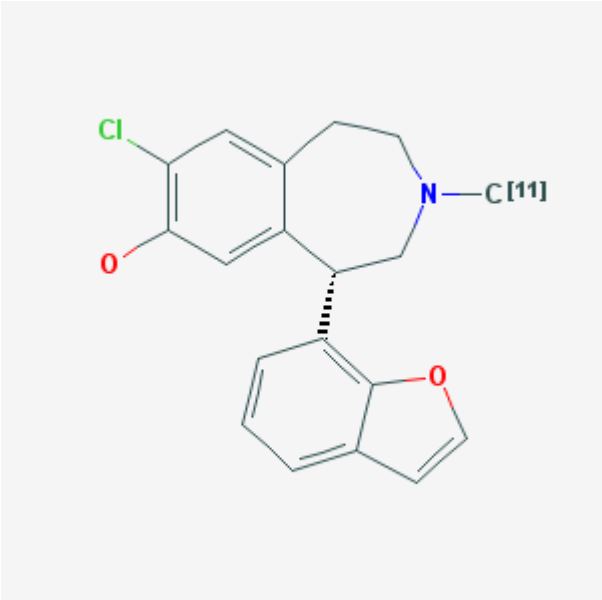
(+)-8-Chloro-5-(7-benzofuranyl)-7-hydroxy-3-[^{11}C]methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine

[^{11}C]NNC 112

Kam Leung, PhD[1]

Created: March 17, 2006; Updated: January 12, 2008.

Chemical name:	(+)-8-Chloro-5-(7-benzofuranyl)-7-hydroxy-3-[^{11}C]methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine
Abbreviated name:	
Synonym:	[^{11}C]NNC 112
Backbone:	Compound
Target:	D_1 dopamine receptors
Mechanism:	Receptor binding
Method of detection:	Positron Emission Tomography (PET)
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals • Non-human primates • Humans



Click on the above structure for additional information in PubChem.

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

Corresponding author.

Background

[PubMed]

Dopamine, a neurotransmitter, plays an important role in the mediation of movement, cognition, and emotion (2, 3). Dopamine receptors are involved in the pathophysiology of neuropsychiatric diseases such as Parkinson's disease, Alzheimer's disease, Huntington's disease, and schizophrenia (4). Five subtypes of dopamine receptors, D_1 through D_5, have been well characterized pharmacologically and biochemically (5). 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 nigrostriatal axons.

(*R*)-(+)-8-Chloro-2,3,4,5-tetrahydro-3-[^{11}C]methyl-5-phenyl-1*H*-3-benzazepin-7-ol ([^{11}C]SCH 23390) was the first positron emission tomography (PET) radioligand for D_1 receptor studies. However, [^{11}C]SCH 23390 exhibits a low neocortex/cerebellum ratio (1.5), which makes it difficult to estimate the D_1 receptor density in the neocortex. (+)-8-Chloro-5-(7-benzofuranyl)-7-hydroxy-3-[^{11}C]methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine ([^{11}C]NNC 112) was also found to be a selective, high-affinity antagonist of D_1 receptors, but to have only a marginal effect on D_2, α_1-adrenergic, muscarinic, and histaminergic receptors and only a slight effect on 5-HT_2 receptors (6, 7). [^{11}C]NNC 112 was found to display higher specific signal/noise ratios than [^{11}C]SCH 23390. [^{11}C]NNC 112 PET has been developed to study D_1 receptor occupancy and density in the striatum and neocortex in humans.

Synthesis

[PubMed]

[^{11}C]NNC 112 was synthesized by alkylation of the desmethyl compound with [^{11}C]methyl triflate (8). Reaction in acetone with subsequent chromatographic separation gave radiochemical yields of 50-60%, with a total synthesis time of 25-30 min and a radiochemical purity >99%. The average specific activity was 111 GBq/µmol (3 Ci/µmol) at the end of synthesis.

NLM Citation: Leung K. (+)-8-Chloro-5-(7-benzofuranyl)-7-hydroxy-3-[^{11}C]methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine. 2006 Mar 17 [Updated 2008 Jan 12]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

NNC 112 has been reported to have selective binding affinity to D_1 (striatum) and 5-HT_2 (frontal cortex) receptor sites in homogenates of rat brain membranes (6, 7). The K_i values for D_1, D_2, and 5-HT_2 were 0.18, 898, and 18 nM, respectively. The affinity for the D_2 receptor is about 4,900-fold lower than that for the D_1 receptor. NNC 112 has a 50% inhibitory concentration (IC_{50}) of 2,300 nM for the α_1-adrenergic receptor. The affinity for the 5-HT_2 receptor is about 100-fold lower than that for the D_1 receptor, suggesting that specific [^{11}C]NNC 112 binding visualized by PET represents mainly binding to D_1 receptors. Farde and Hall (9) reported that the receptor densities of D_1 to D_2 in the human putamen-caudate regions are similar and that there are more D_1 receptors than D_2 receptors in various cortical regions.

Animal Studies

Rodents

[PubMed]

Biodistribution studies in rat brain showed high accumulation of radioactivity in the striatum (2.05 ± 0.43% injected dose (ID)/g), followed by the prefrontal cortex (0.52 ± 0.10% ID/g), hippocampus (0.41 ± 0.09% ID/g), and cerebellum (0.19 ± 0.04% ID/g) at 30 min after injection of [^{11}C]NNC 112 (10). The striatum/cerebellum ratio was 10.79.

Other Non-Primate Mammals

[PubMed]

Using PET, Rosa-Neto et al. (11) directly compared the distributions of dopamine D_1 and $D_{2/3}$ receptors in six Gottingen minipigs. The binding potentials (BPs) of [^{11}C]NNC 112 for dopamine D_1 receptors and [^{11}C]raclopride for dopamine $D_{2/3}$ receptors were calculated in pig striatum by use of metabolite-corrected arterial inputs or with cerebellum used as the reference region. Depending on the method for quantitation, the BP for [^{11}C]NNC 112 was 1.2-5.1 in pig striatum, whereas the BP for [^{11}C]raclopride was 1.0-1.8. The reference tissue method of Logan provided the most stable estimate of BP for [^{11}C]NNC 112. Dopamine D_1 binding was relatively more abundant in the ventral-anterior striatum of the pig, whereas dopamine $D_{2/3}$ binding was greater in the dorsal-posterior striatum. Similar comparisons were made for the BPs of [^{11}C]SCH 23390 for dopamine D_1 receptors and for [^{11}C]raclopride in the brains of six rhesus monkeys. The fraction of unchanged [^{11}C]NNC 112 in plasma was 45, 24, and 3% at 5, 10, and 60 min, respectively.

Non-Human Primates

[PubMed]

Halldin et al. (8) performed PET studies in the brains of cynomolgus monkeys and found high accumulation of radioactivity in the brain (4.2% ID) with higher accumulation in the striatum than in the cerebellum at 4 min after injection of 37 MBq (1 mCi) of [^{11}C]NNC 112. The striatum/cerebellum and neocortex/cerebellum ratios were 5.77 ± 0.31 and 2.36 ± 0.14 at 40-50 min after injection, respectively. Inhibition by the specific D_1 receptor antagonist SCH 23390 (2.5 mg/kg 21-23 min after [^{11}C]NNC 112 injection) was 80% in the striatum and neocortex at 72 min after injection. However, the 5-HT_2 antagonist ketanserin (2 mg/kg before or after [^{11}C]NNC 112 injection) showed no inhibition, indicating that binding of [^{11}C]NNC 112 to D_1 receptors in the brain is specific and reversible.

Human Studies

[PubMed]

In a PET study of D_1 receptor distribution in human brain, Halldin et al. (8) reported that [^{11}C]NNC 112 showed major localization of radioactivity in the striatum and neocortex. The striatum/cerebellum and neocortex/cerebellum ratios were 3.8 and 1.8, respectively. Transient equilibrium was achieved at 40-50 min after injection. Linear graphical analysis gave of distribution volumes for the putamen, frontal cortex, and cerebellum of 15.2, 5.8, and 3.9, respectively. The fraction of unchanged [^{11}C]NNC 112 in plasma was 50% and 18% at 10 and 30 min, respectively.

Abi-Dargham et al. (12) studied 6 healthy volunteers, using kinetic and Logan graphical analysis to estimate four parameters with good reproducibility and good agreement. However, there was noise-dependent bias in the graphical but not in the kinetic analysis. Another PET study by Abi-Dargham et al. (13) in 16 patients with schizophrenia (no psychotropic medication at least 14 days before the study) and in 16 normal subjects revealed that the BP of [^{11}C]NNC 112 was significantly elevated in the dorsolateral prefrontal cortex (DLPFC) of patients with schizophrenia (1.63 ± 0.39 ml/g) compared with the controls (1.27 ± 0.44 ml/g).

Narendran et al. (14) compared regional brain BPs of [^{11}C]NNC 112 in 14 chronic ketamine users and 14 normal volunteers. There was a significant increase in [^{11}C]NNC 112 BP in the DLPFC of ketamine users (1.68 ± 0.40 ml/g) compared with controls (1.35 ± 0.35 ml/g). No significant differences were observed in other cortical, limbic, or striatal regions. Slifstein et al. (15) reported that specific binding of [^{11}C]NNC 112 in the brain cortical regions was reduced by 20-30% after administration of 2 mg of risperidone to inhibit serotonin 5-HT_{2A} receptors in 7 healthy subjects. No inhibition was observed in the striatum. These results suggested that there are ~5-10 fold selectivity of [^{11}C]NNC 112 for D1 versus 5-HT_{2A} receptors.

Cropley et al. (16) reported on PET scans in 7 healthy volunteers after injection of ~710 MBq (19 mCi) of [^{11}C]NNC 112. Absorbed doses were found to be 32.4 µGy/MBq (0.12 rad/mCi) for the gallbladder, 22.2 µGy/MBq (0.082 rad/mCi) for the liver, 16.9 µGy/MBq (0.063 rad/mCi) for the lungs, 16.6 µGy/MBq (0.061 rad/mCi) for the kidneys, 15.7 µGy/MBq (0.058 rad/mCi) for the urinary bladder wall, 9.4 µGy/MBq (0.035 rad/mCi) for the spleen, and 6.9 µGy/MBq (0.026 rad/mCi) for the brain. The effective dose was 5.7 µSv/MBq (21.1mrem/mCi).

Supplemental Information

[Disclaimers]

Chemistry

Synthesis Protocol

Toxicology

NIH Support

Intramural research program, R01 MH59144-01, MH661710-03, K02 MH01603-0

References

1. Slavicek J.M., Hayes-Plazolles N. *The Lymantria dispar nucleopolyhedrovirus contains the capsid-associated p24 protein gene.* Virus Genes. 2003;26(1):15–8. PubMed PMID: 12680688.
2. Carbon M.et al. *Learning networks in health and Parkinson's disease: reproducibility and treatment effects.* Hum Brain Mapp. 2003;19(3):197–211. PubMed PMID: 12811735.
3. Chesselet M.F., Delfs J.M. *Basal ganglia and movement disorders: an update.* Trends Neurosci. 1996;19(10):417–22. PubMed PMID: 8888518.
4. Seeman P.et al. *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.
5. Stoof J.C., Kebabian J.W. *Two dopamine receptors: biochemistry, physiology and pharmacology.* Life Sci. 1984;35(23):2281–96. PubMed PMID: 6390056.
6. Andersen P.H.et al. *NNC-112, NNC-687 and NNC-756, new selective and highly potent dopamine D1 receptor antagonists.* Eur J Pharmacol. 1992;219(1):45–52. PubMed PMID: 1397049.
7. Nielsen E.B., Andersen P.H. *Dopamine receptor occupancy in vivo: behavioral correlates using NNC-112, NNC-687 and NNC-756, new selective dopamine D1 receptor antagonists.* Eur J Pharmacol. 1992;219(1):35–44. PubMed PMID: 1397048.
8. Halldin C.et al. *Carbon-11-NNC 112: a radioligand for PET examination of striatal and neocortical D1-dopamine receptors.* J Nucl Med. 1998;39(12):2061–8. PubMed PMID: 9867142.

9. Farde L., Hall H. *Positron emission tomography--examination of chemical transmission in the living human brain. Development of radioligands.* Arzneimittelforschung. 1992;42(2A):260–4. PubMed PMID: 1316756.
10. Guo N.et al. *Dopamine depletion and in vivo binding of PET D1 receptor radioligands: implications for imaging studies in schizophrenia.* Neuropsychopharmacology. 2003;28(9):1703–11. PubMed PMID: 12813475.
11. Rosa-Neto P., Doudet D.J., Cumming P. *Gradients of dopamine D1- and D2/3-binding sites in the basal ganglia of pig and monkey measured by PET.* Neuroimage. 2004;22(3): 1076–83. PubMed PMID: 15219579.
12. Abi-Dargham A.et al. *Measurement of striatal and extrastriatal dopamine D1 receptor binding potential with [11C]NNC 112 in humans: validation and reproducibility.* J Cereb Blood Flow Metab. 2000;20(2):225–43. PubMed PMID: 10698059.
13. Abi-Dargham A.et al. *Prefrontal dopamine D1 receptors and working memory in schizophrenia.* J Neurosci. 2002;22(9):3708–19. PubMed PMID: 11978847.
14. Narendran R.et al. *Altered prefrontal dopaminergic function in chronic recreational ketamine users.* Am J Psychiatry. 2005;162(12):2352–9. PubMed PMID: 16330601.
15. Slifstein M.et al. *[11C]NNC 112 selectivity for dopamine D1 and serotonin 5-HT(2A) receptors: a PET study in healthy human subjects.* J Cereb Blood Flow Metab. 2007;27(10):1733–41. PubMed PMID: 17311076.
16. Cropley V.L.et al. *Whole-Body Biodistribution and Estimation of Radiation-Absorbed Doses of the Dopamine D1 Receptor Radioligand 11C-NNC 112 in Humans.* J Nucl Med. 2006;47(1):100–4. PubMed PMID: 16391193.