PET Studies on Dopamine D1 Receptors in the Human Brain with Carbon-11-SCH 39166 and Carbon-11-NNC 756

Arto O. Laihinen, Juha O. Rinne, Hanna M. Ruottinen, Kjell Å. Någren, Pertti K. Lehikoinen, Vesa J. Oikonen, Ulla H. Ruotsalainen and Urpo K. Rinne

Department of Neurology, University of Turku, Turku University Cyclotron/PET Center; Radiopharmaceutical Chemistry Laboratory, Turku University Cyclotron/PET Center; PET Unit, Turku, Finland

PET studies were carried out on brain dopamine D1 receptors using two new ligands, [^{11}C]SCH 39166 and [^{11}C]NNC 756. **Methods:** Four normal subjects and eight predominantly unilateral patients with early Parkinson's disease were investigated. Each of them underwent both a PET scan with [^{11}C]SCH 39166 and one with [^{11}C]NNC 756. A dose of about 185 MBq (5 mCi) of these ligands was administered intravenously and a dynamic PET scan with an ECAT 931/08 PET camera was carried out. Ratios between the striatal and cerebellar uptake of these compounds were calculated. **Results:** Both [^{11}C]SCH 39166 and [^{11}C]NNC 756 accumulated in the striatum. There was also some neocortical binding; 75% of the striatal value in the case of [^{11}C]SCH 39166 and 60% with [^{11}C]NNC 756 which displayed higher ($p < 0.01$) uptake in the striatum than [^{11}C]SCH 39166. There were no significant side-to-side differences in the controls nor in the parkinsonian patients. **Conclusions:** These results imply that both [^{11}C]SCH 39166 and [^{11}C]NNC 756 can be used in PET studies for the visualization and quantification of dopamine D1 receptors. Since [^{11}C]NNC 756 has a significantly better signal-to-noise ratio in the striatum than [^{11}C]SCH 39166, it seems to offer definite advantages for studies of D1 receptors.

Key Words: PET; dopamine D1 receptors; SCH 39166; NNC 756; Parkinson's disease

J Nucl Med 1994; 35:1916–1920

Dopamine has a variety of receptor systems in the brain, which have been characterized mainly with in vitro techniques (*1*). PET has created a new possibility to analyze the functional role of these receptors in vivo both in normal volunteers and in patients with various neurological disease conditions. So far, the function of dopamine D2 receptors has been elucidated better than that of other dopamine receptors (*1*). The first relatively specific compound for the study of dopamine D1 receptors in vivo was SCH 23390 (*2,3*). However, since this substance has some affinity both for D1 receptors and also for 5-HT receptors (*2*), it is not ideal for the exact study of dopamine D1 receptors. Recently, new, more specific ligands for dopamine D1 receptors have been developed: SCH 39166 (*4*) and NNC 756 (*5,6*), which are structurally closely related to SCH 23390. The aim of this study was the PET examination of dopamine D1 receptors in the human brain with two novel ^{11}C-labeled compounds, [^{11}C]SCH 39166 and [^{11}C]NNC 756.

Received Dec. 17, 1993; revision accepted Jun. 23, 1994.

For correspondence and reprint requests contact: Dr. Arto Laihinen, MD, Dept. of Neurology, University of Turku, FIN-20520 Turku, Finland.

METHODS

Subjects

Four normal age-matched volunteers were studied (3 males, 1 female, age 52–63 yr, mean ± s.e.m., 58.8 ± 2.0 yr) and 8 predominantly unilateral patients with early idiopathic Parkinson's disease (3 males, 5 females, age 34–73 yr, mean ± s.e.m., 55.9 ± 4.1 yr, Hoehn and Yahr stage I for three patients, stage II for five patients). The duration of Parkinson's disease was 1.5 ± 0.4 yr (mean ± s.e.m.). None of these patients had received any levodopa or dopamine agonist treatment before the PET scan was carried out. Every subject gave his or her informed consent. The study was approved by the Ethical Committee of the Turku University Central Hospital.

Radioligands

Carbon-11-NNC 756 ([methyl-^{11}C]-(S)-(+)-8-chloro-5-(2,3-dihydrobenzofuran-7-yl)-7-hydroxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine) and [^{11}C]SCH 39166 ([methyl-^{11}C]-(−)-trans-6,7,7a,8,9,13b-hexahydro-3-chloro-2-hydroxy-N-methyl-5H-benzo(d)naphto-(2,1-b)azepine) were prepared as described previously (*7,8,9*). Carbon-11-methyliodide, prepared by a one-pot reaction set-up according to the standard procedure at our radiochemistry laboratory (*10*) from [^{11}C]carbon dioxide produced with an Efremov 103-cm isochroronous cyclotron, was thus used in alkylation reactions of the N-desmethyl precursors SCH 40853 (Schering-Plough Corporation, Bloomfield, NJ) and NNC 1596 (Novo Nordisk A/S, Bagsvaerd, Denmark). The volume of the formulated (physiological 0.1 *M* phosphate buffer) [^{11}C]NNC 756 and [^{11}C]SCH 39166 solutions was determined by weighing before and after sterile filtration. The concentrations of [^{11}C]SCH 39166 and [^{11}C]NNC 756 solutions were assessed by reversed-phase HPLC (25% acetonitrile, 75% 0.05 *M* sodium dihydrogen phosphate, 2 ml/min) with UV detection at 204 nm. Samples of [^{11}C]SCH 39166 and [^{11}C]NNC 756 were analyzed in triplicate and

the concentrations determined from calibration curves made by injection of three known concentrations of SCH 39166 or NNC 756 (obtained from the same source as the precursors for radiolabeling) on the same day as the [^{11}C]-synthesis, the standard deviation being less than 2%.

PET Imaging

The PET scans were carried out with an eight-ring whole-body PET scanner (ECAT 931/08-12) with an in-plane spatial resolution of 6.5 mm full-width at half maximum (FWHM) and with an axial resolution of 6.75 mm measured according to Spinks et al. (*11*). The subject's head was fixed in the tomograph with an individually prepared Styrox frame. The PET examinations with [^{11}C]SCH 39166 and [^{11}C]NNC 756 were carried out as dynamic studies between 0 and 80 min in all of the four normal subjects and in five of the patients; in three patients, the duration of the [^{11}C]SCH 39166 and [^{11}C]NNC 756 PET studies was 60 min. The injected doses of [^{11}C]NNC 756 were 135.8–211.6 MBq (3.67–5.72 mCi) and those of [^{11}C]SCH 39166 varied between 165.8–199.4 MBq (4.48–5.39 mCi). The duration of the intravenous injection was 10 sec. The specific radioactivity at the time of injection was 2.7–12.3 GBq/μmole (72.9–332.7 mCi/μmole) for [^{11}C]SCH 39166 and 6.6–31.8 GBq/μmole (178.7–860.2 mCi/μmole) for [^{11}C]NNC 756. No untoward effects of these compounds were observed in the normal subjects or patients studied.

The region of interest (ROI) analysis was carried out by taking the head of the caudate and the putamen, as well as the total striatum, as separate ROIs. Moreover, frontal, temporal and parietal cortical ROIs were made. All the striatal and cortical ROIs were drawn freely (trace ROI), whereas an elliptical ROI was used to depict the cerebellum. In this context, high-field (1.5 T) MRI images of the brain were available for reference. Ratios between these regions and the cerebellum were determined by calculating the mean ratio using the time frames from 55 min to 80 min from the injection reflecting the maximum striatum-to-cerebellum ratio during the PET scan approaching equilibrium at the end of the study. The ratio method could be applied here because [^{11}C]SCH 39166 and [^{11}C]NNC 756 have mainly conjugated peripheral metabolites which do not penetrate the blood-brain barrier (*12–14*). Similar quantification was applied to all those subjects (four controls and five parkinsonian patients) with whom an 80-min PET study had been carried out. Blood samples consisting of arterialized venous blood (23 samples; 10 during the first 3 min and then at 5, 7, 8, 10, 15, 20, 25, 30, 40, 50, 60, 70 and 80 min after the injection) were drawn from an antecubital vein during the PET scan for assessment of radioactivity.

Statistics

After the dynamic time-activity curves had been generated, the differences between the striatum-to-cerebellum ratios of [^{11}C]NNC 756 and those of [^{11}C]SCH 39166 were compared using the paired t-test. Moreover, in parkinsonian patients, the difference between the affected hemisphere and the intact one was compared using the same procedure. Correlation analyses concerning the effects of age and specific radioactivity on the region-to-cerebellum ratios were calculated with Pearson's method.

RESULTS

A peak of radioactivity was observed in the venous blood within 2 min of the injection (Fig. 1). After that, there was a decline of radioactivity in the blood, though the radioactivity level was somewhat higher with [^{11}C]NNC

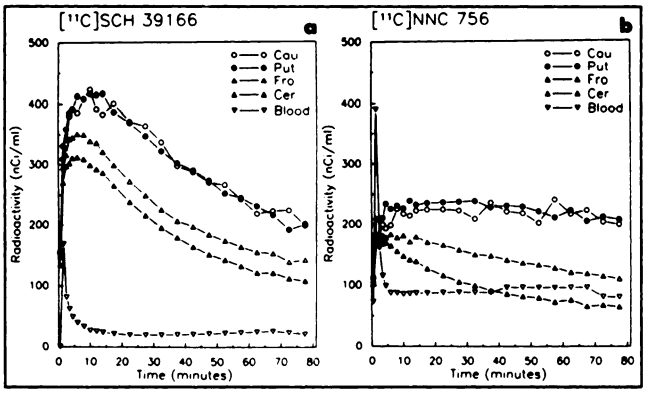

FIGURE 1. Radioactivity in brain regions and venous blood of five parkinsonian patients after intravenous injection of [^{11}C]SCH 39166 (a) and [^{11}C]NNC 756 (b) Cau = caudate, Put = putamen, Fro = frontal cortex and Cer = cerebellum.

756 than with [^{11}C]SCH 39166. There was a rapid transfer of radioactivity into the brain (Figs. 1 and 2). Both [^{11}C]SCH 39166 and [^{11}C]NNC 756 were taken up into the striatum and, to a lesser extent, the neocortex (Figs. 3A and 3B). Carbon-11-SCH 39166 activity was also noticeable in the thalamus (Fig. 3A) whereas the accumulation of [^{11}C]NNC 756 in the thalamus was negligible (Fig. 3B). The uptake of [^{11}C]NNC 756 into the caudate and putamen was different from that of [^{11}C]SCH 39166 (Figs. 1 and 2). With reference to total radioactivity in the tissue, [^{11}C]SCH 39166 accumulated rapidly during the first 20 min and thereafter showed a moderate decline (Fig. 1A), whereas [^{11}C]NNC 756 was taken up into the tissue without a high initial rise but with a relatively long plateau phase up to 80 min (Fig. 1B). Figure 2B shows the time-course of the region-to-cerebellum ratio, reflecting the fact that [^{11}C]NNC 756 had a persistent high uptake into the caudate and putamen after 20 min from the injection lasting until the end of the PET study. As shown in Figure 4, [^{11}C]NNC 756 displayed higher ($p < 0.01$) uptake into the striatum than [^{11}C]SCH 39166, in both normal subjects and in parkinso-

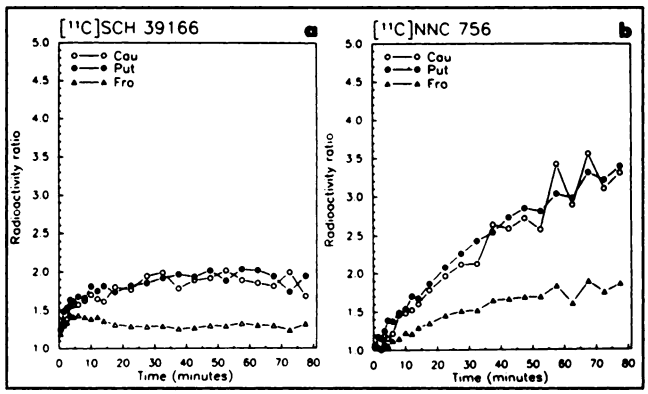

FIGURE 2. Radioactivity ratios of caudate-to-cerebellum, putamen-to-cerebellum and frontal cortex-to-cerebellum of five parkinsonian patients after intravenous injection of [^{11}C]SCH 39166 (a) and [^{11}C]NNC 756 (b).

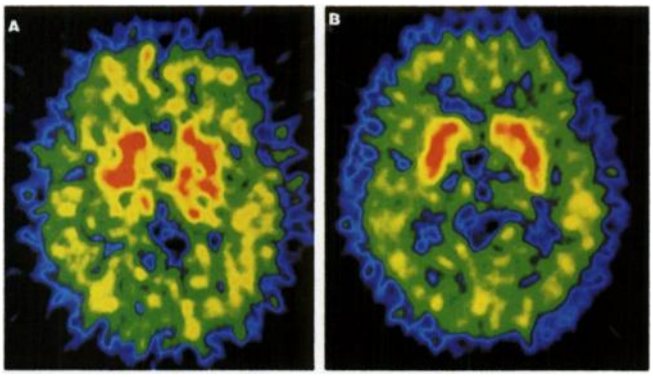

FIGURE 3. PET images through the caudate/putamen level of a normal subject: (A) [^{11}C]SCH 39166 and (B) [^{11}C]NNC 756. Note the different distribution of radioactivity in A and B; [^{11}C]SCH 39166 displays more accumulation of radioactivity in the neocortex and the thalamus than [^{11}C]NNC 756 though the caudate and the putamen are better delineated with [^{11}C]NNC 756.

nian patients. In general, the scatter of values took place within narrower limits with [^{11}C]SCH 39166 than with [^{11}C]NNC 756 (Fig. 4).

The striatum-to-cerebellum ratios in normal subjects were 1.67 ± 0.02 (mean ± s.e.m.) for [^{11}C]SCH 39166 and 3.12 ± 0.11 (mean ± s.e.m.) for [^{11}C]NNC 756. In the case of parkinsonian patients, the corresponding ratios were 1.76 ± 0.06 (mean ± s.e.m.) and 3.00 ± 0.25 (mean ± s.e.m.).

With the parkinsonian patients, the accumulation of [^{11}C]NNC was similar in the caudate and the putamen, whereas [^{11}C]SCH 39166 seemed to display slightly more uptake into the caudate than into the putamen ($p < 0.05$). There was no significant side-to-side difference in the controls nor parkinsonian patients as measured with [^{11}C]NNC 756 or [^{11}C]SCH 39166. On the other hand, there was no significant difference between the parkinsonian patients and controls as far as the striatal or cortical uptake of these compounds was concerned.

Although the main accumulation of these ligands was observed in the striatum, there was some extrastriatal uptake in the frontal neocortex (Fig. 4). There was a significant difference between [^{11}C]NNC 756 and [^{11}C]SCH 39166 concerning this neocortical binding; in the normal subjects, the cortical binding was 75% of the striatal value with [^{11}C]SCH 39166 and 60% in the case of [^{11}C]NNC 756 ($p < 0.01$); the corresponding values for parkinsonian patients were 70% and 50%, respectively ($p < 0.05$). The accumulation of these ligands in the temporal and parietal cortex was of the same order. There were no significant differences between the normal subjects and the parkinsonian patients as far as this cortical accumulation was concerned.

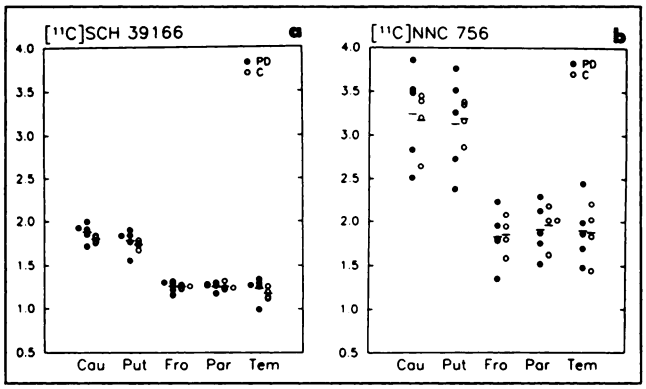

FIGURE 4. Region-to-cerebellum ratios of [^{11}C]SCH 39166 (A) and [^{11}C]NNC 756 (B) Par = parietal cortex, Tem = temporal cortex. PD = Parkinson's disease. C = control.

DISCUSSION

Our results show that both [^{11}C]NNC 756 and [^{11}C]SCH 39166 display uptake into the striatum and, to a lesser extent, into the cerebral cortex both in normal subjects and in parkinsonian patients. However, the uptake of [^{11}C]NNC 756 into the striatum is significantly higher than that of [^{11}C]SCH 39166 and when taken as a percentage of the striatal binding, [^{11}C]NNC 756 has significantly less cortical uptake than [^{11}C]SCH 39166. These findings may be taken as evidence that in vivo NNC 756 is more specific for dopamine D1 receptors than SCH 39166, although in vitro both the ligands show a good binding affinity for D1 receptors (*4,15,16*). This discrepancy between in vitro and in vivo data can also be explained on the basis of several factors operating in the living brain, which are lacking in vitro. One of these is competition by endogenous dopamine, which might affect various ligands in different ways. On the other hand, there may also be differences in lipophilicity, which account for different capabilities to cross the blood-brain barrier. Displacement experiments with cold SCH 23390 have been carried out both with [^{11}C]SCH 39166 (*8*) and [^{11}C]NNC 756 (*17,18*) and they have shown the specificity of these ligands for dopamine D1 receptors, though they do not allow a direct comparison of these compounds. Moreover, it has been shown (*17–19*) that ketanserin does not displace these compounds, which means that their binding to 5-HT$_2$ receptors is negligible.

The relatively high uptake of [^{11}C]SCH 39166 in the cortex could mean that this compound has affinity to other than D1 receptors. Lidow et al. (*20*) suggested that [^{3}H]SCH 39166 may have a high affinity to more than the D1 receptor subtype bound by SCH 23390 or *cis*-flupentixol in the cortex. Also, these additional sites are likely to be different from 5-HT$_2$ or 5-HT$_{1c}$ receptors since the latter sites were not displaced by 1 μM SCH 23390. From the quantitative point of view, however, most of [^{3}H]SCH 39166 is bound by D1 receptors.

In this study, there was a relatively wide variance in the specific radioactivity of [^{11}C]SCH 39166 and [^{11}C]NNC 756 administered (72.9–860.2 mCi/μmole). However, a calculation using the lowest specific radioactivity and the specific binding of [^{11}C]SCH 39166 in the putamen (125 nCi/ml) show that 1.7 pmole/ml of the D1 receptors in putamen

were occupied by [^{11}C]SCH 39166. Sedvall et al. (*21*) have reported a B_{max} value of 50–60 pmole/ml for the D1 receptors in the putamen of healthy control subjects. The number of receptor sites blocked by cold SCH 39166 was thus at the maximum 2%–4% of the available sites.

The findings in this PET study are in agreement with those obtained in animal experiments (*15,16,22,23*) using both ligand binding and autoradiography techniques. It was shown by Alburges et al. (*22*) in a study using quantitative autoradiographic analysis of [^{3}H]SCH 39166 and [^{3}H]SCH 23390 that there is a high D1 receptor density in the caudate-putamen, whereas low levels of binding were detected with [^{3}H]SCH 39166 in lamina intravenously of the rat cortex. Hall et al. (*24*) showed with these autoradiographic approaches in human postmortem brain tissue specific [^{3}H]SCH 39166 binding in the caudate nucleus and putamen.

In this study, the putamen-to-cerebellum and caudate-to-cerebellum ratios for [^{11}C]NNC 756 were in the order of 3, which is lower than that reported by Karlsson et al. (*17,18*): about 10 in the monkey brain and 5 in the human brain. This discrepancy may be due to several factors. First of all, Karlsson had four subjects, who were considerably younger (20–26 yr of age) than those in the present study. Suhara et al. (*25*) found in a PET study with [^{11}C]SCH 23390 that there was a 35% decline in brain dopamine D1 receptor function over the age range 20–72 yr. However, in our study no statistically significant correlation between age and region-to-cerebellum ratios was observed, which may be due to a narrow age range of the subjects and their small number. Secondly, there were differences between the specific activities and the injected amounts of radioactivity, which were higher in Karlsson's PET study, but in our study, the correlation between the region-to-cerebellum ratios and the specific activities is not significant. On the other hand, the kinetics of [^{11}C]NNC 756 characterized by the relatively slow accumulation of the tracer are very similar in the current study and that of Karlsson (*17,18*). Preliminary PET studies in monkeys with [^{11}C]SCH 39166 have been reported (*7,19*), but they do not contain any direct comparison with other D1 ligands.

It has been shown earlier (*26,27*) that there may not be changes in D1 receptor function in early Parkinson's disease, which is also the principal result of this present study concerning the comparison between parkinsonian patients and normal subjects. Previous postmortem studies have indicated no, or only slight changes in striatal dopamine D1 receptors, which might be related to dopaminergic treatment (*27–31*). Our present finding that [^{11}C]SCH 39166 displays slightly higher uptake into the caudate than in the putamen in parkinsonian patients may lack biological significance, since this observation was made only with one of the compounds, in a relatively small patient population. This aspect requires further elucidation.

Both [^{11}C]NNC 756 and [^{11}C]SCH 39166 are useful PET ligands when dopamine D1 receptors of the human brain are studied in vivo. These ligands can be used instead of or in addition to [^{11}C]SCH 23390. On the basis of the present study, however, no direct comparison between [^{11}C]SCH 23390 and these new ligands is possible because the normal subjects and parkinsonian patients here underwent only PET examinations with [^{11}C]SCH 39166 and [^{11}C]NNC 756, but not with [^{11}C]SCH 23390.

Carbon-11-NNC 756, according to our results, displays higher uptake into the striatum than [^{11}C]SCH 39166 and, therefore, it seems to offer definite advantages for imaging D1 receptors compared with [^{11}C]SCH 39166. Using these compounds, there may be new ways to investigate the functional role of dopamine D1 receptors in the normal and diseased brain.

ACKNOWLEDGMENTS

The generous supply of the precursors by Schering-Plough Corp., Bloomfield, NJ and Novo Nordisk A/S, Bagsvaerd, Denmark is gratefully acknowledged. The Medical Research Council of the Academy of Finland has also supported this work.

REFERENCES

1. Sibley DR, Monsma FJ, Shen Y. Molecular neurobiology of dopaminergic receptors. In: Bradley RJ, Harris RA, eds. *International review of neurobiology*. San Diego: Academic Press, Inc.; 1993:391–415.
2. Hyttel J. SCH 23390—the first selective dopamine D-1 antagonist. *Eur J Pharmacol* 1983;91:153–154.
3. Iorio LC, Barnett A, Leitz FH, Houser VP, Korduba CA. SCH 23390, a potential benzazepine antipsychotic with unique interactions on dopaminergic systems. *J Pharmacol Exp Ther* 1983;226:462–468.
4. Chipkin RE, Iorio LC, Coffin VL, McQuade RD, Berger JG, Barnett A. Pharmacological Profile of SCH39166: a dopamine D1 selective benzonaphthazepine with potential antipsychotic activity. *J Pharmacol Exp Ther* 1988; 247:1093–1102.
5. Andersen PH, Grønvald FC, Hohlweg R, Hansen LB, Guddal E, Braestrup C. NO-112, NO-756—new dopamine D1 selective antagonists. *Soc Neurosci Abst* 1988;14:935.
6. Nielsen EB, Hansen LB, Grønvald FC, Hohlweg R, Guddal E, Andersen PH. NO-112 and NO-756, new potent benzazepine D-1 antagonists: pharmacological characterization. *Soc Neurosci Abst* 1988;14:935.
7. Halldin C, Farde L, Barnett A, Sedvall G. Synthesis of carbon-11 labelled SCH 39166, a new selective dopamine D-1 receptor ligand, and preliminary PET investigations. *Appl Radiat Isot* 1991;42:451–455.
8. Halldin C, Hansen K, Foged C, Grønvald F, Farde L. Preparation of [C-11]NNC756, a new selective dopamine D1 receptor ligand for PET. *J Nucl Med* 1991;32:934–935.
9. Halldin C, Foged C, Farde L, et al. [^{11}C]NNC 687 and [^{11}C]NNC 756, dopamine D1 receptor ligands. Preparation, autoradiography and PET investigation in monkeys. *Nucl Med Biol* 1993;20:945–953.
10. Någren K, Takahashi T, Lehikoinen P, Bergman J. Preparation of the antioestrogenic compound *N*-[Methyl-^{11}C]-toremifene for the study of oestrogen-receptor positive tumors in vivo. *J Labelled Compd Radiopharm* 1991;29:1085–1089.
11. Spinks TJ, Jones T, Gilardi MC, Heather JD. Physical performance of the latest generation of commercial positron scanner. *IEEE Trans Nucl Sci* 1988;35:721–725.
12. Hansen KT, Thomsen KF, Bundgaard H. Glucuronidation of the dopamine D-1 receptor antagonists NNC 0756 and NNC 0772 in liver microsomes. *Drug Metab Disp* 1992;20:172–178.
13. Swahn C-G, Halldin C, Farde L, Karlsson P, Sedvall G. Metabolism in human plasma determined by HPLC for five ^{11}C-labelled benzazepines—radioligands for PET examination of the dopamine D-1 receptor. *J Labelled Compd Radiopharm* 1994;35:540–542.
14. Swahn C-G, Halldin C, Farde L, Sedvall G. Metabolism of the PET Ligand [^{11}C]SCH 23390. Identification of two radiolabelled metabolites with HPLC. *Human Psychopharmacology* 1994:in press.
15. Nielsen EB, Andersen PH. Dopamine receptor occupancy in vivo: behav-

ioral correlates using NNC-112, NNC-687 and NNC-756, new selective dopamine D_1 receptor antagonists. *Eur J Pharmacol* 1992;219:35–44.
16. Andersen PH, Grønvald FC, Hohlweg R, et al. NNC-112, NNC-687 and NNC-756, new selective and highly potent dopamine D_1 receptor antagonists. *Eur J Pharmacol* 1992;219:45–52.
17. Karlsson P, Farde L, Halldin C, et al. Examination of [^{11}C]NNC 687 and [^{11}C]NNC 756 binding to D1-dopamine receptors in monkey and human brain. In: Voipio-Pulkki L-M, Wegelius U, eds. *Medical application of cyclotrons VI. Proceedings of the Sixth Symposium on the Medical Application of Cyclotrons*. June 1–4, 1992, Turku, Finland. Annales Universitatis Turkuensis, Ser. D. Medica-odontologica, Vol. 88. Turku: Turun yliopisto; 1992:A95–A96.
18. Karlsson P, Farde L, Halldin C, et al. PET examination of [^{11}C]NNC 687 and [^{11}C]NNC 756 as new radioligands for the D_1-dopamine receptor. *Psychopharmacology* 1993;113:149–156.
19. Sedvall G, Farde L, Barnett A, Hall H, Halldin C. Carbon-11-SCH 39166, a selective ligand for visualization of dopamine-D_1 receptor binding in the monkey using PET. *Psychopharmacology* 1991;103:150–153.
20. Lidow MS, Goldman-Rakic PS, Rakic P, Gallager DW. Autoradiographic comparison of D_1-specific binding of [^{3}H]SCH39166 and [^{3}H]SCH23390 in the primate cerebral cortex. *Brain Res* 1990;537:349–354.
21. Sedvall G, Karlsson P, Lundin A, et al. Dopamine D_1 receptor number—a sensitive PET marker for early brain degeneration in Huntington's disease. *Eur Arch Psychiatry Clin Neurosci* 1994;243:249–255.
22. Alburges ME, Hunt MAE, McQuade RD, Wamsley JK. D_1-Receptor antagonists: comparison of [^{3}H]SCH39166 to [^{3}H]SCH23390. *J Chem Neuroanat* 1992;5:357–366.
23. McQuade RD, Duffy RA, Anderson CC et al. [^{3}H]SCH 39166, a new D_1-selective radioligand: in vitro and in vivo binding analyses. *J Neurochem* 1991;57:2001–2010.
24. Hall H, Halldin C, Sedvall G. Binding of [^{3}H]SCH39166 to human postmortem brain tissue. *Pharmacol Toxicol* 1993;72:152–158.
25. Suhara T, Fukuda H, Inoue O, et al. Age-related changes in human D1 dopamine receptors measured by positron emission tomography. *Psychopharmacology* 1991;103:41–45.
26. Rinne JO, Laihinen A, Någren K, et al. PET demonstrates different behaviour of striatal dopamine D-1 and D-2 receptors in early Parkinson's disease. *J Neurosci Res* 1990;27:494–499.
27. Shinotoh H, Inoue O, Hirayama K, et al. Dopamine D1 receptors in Parkinson's disease and striatonigral degeneration: a positron emission tomography study. *J Neurol Neurosurg Psychiatry* 1993;56:467–472.
28. Pierot L, Desnos C, Blin J, et al. D1 and D2-type dopamine receptors in patients with Parkinson's disease and progressive supranuclear palsy. *J Neurol Sci* 1988;86:291–306.
29. Raisman R, Cash M, Ruberg M, Javoy-Agid F, Agid Y. Binding of [^{3}H]SCH 23390 to D-1 receptors in the putamen of control and parkinsonian brain. *Eur J Pharmacol* 1985;113:467–468.
30. Rinne JO, Rinne JK, Laakso K, Lönnberg P, Rinne UK. Dopamine D-1 receptors in parkinsonian brain. *Brain Res* 1985;359:306–310.
31. Rinne JO, Laihinen A, Lönnberg P, Marjamäki P, Rinne UK. A postmortem study on brain dopamine D-1 and D-2 receptors in Parkinson's disease. *Brain Res* 1991;556:117–122.