}C]Raclopride BP_{ND} values were significantly reduced by 9.7 ± 4.4, 8.4 ± 4.2, and 14.7 ± 4.8% after amphetamine administration in the VST, CAD, and PUT, respectively. [^{11}C]NPA BP_{ND} values were also reduced significantly by 16.0 ± 7.0, 16.1 ± 6.1, and 21.9 ± 4.9% after the same dose of amphetamine in the VST, CAD, and PUT, respectively. [^{11}C]NPA was more vulnerable to endogenous competition by dopamine compared with [^{11}C]raclopride by a factor of 1.49 - 1.90, which suggests that $D_{2/3}$ agonist [^{11}C]NPA is more vulnerable to endogenous competition by dopamine than $D_{2/3}$ antagonist [^{11}C]raclopride.

Lagmon et al. (24) performed dosimetry of [^{11}C]NPA in 6 healthy subjects with PET scans after injection of 370 MBq (10 mCi). The highest organ dose was to the gallbladder wall, which received 2.81 x 10^{-2} mSv/MBq. An effective dose was 3.17 x 10^{-3} mSv/MBq.

NIH Support

K08-MH068762, R21-DA023450, K02-MH01603-01, R01MH62089-01, MH59342-01

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. George S.R., Watanabe M., Di Paolo T., Falardeau P., Labrie F., Seeman P. *The functional state of the dopamine receptor in the anterior pituitary is in the high affinity form.* Endocrinology. 1985;117(2):690–7. PubMed PMID: 4017954.
6. 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.
7. 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.
8. 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.
9. 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.
10. 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.
11. Grunder, G., C. Landvogt, I. Vernaleken, H.G. Buchholz, J. Ondracek, T. Siessmeier, S. Hartter, M. Schreckenberger, P. Stoeter, C. Hiemke, F. Rosch, D.F. Wong, and P. Bartenstein, *The Striatal and Extrastriatal D2/D3 Receptor-Binding Profile of Clozapine in Patients with Schizophrenia.* Neuropsychopharmacology, 2005
12. 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.
13. Riccardi, P., R. Li, M.S. Ansari, D. Zald, S. Park, B. Dawant, S. Anderson, M. Doop, N. Woodward, E. Schoenberg, D. Schmidt, R. Baldwin, and R. Kessler, *Amphetamine-Induced Displacement of [(18)F] Fallypride in Striatum and Extrastriatal Regions in Humans.* Neuropsychopharmacology, 2005
14. Gardner B., Strange P.G. *Agonist action at D2(long) dopamine receptors: ligand binding and functional assays.* Br J Pharmacol. 1998;124(5):978–84. PubMed PMID: 9692784.
15. Lahti R.A., Mutin A., Cochrane E.V., Tepper P.G., Dijkstra D., Wikstrom H., Tamminga C.A. *Affinities and intrinsic activities of dopamine receptor agonists for the hD21 and hD4.4 receptors.* Eur J Pharmacol. 1996;301(1-3):R11–3. PubMed PMID: 8773470.
16. Seeman P., Watanabe M., Grigoriadis D., Tedesco J.L., George S.R., Svensson U., Nilsson J.L., Neumeyer J.L. *Dopamine D2 receptor binding sites for agonists. A tetrahedral model.* Mol Pharmacol. 1985;28(5):391–9. PubMed PMID: 2932631.
17. Neumeyer J.L., Neustadt B.R., Oh K.H., Weinhardt K.K., Boyce C.B., Rosenberg F.J., Teiger D.G. *Aporphines. 8. Total synthesis and pharmacological evaluation of (plus or minus)-apomorphine, (plus or minus)-apocodeine, (plus or minus)-N-n-*

propylnorapomorphine, and (plus or minus)-N-n-propylnorapocodeine. J Med Chem. 1973;16(11):1223–8. PubMed PMID: 4201182.

18. Hwang D.R., Kegeles L.S., Laruelle M. *(-)-N-[(11)C]propyl-norapomorphine: a positron-labeled dopamine agonist for PET imaging of D(2) receptors.* Nucl Med Biol. 2000;27(6):533–9. PubMed PMID: 11056366.
19. 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.
20. Hwang D.R., Narendran R., Huang Y., Slifstein M., Talbot P.S., Sudo Y., Van Berckel B.N., Kegeles L.S., Martinez D., Laruelle M. *Quantitative analysis of (-)-N-(11)C-propyl-norapomorphine in vivo binding in nonhuman primates.* J Nucl Med. 2004;45(2):338–46. PubMed PMID: 14960658.
21. Narendran R., Hwang D.R., Slifstein M., Talbot P.S., Erritzoe D., Huang Y., Cooper T.B., Martinez D., Kegeles L.S., Abi-Dargham A., Laruelle M. *In vivo vulnerability to competition by endogenous dopamine: comparison of the D2 receptor agonist radiotracer (-)-N-[11C]propyl-norapomorphine ([11C]NPA) with the D2 receptor antagonist radiotracer [11C]-raclopride.* Synapse. 2004;52(3):188–208. PubMed PMID: 15065219.
22. Narendran R., Hwang D.R., Slifstein M., Hwang Y., Huang Y., Ekelund J., Guillin O., Scher E., Martinez D., Laruelle M. *Measurement of the proportion of D2 receptors configured in state of high affinity for agonists in vivo: a positron emission tomography study using [11C]N-propyl-norapomorphine and [11C]raclopride in baboons.* J Pharmacol Exp Ther. 2005;315(1):80–90. PubMed PMID: 16014571.
23. Narendran R., Mason N.S., Laymon C.M., Lopresti B.J., Velasquez N.D., May M.A., Kendro S., Martinez D., Mathis C.A., Frankle W.G. *A comparative evaluation of the dopamine D(2/3) agonist radiotracer [11C](-)-N-propyl-norapomorphine and antagonist [11C]raclopride to measure amphetamine-induced dopamine release in the human striatum.* J Pharmacol Exp Ther. 2010;333(2):533–9. PubMed PMID: 20103586.
24. Laymon C.M., Mason N.S., Frankle W.G., Carney J.P., Lopresti B.J., Litschge M.Y., Mathis C.A., Mountz J.M., Narendran R. *Human biodistribution and dosimetry of the D2/3 agonist 11C-N-propylnorapomorphine (11C-NPA) determined from PET.* J Nucl Med. 2009;50(5):814–7. PubMed PMID: 19372487.