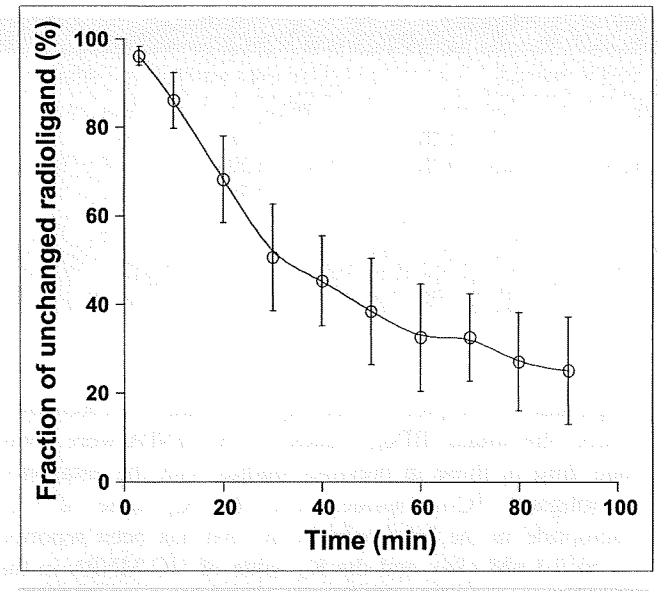

FIGURE 3. Average (n = 10) percentage of unchanged ^{11}C-MNPA in plasma vs. time. Bars indicate SD.

the 2 regions might affect the BP_{ND} calculated by the SRTM and transient equilibrium methods. Furthermore, changes in K_1 due to changes in CBF might be caused by neurologic or psychiatric diseases. The K_1 value for ^{11}C-MNPA was about 0.44 mL/cm^3/min in gray matter. When the CBF value in gray matter is assumed to be 0.50 mL/cm^3/min (*29*), the first-pass extraction fraction of ^{11}C-MNPA is 88%. The capillary permeability–surface area product (PS) value, using this extraction fraction and a K_1 value of 0.44 mL/cm^3/min, was calculated (*30,31*). With the PS value of 1.06 mL/cm^3/min, the K_1 range of 0.20–0.60 mL/cm^3/min corresponds to the CBF range of 0.20–0.85 mL/cm^3/min (*28*).

RESULTS

All 10 subjects participated in the study according to the protocol. Representative summated PET images (60–90 min) and T1-weighted MR images are shown in Figure 1, and the corresponding regional time–activity curves are shown in Figure 2. Regional radioactivity was highest in the putamen and lower in the caudate and thalamus. The average percentage of unchanged ^{11}C-MNPA in plasma was 95.1% ± 2.1% at 3 min, decreasing to 25.1% ± 12.0% at 90 min (i.e., at the end of PET data acquisition) (Fig. 3). Other than MNPA, there were no more lipophilic-labeled metabolites in the plasma.

[Fig. 1] [Fig. 2] [Fig. 3]

After an intravenous injection of ^{11}C-MNPA, total radioactivity in the brain peaked at 6.7 ± 1.2 min (range, 4.5–9.0 min), and the fraction of uptake in the brain was 6.0% ± 1.0% (range, 4.3%–7.3%) of the injected radioactivity.

The blood volume and rate constants for each brain region obtained by conventional nonlinear least-squares fit of the 2-compartment model are shown in Table 1. The BP_{ND} values of the putamen, caudate, and thalamus calculated by the 3 different methods are shown in Table 2. Specific binding, as defined by the transient equilibrium method, reached a peak within 60 min in the putamen, caudate, and thalamus (Table 2).

[Table 1] [Table 2]

BP_{ND} values determined by the SRTM method on the basis of data acquired for 90 and 60 min and those determined by the transient equilibrium method were compared with values calculated by the indirect kinetic method. BP_{ND} values obtained by the SRTM method were in good agreement with those obtained by the indirect kinetic method with data obtained for 90 and 60 min (Fig. 4), and BP_{ND} values obtained by the transient equilibrium method were in good agreement with those obtained by the indirect kinetic method with data for 90 min (Fig. 5). The highest coefficient of correlation was observed between the SRTM and the indirect kinetic methods with data acquired for 90 min (r = 0.98, $P < 0.001$).

[Fig. 4] [Fig. 5]

When BP_{ND} values determined by the indirect kinetic and SRTM methods with 60-min data were compared with values determined by the same 2 methods with 90-min data, good agreement was observed (r = 0.99, r = 0.92, $P < 0.001$) (Fig. 6).

[Fig. 6]

To estimate the sensitivity of the SRTM and transient equilibrium methods for rate constants (indirect blood flow) over an interval with values lower and higher than average, a simulation study was performed. BP_{ND} values determined by the indirect kinetic method with data acquired for 60 and 90 min were compared with BP_{ND} values determined by the SRTM and transient equilibrium methods with data acquired for 60 and 90 min from simulated time–activity curves. The error in BP_{ND} calculated by the SRTM method with data acquired for 90 min was smallest (−24.8% to 1.5%; mean, −4.3%), and the difference in K_1 between the brain region and cerebellum had only a minor effect on

TABLE 1. Rate Constants Obtained by Conventional Nonlinear Least-Squares Fit of 2-Tissue-Compartment Model

Region	Blood volume	Rate constant			
		K_1 (mL/cm^3/min)	k_2 (min^{-1})	k_3 (min^{-1})	k_4 (min^{-1})
Putamen	0.07 ± 0.02	0.44 ± 0.05	0.07 ± 0.01	0.15 ± 0.06	0.19 ± 0.07
Caudate	0.06 ± 0.02	0.39 ± 0.05	0.06 ± 0.01	0.11 ± 0.06	0.20 ± 0.11
Thalamus	0.07 ± 0.02	0.43 ± 0.05	0.07 ± 0.01	0.03 ± 0.01	0.13 ± 0.06
Cerebellum (1TCM)	0.07 ± 0.02	0.41 ± 0.03	0.06 ± 0.01		

1TCM = 1-tissue-compartment model.
Values are mean ± SD.

TABLE 2. BP_{ND} Values Obtained by Different Methods and Scan Times

	Indirect kinetic method		SRTM method		Transient equilibrium method	
Region	90 min	60 min	90 min	60 min	BP_{ND}	Time (min)*
Putamen	0.82 ± 0.09	0.83 ± 0.09	0.78 ± 0.07	0.79 ± 0.08	0.76 ± 0.07	36.4 ± 4.5
Caudate	0.59 ± 0.11	0.59 ± 0.10	0.55 ± 0.09	0.56 ± 0.13	0.60 ± 0.09	39.6 ± 5.7
Thalamus	0.28 ± 0.06	0.28 ± 0.05	0.24 ± 0.04	0.31 ± 0.18	0.23 ± 0.05	29.2 ± 11.3

*Time of transient equilibrium (min).
Values are mean ± SD.

BP_{ND}. The error in BP_{ND} calculated by the transient equilibrium method was smallest when the K_1 value was 0.44, but BP_{ND} was overestimated when the K_1 value was lower than 0.36 and was underestimated when it was higher than 0.52 (Fig. 7). [Fig. 7]

DISCUSSION

Studies using agonist radioligands such as ^{11}C-PHNO to examine the high-affinity state of the dopamine D_2 receptor in the human brain have been reported previously (*32*). Our study describes the first, to our knowledge, PET examination using the agonist radioligand ^{11}C-MNPA to visualize binding to G-protein–coupled receptors in the human brain. After the intravenous injection of ^{11}C-MNPA, radioactivity appeared rapidly in the brain and was washed out in a fashion similar to that previously reported in nonhuman primates (*20*). Radioactivity was highest in the putamen and slightly lower in the caudate, moderate in the thalamus, and lowest in the cerebellum. This regional distribution is similar to that shown in nonhuman primates with ^{11}C-MNPA (*20,21*) and is in accordance with the known distribution of dopamine D_2 receptors, as demonstrated with antagonist radioligands such as ^{11}C-raclopride in the human brain (*33*). Finnema also reported blocking data with a dopamine D_2 antagonist in nonhuman primates (*20*). The pretreatment with raclopride, compared with the baseline condition, demonstrated high specific binding of the dopamine D_2 receptor by reducing the striatum-to-cerebellum ratio. The striatal BP_{ND} values of ^{11}C-MNPA were about one third of those in previous studies with the antagonist radioligand ^{11}C-raclopride (*33*). The K_d value of ^{11}C-raclopride in the human brain in vivo has been reported to be 9.1 nM (*34*), and the K_d value of ^{11}C-MNPA in the monkey brain in vivo has been reported to be 11.6 nM (*35*). Because the K_d values of ^{11}C-MNPA and ^{11}C-raclopride are similar in vitro, the difference in striatal BP_{ND} between ^{11}C-MNPA and ^{11}C-raclopride may reflect a difference in the density of available receptors (B_{max}) of the 2 radioligands. This interpretation is in line with the view that an agonist radioligand labels only the receptors in the high-affinity state, whereas an antagonist radioligand labels both high- and low-affinity-state dopamine D_2 receptors (*21,35*).

Ginovart et al. reported that ^{11}C-PHNO and ^{11}C-NPA in the cat were more sensitive to amphetamine-induced dopamine release than was ^{11}C-raclopride (*36*). The observation that ^{11}C-MNPA in nonhuman primates is also more sensitive to amphetamine-induced dopamine release than is ^{11}C-raclopride (*21*) has been taken as evidence for selective labeling of D_2 receptors in the high-affinity state. The relatively low BP_{ND} in the present study corroborates this view.

In this study, the indirect kinetic method with arterial blood sampling was used as the gold standard (*25*). Because arterial blood sampling is invasive, we examined the accuracy of the SRTM and transient equilibrium methods

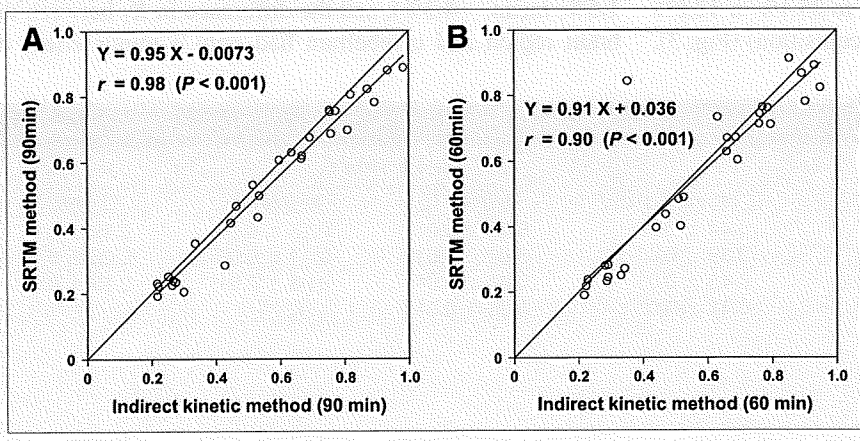

FIGURE 4. Comparison of BP_{ND} values in 3 regions (putamen, caudate, and thalamus) of 10 control subjects calculated by indirect kinetic and SRTM methods on the basis of data acquired over 90 (A) and 60 min (B).

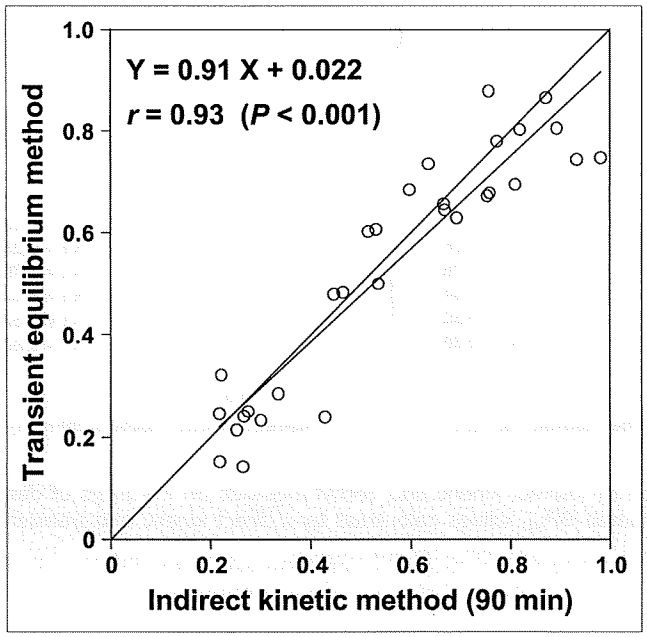

FIGURE 5. Comparison of BP_{ND} values in 3 regions (putamen, caudate, and thalamus) in 10 control subjects calculated by indirect kinetic and transient equilibrium methods.

for quantifying ^{11}C-MNPA binding using the cerebellum as the reference brain region. The SRTM and transient equilibrium methods had previously been validated for antagonist radioligands such as ^{11}C-raclopride and ^{11}C-FLB457 (*15,25,28*). In the present study, BP_{ND} of ^{11}C-MNPA obtained by the SRTM method was in good agreement with that obtained by the indirect kinetic method with data acquired for 60 and 90 min. The BP_{ND} value obtained by the transient equilibrium method was also in good agreement with the value obtained by the indirect kinetic method with data acquired for 90 min. Thus, it should be possible to use simplified protocols with no arterial blood sampling in applied clinical studies in humans.

In the simulation study, BP_{ND} calculated by the SRTM method was in good agreement with that calculated by the indirect kinetic method, although BP_{ND} was slightly overestimated. These results demonstrate the validity of the SRTM method for quantitating ^{11}C-MNPA binding also when blood flow and rate constants might be deviant. The present observation is in line with an ^{11}C-FLB457 study showing that the BP_{ND} value calculated by the SRTM method was not greatly affected by differences in K_1 between the brain regions and the cerebellum (*25*). Thus, the SRTM method is suitable for quantifying ^{11}C-MNPA binding when using a reference brain region without arterial blood sampling.

BP_{ND} calculated by the transient equilibrium method was not in good agreement with that calculated by the indirect kinetic method in the simulation study when the K_1 value in the brain region was small. The errors in BP_{ND} calculated by the transient equilibrium method were within the range of −15% to +15% when the K_1 value was 0.44 and 0.52 mL/cm^3/min, corresponding to 0.5–0.65 mL/cm^3/min of CBF. Although the transient equilibrium method might not be suitable for determining BP_{ND} in patients with low CBF, it is still a useful method for determining BP_{ND} without arterial blood sampling.

For clinical research, a short scanning time is preferred. In the present study, the BP_{ND} values calculated by the SRTM method with data acquired for 90 min were in good agreement with those obtained with data acquired for 60 min. In the simulation study, the BP_{ND} values obtained by the SRTM method with data acquired for 60 min were in good agreement with BP_{ND} values obtained by the indirect kinetic method, except with extremely low K_1. These results suggest that the SRTM method with data acquired for 60 min is valid for clinical studies in patients with neuropsychiatric disorders such as schizophrenia and depression.

CONCLUSION

The regional distribution of ^{11}C-MNPA was in good agreement with previous PET studies of dopamine D_2 receptors in the human brain using antagonist radioligands such as ^{11}C-raclopride and ^{11}C-FLB457. The BP_{ND} values

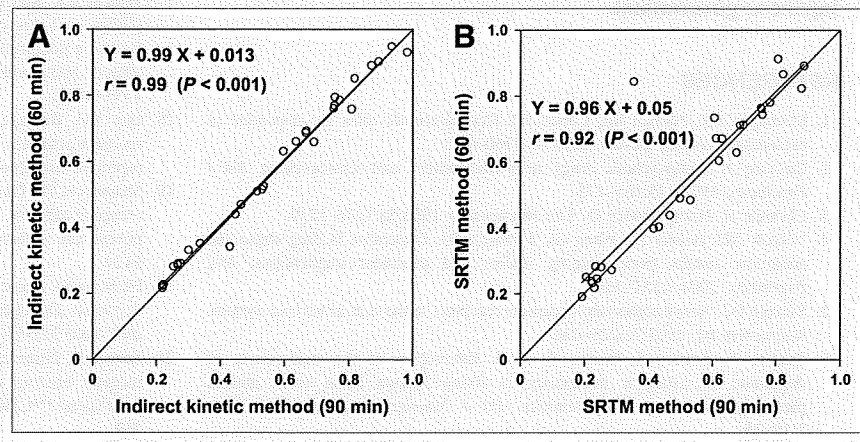

FIGURE 6. Comparison of BP_{ND} values in 3 regions (putamen, caudate, and thalamus) in 10 control subjects calculated by indirect kinetic (A) and SRTM (B) methods on the basis of data acquired over 90 and 60 min.

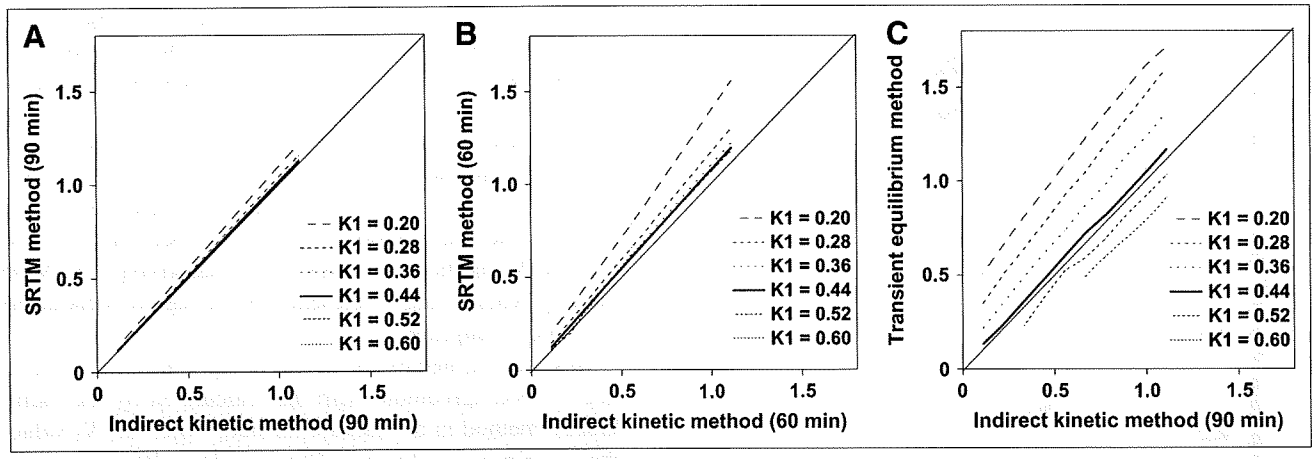

FIGURE 7. Comparison of simulated BP_{ND} values calculated by indirect kinetic and SRTM methods on the basis of data acquired over 90 (A) and 60 min (B). (C) Comparison of simulated BP_{ND} values calculated by indirect kinetic and transient equilibrium methods.

measured by the indirect kinetic model were in good agreement with those measured by the SRTM method with data acquired for 60 and 90 min. The BP_{ND} values measured by the transient equilibrium method also corresponded well with those measured by the indirect kinetic model with data acquired for 90 min. Simulation studies showed that errors in BP_{ND} measured by the SRTM method were small. The SRTM method with data acquired for 60 and 90 min is suitable for estimation of dopamine D_2 receptor bindings using ^{11}C-MNPA.

ACKNOWLEDGMENTS

We thank Katsuyuki Tanimoto, Takahiro Shiraishi, and Akira Ando for their assistance in performing the PET experiments at the National Institute of Radiological Sciences. We also thank Yoshiko Fukushima of the National Institute of Radiological Sciences for her help as clinical research coordinator. This study was supported by a consignment expense for the Molecular Imaging Program on "Research Base for PET Diagnosis" from the Ministry of Education, Culture, Sports, Science and Technology, Japanese government.

REFERENCES

1. Montague PR, Hyman SE, Cohen JD. Computational roles for dopamine in behavioural control. *Nature.* 2004;431:760–767.
2. Carlsson A. Antipsychotic drugs, neurotransmitters, and schizophrenia. *Am J Psychiatry.* 1978;135:165–173.
3. Ehringer H, Hornykiewicz O. *Klin Wochenschr.* 1960;38:1236–1239.
4. Volkow ND, Fowler JS, Wang GJ, Swanson JM. Dopamine in drug abuse and addiction: results from imaging studies and treatment implications. *Mol Psychiatry.* 2004;9:557–569.
5. Strange PG. New insights into dopamine receptors in the central nervous system. *Neurochem Int.* 1993;22:223–236.
6. Takano A, Suhara T, Ikoma Y, et al. Estimation of the time-course of dopamine D_2 receptor occupancy in living human brain from plasma pharmacokinetics of antipsychotics. *Int J Neuropsychopharmacol.* 2004; 7:19–26.
7. Yasuno F, Suhara T, Okubo Y, et al. Low dopamine D_2 receptor binding in subregions of the thalamus in schizophrenia. *Am J Psychiatry.* 2004;161:1016–1022.
8. Suhara T, Okubo Y, Yasuno F, et al. Decreased dopamine D_2 receptor binding in the anterior cingulate cortex in schizophrenia. *Arch Gen Psychiatry.* 2002;59: 25–30.
9. Yasuno F, Suhara T, Okubo Y, et al. Dose relationship of limbic-cortical D_2-dopamine receptor occupancy with risperidone. *Psychopharmacology (Berl).* 2001;154:112–114.
10. Talvik M, Nordstrom AL, Okubo Y, et al. Dopamine D_2 receptor binding in drug-naive patients with schizophrenia examined with [^{11}C]raclopride and positron emission tomography. *Psychiatry Res.* 2006;148:165–173.
11. Talvik M, Nordstrom AL, Olsson H, Halldin C, Farde L. Decreased thalamic D_2/D_3 receptor binding in drug-naive patients with schizophrenia: a PET study with [^{11}C]FLB 457. *Int J Neuropsychopharmacol.* 2003;6:361–370.
12. Sibley DR, 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;257:6351–6361.
13. Halldin C, Gulyas B, Langer O, Farde L. Brain radioligands: state of the art and new trends. *Q J Nucl Med.* 2001;45:139–152.
14. Olsson H, Halldin C, Swahn CG, Farde L. Quantification of [^{11}C]FLB 457 binding to extrastriatal dopamine receptors in the human brain. *J Cereb Blood Flow Metab.* 1999;19:1164–1173.
15. Farde L, Eriksson L, Blomquist G, Halldin C. Kinetic analysis of central [^{11}C]raclopride binding to D_2-dopamine receptors studied by PET: a comparison to the equilibrium analysis. *J Cereb Blood Flow Metab.* 1989;9:696–708.
16. Hwang DR, Kegeles LS, Laruelle M. (-)-*N*-[^{11}C]propyl-norapomorphine: a positron-labeled dopamine agonist for PET imaging of D_2 receptors. *Nucl Med Biol.* 2000;27:533–539.
17. Wilson AA, McCormick P, Kapur S, et al. Radiosynthesis and evaluation of [^{11}C]-(+)-4-propyl-3,4,4a,5,6,10b-hexahydro-2H-naphtho[1,2-b][1,4]oxazin-9-ol as a potential radiotracer for in vivo imaging of the dopamine D_2 high-affinity state with positron emission tomography. *J Med Chem.* 2005;48: 4153–4160.
18. Gao YG, Baldessarini RJ, Kula NS, Neumeyer JL. Synthesis and dopamine receptor affinities of enantiomers of 2-substituted apomorphines and their *N*-n-propyl analogues. *J Med Chem.* 1990;33:1800–1805.
19. Neumeyer JL, Gao YG, Kula NS, Baldessarini RJ. Synthesis and dopamine receptor affinity of (*R*)-(-)-2-fluoro-*N*-n-propylnorapomorphine: a highly potent and selective dopamine D_2 agonist. *J Med Chem.* 1990;33:3122–3124.
20. Finnema SJ, Seneca N, Farde L, et al. A preliminary PET evaluation of the new dopamine D_2 receptor agonist [^{11}C]MNPA in cynomolgus monkey. *Nucl Med Biol.* 2005;32:353–360.
21. Seneca N, Finnema SJ, Farde L, et al. Effect of amphetamine on dopamine D_2 receptor binding in nonhuman primate brain: a comparison of the agonist radioligand [^{11}C]MNPA and antagonist [^{11}C]raclopride. *Synapse.* 2006;59:260–269.

22. Friston KJ, Frith CD, Liddle PF, Dolan RJ, Lammertsma AA, Frackowiak RS. The relationship between global and local changes in PET scans. *J Cereb Blood Flow Metab.* 1990;10:458–466.
23. Innis RB, Cunningham VJ, Delforge J, et al. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. *J Cereb Blood Flow Metab.* 2007;27:1533–1539.
24. Martres MP, Bouthenet ML, Sales N, Sokoloff P, Schwartz JC. Widespread distribution of brain dopamine receptors evidenced with [^{125}I]iodosulpride, a highly selective ligand. *Science.* 1985;228:752–755.
25. Ito H, Sudo Y, Suhara T, Okubo Y, Halldin C, Farde L. Error analysis for quantification of [^{11}C]FLB 457 binding to extrastriatal D_2 dopamine receptors in the human brain. *Neuroimage.* 2001;13:531–539.
26. Ito H, Ota M, Ikoma Y, et al. Quantitative analysis of dopamine synthesis in human brain using positron emission tomography with L-[beta-^{11}C]DOPA. *Nucl Med Commun.* 2006;27:723–731.
27. Lammertsma AA, Hume SP. Simplified reference tissue model for PET receptor studies. *Neuroimage.* 1996;4:153–158.
28. Ito H, Hietala J, Blomqvist G, Halldin C, Farde L. Comparison of the transient equilibrium and continuous infusion method for quantitative PET analysis of [^{11}C]raclopride binding. *J Cereb Blood Flow Metab.* 1998;18:941–950.
29. Hatazawa J, Fujita H, Kanno I, et al. Regional cerebral blood flow, blood volume, oxygen extraction fraction, and oxygen utilization rate in normal volunteers measured by the autoradiographic technique and the single breath inhalation method. *Ann Nucl Med.* 1995;9:15–21.
30. Renkin EM. Transport of potassium-42 from blood to tissue in isolated mammalian skeletal muscles. *Am J Physiol.* 1959;197:1205–1210.
31. Crone C. The permeability of capillaries in various organs as determined by use of the 'indicator diffusion' method. *Acta Physiol Scand.* 1963;58:292–305.
32. Willeit M, Ginovart N, Kapur S, et al. High-affinity states of human brain dopamine $D_{2/3}$ receptors imaged by the agonist [^{11}C]-(+)-PHNO. *Biol Psychiatry.* 2006;59:389–394.
33. Ito H, Takahashi H, Arakawa R, Takano H, Suhara T. Normal database of dopaminergic neurotransmission system in human brain measured by positron emission tomography. *Neuroimage.* 2008;39:555–565.
34. Farde L, Hall H, Pauli S, Halldin C. Variability in D_2-dopamine receptor density and affinity: a PET study with [^{11}C]raclopride in man. *Synapse.* 1995;20:200–208.
35. Finnema SJ, Seneca N, Farde L, et al. Scatchard analysis of the D_2 receptor agonist [^{11}C]MNPA in the monkey brain using PET [abstract]. *Eur J Nucl Med Mol Imaging.* 2005;32(S82):293.
36. Ginovart N, Galineau L, Willeit M, et al. Binding characteristics and sensitivity to endogenous dopamine of [^{11}C]-(+)-PHNO, a new agonist radiotracer for imaging the high-affinity state of D_2 receptors in vivo using positron emission tomography. *J Neurochem.* 2006;97:1089–1103.

Journal of Psychiatric Research 43 (2009) 1219–1223

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Increase in thalamic binding of [^{11}C]PE2I in patients with schizophrenia: A positron emission tomography study of dopamine transporter

Ryosuke Arakawa [a,b], Tetsuya Ichimiya [a,b], Hiroshi Ito [a], Akihiro Takano [a], Masaki Okumura [a,b], Hidehiko Takahashi [a], Harumasa Takano [a], Fumihiko Yasuno [a], Motoichiro Kato [c], Yoshiro Okubo [b], Tetsuya Suhara [a,*]

[a] Molecular Neuroimaging Group, Molecular Imaging Center, National Institute of Radiological Sciences, 4-9-1, Anagawa, Inage-ku, Chiba 263-8555, Japan
[b] Department of Neuropsychiatry, Nippon Medical School, Tokyo, Japan
[c] Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan

ARTICLE INFO

Article history:
Received 15 January 2009
Received in revised form 5 March 2009
Accepted 21 April 2009

Keywords:
Dopamine transporter
Schizophrenia
Thalamus
Positron emission tomography
[^{11}C]PE2I
PANSS

ABSTRACT

Previous *in vivo* imaging studies reported no difference in dopamine transporter (DAT) bindings in the striatum between control subjects and patients with schizophrenia. However, as the signals of radioligands with moderate affinity were insufficient for allowing the evaluation of small amounts of DAT, DAT binding in extrastriatal regions has not been determined. Positron emission tomography scanning using [^{11}C]PE2I was performed on eight patients with schizophrenia and twelve normal control subjects. Binding potential (BP_{ND}) for DAT in the caudate, putamen, thalamus and substantia nigra was calculated, using the cerebellum as reference region. In patients with schizophrenia, clinical symptoms were evaluated by Positive and Negative Syndrome Scale (PANSS). BP_{ND} in the thalamus of patients with schizophrenia was significantly higher than in control subjects ($P = 0.044$). In patients with schizophrenia, there were significantly positive correlations between BP_{ND} in the thalamus and total ($r = 0.75$), positive ($r = 0.78$) and negative PANSS scores ($r = 0.82$). Altered DAT in the thalamus might be related to the pathophysiology and clinical symptoms of schizophrenia.

1. Introduction

One of the most accepted hypotheses concerning the pathophysiology of schizophrenia are the hyperactivity of dopaminergic neurotransmission. This 'dopamine hypothesis' is supported by the facts that antipsychotic effects are mainly related to dopamine D_2 receptor antagonism and that dopamine stimulating agents can cause psychotic symptoms such as hallucination or delusion. Dopamine transporter (DAT) plays a role in the reuptake of dopamine into pre-synaptic nerves and regulates dopaminergic transmission in the synaptic cleft. DAT inhibitors such as cocaine increase dopamine concentration in the synaptic cleft (Schlaepfer et al., 1997) and worsen the clinical course of schizophrenia, e.g., exacerbating positive and negative symptoms, increasing the risk of relapse, or hospitalization (Green, 2005).

Previous *in vivo* imaging studies using positron emission tomography (PET) or single photon emission computed tomography (SPECT) reported no difference in DAT bindings between control subjects and patients with schizophrenia (Hsiao et al., 2003; Laakso et al., 2000; Laruelle et al., 2000; Lavalaye et al., 2001; Schmitt et al., 2005, 2006, 2008; Yang et al., 2004) except for one study reporting lower binding in patients with schizophrenia as compared with controls (Mateos et al., 2007). However, those studies evaluated DAT binding only in the striatum, as DAT density in extrastriatal regions is very low (in a postmortem human study, [^{125}I]PE2I binding in the thalamus was reported to be 15% of that in the striatum and negligible in the cortex) (Hall et al., 1999). The recent development of [^{11}C]PE2I, which has high affinity ($K_i = 17$ nM) and selectivity (more than 30-fold for other monoamine transporters) for DAT, allows the evaluation of extrastiatal DAT bindings (Halldin et al., 2003; Hirvonen et al., 2008; Jucaite et al., 2006). In this study, we evaluated DAT binding in the striatal and extrastriatal regions of patients with schizophrenia using [^{11}C]PE2I.

2. Materials and methods

2.1. Subjects

Eight patients (age range 25–52 yr, mean ± SD: 36.5 ± 9.5 yr) diagnosed with schizophrenia or schizophreniform disorder according to DSM-IV criteria participated in this study. Four patients with schizophreniform disorder met the criteria for schizophrenia at six month follow-up. Exclusion criteria were current

* Corresponding author. Tel.: +81 43 206 3251; fax: +81 43 253 0396.
E-mail address: suhara@nirs.go.jp (T. Suhara).

0022-3956/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jpsychires.2009.04.009

Table 1
Demographic and clinical characteristics.

	Controls	Patients
N	12	8
Age (years)	33.2 ± 12.0	36.5 ± 9.5
Gender (M/F)	10/2	6/2
Naïve/free		6/2
Duration of illness (months)		32.1 ± 42.8
PANSS (total)		77.8 ± 18.8
Positive		17.8 ± 4.8
Negative		18.9 ± 6.5
General		41.1 ± 10.8

Values are mean ± SD.

or past substance abuse, organic brain disease, or epilepsy. Demographic and clinical data are shown in Table 1. Six of the patients were antipsychotic naïve and two had been antipsychotic-free for at least six months before the PET scan. Three patients had taken benzodiazepines the night before the PET scan.

Psychopathological symptoms were assessed by three experienced psychiatrists on the same day as the PET scans using the Positive and Negative Syndrome Scale (PANSS), and consensus ratings were used. PANSS scores used were total score and subscores for positive symptom, negative symptom and general symptom.

Twelve normal control subjects (age range 23–56 yr, mean ± SD: 33.2 ± 12.0 yr) also participated. None of them had a history of psychiatric or neurological disorders, brain injury, chronic somatic illness, or substance abuse. None had taken any drugs within two weeks before the PET scan.

After complete description of this study, written informed consent was obtained from all subjects. The study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Chiba, Japan. Data were collected from 4/2003 to 8/2006.

2.2. PET procedure

A PET scanner system, ECAT EXACT HR+(CTI-Siemens, Knoxville, TN, USA), was used for all measurements. A head fixation device was used to minimize head movement. A transmission scan for attenuation correction was performed using a ^{68}Ge–^{68}Ga source before each scan. A dynamic PET scan was performed for 90 min (20 s × 9, 1 min × 5, 2 min × 4, 4 min × 11, 5 min × 6) after intravenous bolus injection of 214.7 ± 13.7 MBq (mean ± SD) of [^{11}C]PE2I. The specific radioactivity of [^{11}C]PE2I was 344.5 ± 355.3 MBq/nmol. Injected dose and specific radioactivity between the control and patient groups were not significantly different (two-tailed *t*-test; $P = 0.15$ and $P = 0.16$, respectively). Since two previous quantitative studies of [^{11}C]PE2I had reported good reliability with scan times of 63 and 69 min, the scan time of 90 min was considered sufficient for estimation of DAT bindings especially in extrastriatal regions (Hirvonen et al., 2008; Jucaite et al., 2006). Magnetic resonance (MR) images of the brain were acquired with a 1.5 Tesla MR imaging system, Gyroscan NT (Philips Medical Systems, Best, Netherlands). T1-weighted images were obtained at 1 mm slices. All subjects were free of organic brain lesions.

2.3. Data analysis

All MR images were coregistered to the PET images using the statistical parametric mapping (SPM2) system. MR images were transformed into the standard brain size and shape by SPM2 (anatomic standardization). All PET images were also transformed into the standard brain size and shape using the same parameters as the MR image standardization. Thus, brain images of all subjects had the same anatomic format (Ito et al., 2008). Motion corrections were not made.

Regions of interest (ROIs) were drawn on all anatomically standardized PET images with reference to the T1-weighted MR images. ROIs were defined for the cerebellar cortex, caudate head, putamen, substantia nigra and thalamus (Fig. 1).

Binding potential (BP_{ND}) was calculated by the simplified reference tissue model (SRTM) method. The cerebellum was used as reference region because of its negligible density of DAT (Hall et al., 1999). In this study, the software package PMOD (PMOD Technologies, Zurich, Switzerland) was used to calculate BP_{ND}.

2.4. Statistics

Statistical analysis concerning the difference of BP_{ND} for each ROI between patients and controls was performed by two-tailed *t*-test. Correlations between BP_{ND} of patients with schizophrenia and age, duration of illness, and PANSS scores were evaluated using Pearson's correlation coefficient. In all analyses, $P < 0.05$ was considered significant.

3. Results

The BP_{ND} values of control subjects and patients with schizophrenia are shown in Table 2. The BP_{ND} value in the thalamus was significant higher in patients with schizophrenia than in con-

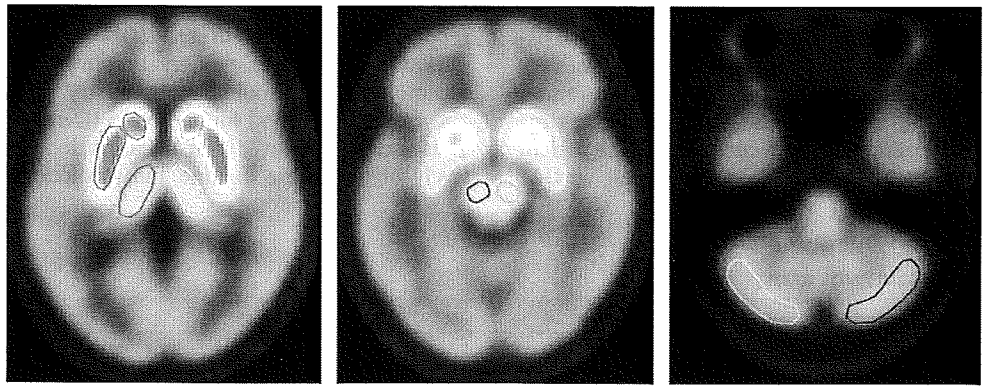

Fig. 1. Summated images of [^{11}C]PE2I with regions of interest. Average normalized images of twelve control subjects are shown at the level of caudate, putamen and thalamus (A), substantia nigra (B) and cerebellum (C).

Table 2
BP_{ND} in all regions.

	BP_{ND}[a]				*t*-test	
Region	Controls	Patients	% Change[b]	Effect size	*t*	*P*
Caudate	7.54 ± 1.22	8.21 ± 1.38	8.9 ± 18.4 (−6.5–24.2)%	0.55	1.14	0.27
Putamen	7.54 ± 1.25	8.23 ± 0.71	9.2 ± 9.4 (1.3–17.0)%	0.55	1.41	0.18
Thalamus	0.28 ± 0.08	0.36 ± 0.07	27.9 ± 25.8 (6.3–49.5)%	1.0	2.16	0.044*
Substantia nigra	1.09 ± 0.16	1.13 ± 0.12	4.1 ± 11.3 (−5.3–13.6)%	0.25	0.66	0.52

[a] Values are mean ± SD.
[b] Values are mean ± SD and 95% confidence interval.
* $P < 0.05$.

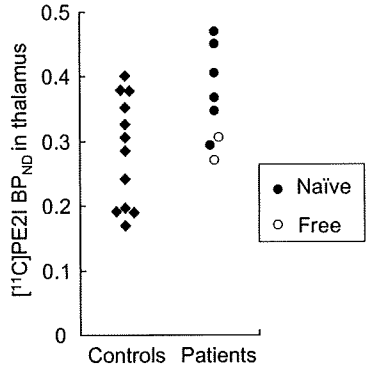

Fig. 2. BP_{ND} in the thalamus of normal controls and patients with schizophrenia. BP_{ND} of patients with schizophrenia was significantly higher than that of the control group (df = 18, $t = 2.16$, $P = 0.044$).

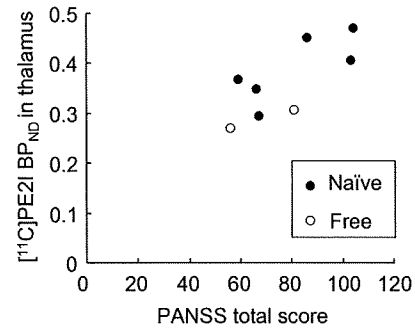

Fig. 3. Relationship between BP_{ND} in the thalamus of patients with schizophrenia and total PANSS score. There were significantly positive correlations between BP_{ND} and total PANSS score ($r = 0.75$, $P = 0.032$).

trols (df = 18, $t = 2.16$, $P = 0.044$) (Table 2, Fig. 2). There were no significant differences in BP_{ND} between the two groups in the caudate, putamen or substantia nigra. In patients with schizophrenia, there were significant positive correlations between BP_{ND} in the thalamus and total PANSS score ($r = 0.75$, $P = 0.032$), positive ($r = 0.78$, $P = 0.023$) and negative PANSS scores ($r = 0.82$, $P = 0.014$), but no correlation was observed with the general PANSS score (Table 3, Fig. 3). There was no significant correlation between BP_{ND} in other regions and clinical symptoms. There was also no significant correlation between BP_{ND} in each region and age or duration of illness.

4. Discussion

The *in vivo* evaluation of thalamic DAT had not been previously performed in detail due to its very low density as compared to that in the striatum (Hall et al., 1999). [^{11}C]PE2I allows the estimation of specific binding in low density regions because of its high affinity and selectivity for DAT (Halldin et al., 2003; Hirvonen et al., 2008; Jucaite et al., 2006). In this study, BP_{ND} in the thalamus of patients with schizophrenia was significantly higher than that of control subjects and was positively correlated with clinical symptoms. There was no significant difference in the area under the time activity curves of the cerebellum between controls and the patient group (two-tailed *t*-test; $P = 0.37$), suggesting that the higher DAT bindings were not due to cerebellar difference. An effect of endogenous dopamine on [^{11}C]PE2I binding has not been reported. However, as [^{11}C]PE2I is a high-affinity radioligand ($K_i = 17$ nM), it is reasonable to expect such an effect based on the result from a high-affinity ralioligand for serotonin transporter, [^{11}C]DASB ($K_i = 1.1$ nM) (Wilson et al., 2000). [^{11}C]DASB binding did not change by manipulation of endogenous serotonin in human brain (Praschak-Rieder et al., 2005; Talbot et al., 2005). Although these results may not apply directly to [^{11}C]PE2I binding, high [^{11}C]PE2I binding can nevertheless be interpreted as high DAT density.

The thalamus has been considered as the key brain structure of processing or integrating sensory information related to emotional or cognitive functions (Clinton and Meador-Woodruff, 2004). Several studies have reported morphological abnormalities of the thalamus in patients with schizophrenia using MR imaging or postmortem studies (Clinton and Meador-Woodruff, 2004). Regarding dopaminergic transmission, increased dopamine concentrations in the thalamus of patients with schizophrenia were reported in a postmortem study (Oke and Adams, 1987). The distribution of dopaminergic innervation in the thalamus was reported recently using immunohistochemistry in monkey (Melchitzky and Lewis, 2001) and human brain (Garcia-Cabezas et al., 2007). These studies reported that thalamic dopamine or DAT was relatively higher in the midline and mediodorsal nuclei. In patients

Table 3
Correlation between regional BP_{ND} and PANSS scores.

	Total		Positive		Negative		General	
Region	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Caudate	−0.04	0.93	0.03	0.95	0.10	0.81	−0.14	0.74
Putamen	−0.44	0.28	−0.42	0.31	−0.03	0.93	−0.55	0.15
Thalamus	0.75	0.032*	0.78	0.023*	0.82	0.014*	0.47	0.24
Substantia nigra	0.04	0.93	0.26	0.53	0.03	0.94	−0.07	0.86

* $P < 0.05$.

with schizophrenia, lower dopamine D_2 receptor binding was observed in the thalamus using PET with [^{11}C]FLB457 (Buchsbaum et al., 2006; Talvik et al., 2003; Yasuno et al., 2004) and [^{11}C]raclopride (Talvik et al., 2006). Significant differences in calcyon and spinophilin, dopamine receptor-associated intracellular proteins, and no difference in vesicular monoamine transporter (VMAT) binding of the thalamus were reported in a postmortem study of patients with schizophrenia and controls (Clinton et al., 2005). Assuming that low dopamine D_2 receptor binding is related to the disruption of the feedback system of dopamine release mediated by GABA interneuron (Takahashi et al., 2006), a high turnover of dopamine at the synapse would exist as a hyper-dopaminergic state. Although the function of DAT in the thalamus has remained unclear, high DAT bindings may suggest a hyper-dopaminergic state of pre-synaptic dopamine function in patients with schizophrenia.

Most of the previous PET and SPECT studies reported that DAT binding in the striatum did not differ between subjects and patients with schizophrenia (Hsiao et al., 2003; Laakso et al., 2000; Laruelle et al., 2000; Lavalaye et al., 2001; Schmitt et al., 2005, 2006, 2008; Yang et al., 2004), and our present results were in line with these reports. DAT binding in the substantia nigra also showed no difference between control subjects and patients with schizophrenia. However, BP_{ND} in the striatum using SRTM can be underestimated as compared to the values by kinetic model analyses with arterial blood sampling (Hirvonen et al., 2008; Jucaite et al., 2006). This might affect the results in the striatum.

In this study, the number of subjects was small, and in the statistical analysis we did not perform multiple comparisons regarding group differences of BP_{ND} between patients and controls to avoid type II error. Moreover, two of the eight patients were in a drug-free state, not drug-naïve state. Nonetheless, even when the two drug-free patients were excluded, the group difference of BP_{ND} in the thalamus was still observed (two-tailed t-test; $P = 0.018$). Further study with larger numbers of subjects in a drug-naïve state will be needed.

In conclusion, [^{11}C]PE2I binding in the thalamus of patients with schizophrenia was significantly higher than in control subjects and was correlated with clinical symptoms. Altered DAT in the thalamus might be related to the pathophysiology and clinical symptoms of schizophrenia.

Conflict of interest

All authors have no conflicts of interest.

Contributors

R. Arakawa, T. Ichimiya, A. Takano, F. Yasuno, and T. Suhara designed the study and wrote the protocol. R. Arakawa, T. Ichimiya, A. Takano, M. Okumura, H. Takahashi, H. Takano, F. Yasuno, M. Kato, and Y. Okubo recruited the patients and made psychiatric evaluations. R. Arakawa, H. Ito, M. Okumura, H. Takahashi, and H. Takano participated in the data analysis. R. Arakawa wrote the first draft of the manuscript. R. Arakawa, H. Ito, H. Takahashi, H. Takano, M. Kato, Y. Okubo, and T. Suhara had discussions and corrected the manuscript. All authors contributed to and have approved the final manuscript.

Role of funding source

This study was supported by a consignment expense for the Molecular Imaging Program on "Research Base for PET Diagnosis" from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japanese Government. The sponsors of the study had no role in the study design, collection, analysis, and interpretation of data, in the writing of the report, or in the decision to submit the paper for publication.

Acknowledgements

We thank Mr. Katsuyuki Tanimoto, Mr. Takahiro Shiraishi, Mr. Akira Ando and Mr. Toshio Miyamoto for their assistance in performing the PET experiments, and Ms. Yoshiko Fukushima for her help as clinical research coordinator at the National Institute of Radiological Sciences.

References

Buchsbaum MS, Christian BT, Lehrer DS, Narayanan TK, Shi B, Mantil J, et al. D2/D3 dopamine receptor binding with [F-18]fallypride in thalamus and cortex of patients with schizophrenia. Schizophrenia Research 2006;85:232–44.

Clinton SM, Meador-Woodruff JH. Thalamic dysfunction in schizophrenia: neurochemical, neuropathological, and in vivo imaging abnormalities. Schizophrenia Research 2004;69:237–53.

Clinton SM, Ibrahim HM, Frey KA, Davis KL, Haroutunian V, Meador-Woodruff JH. Dopaminergic abnormalities in select thalamic nuclei in schizophrenia: involvement of the intracellular signal integrating proteins calcyon and spinophilin. The American Journal of Psychiatry 2005;162:1859–71.

Garcia-Cabezas MA, Rico B, Sanchez-Gonzalez MA, Cavada C. Distribution of the dopamine innervation in the macaque and human thalamus. NeuroImage 2007;34:965–84.

Green AI. Schizophrenia and comorbid substance use disorder: effects of antipsychotics. The Journal of Clinical Psychiatry 2005;66(Suppl. 6):21–6.

Hall H, Halldin C, Guilloteau D, Chalon S, Emond P, Besnard J, et al. Visualization of the dopamine transporter in the human brain postmortem with the new selective ligand [125I]PE2I. NeuroImage 1999;9:108–16.

Halldin C, Erixon-Lindroth N, Pauli S, Chou YH, Okubo Y, Karlsson P, et al. [11C]PE2I: a highly selective radioligand for PET examination of the dopamine transporter in monkey and human brain. European Journal of Nuclear Medicine and Molecular Imaging 2003;30:1220–30.

Hirvonen J, Johansson J, Teras M, Oikonen V, Lumme V, Virsu P, et al. Measurement of striatal and extrastriatal dopamine transporter binding with high-resolution PET and [11C]PE2I: quantitative modeling and test-retest reproducibility. Journal of Cerebral Blood Flow and Metabolism 2008;28:1059–69.

Hsiao MC, Lin KJ, Liu CY, Tzen KY, Yen TC. Dopamine transporter change in drug-naive schizophrenia: an imaging study with 99mTc-TRODAT-1. Schizophrenia Research 2003;65:39–46.

Ito H, Takahashi H, Arakawa R, Takano H, Suhara T. Normal database of dopaminergic neurotransmission system in human brain measured by positron emission tomography. NeuroImage 2008;39:555–65.

Jucaite A, Odano I, Olsson H, Pauli S, Halldin C, Farde L. Quantitative analyses of regional [11C]PE2I binding to the dopamine transporter in the human brain: a PET study. European Journal of Nuclear Medicine and Molecular Imaging 2006;33:657–68.

Laakso A, Vilkman H, Alakare B, Haaparanta M, Bergman J, Solin O, et al. Striatal dopamine transporter binding in neuroleptic-naive patients with schizophrenia studied with positron emission tomography. The American Journal of Psychiatry 2000;157:269–71.

Laruelle M, Abi-Dargham A, van Dyck C, Gil R, D'Souza DC, Krystal J, et al. Dopamine and serotonin transporters in patients with schizophrenia: an imaging study with [123I]beta-CIT. Biological Psychiatry 2000;47:371–9.

Lavalaye J, Linszen DH, Booij J, Dingemans PM, Reneman L, Habraken JB, et al. Dopamine transporter density in young patients with schizophrenia assessed with [123]FP-CIT SPECT. Schizophrenia Research 2001;47:59–67.

Mateos JJ, Lomena F, Parellada E, Mireia F, Fernandez-Egea E, Pavia J, et al. Lower striatal dopamine transporter binding in neuroleptic-naive schizophrenic patients is not related to antipsychotic treatment but it suggests an illness trait. Psychopharmacology 2007;191:805–11.

Melchitzky DS, Lewis DA. Dopamine transporter-immunoreactive axons in the mediodorsal thalamic nucleus of the macaque monkey. Neuroscience 2001;103:1033–42.

Oke AF, Adams RN. Elevated thalamic dopamine: possible link to sensory dysfunctions in schizophrenia. Schizophrenia Bulletin 1987;13:589–604.

Praschak-Rieder N, Wilson AA, Hussey D, Carella A, Wei C, Ginovart N, et al. Effects of tryptophan depletion on the serotonin transporter in healthy humans. Biological Psychiatry 2005;58:825–30.

Schlaepfer TE, Pearlson GD, Wong DF, Marenco S, Dannals RF. PET study of competition between intravenous cocaine and [11C]raclopride at dopamine receptors in human subjects. The American Journal of Psychiatry 1997;154:1209–13.

Schmitt GJ, Meisenzahl EM, Frodl T, La Fougere C, Hahn K, Moller HJ, et al. The striatal dopamine transporter in first-episode, drug-naive schizophrenic patients: evaluation by the new SPECT-ligand[99mTc]TRODAT-1. Journal of Psychopharmacology 2005;19:488–93.

Schmitt GJ, Frodl T, Dresel S, la Fougere C, Bottlender R, Koutsouleris N, et al. Striatal dopamine transporter availability is associated with the productive psychotic state in first episode, drug-naive schizophrenic patients. European Archives of Psychiatry and Clinical Neuroscience 2006;256:115–21.

Schmitt GJ, la Fougere C, Dresel S, Frodl T, Hahn K, Moller HJ, et al. Dual-isotope SPECT imaging of striatal dopamine: first episode, drug naive schizophrenic patients. Schizophrenia Research 2008;101:133–41.

Takahashi H, Higuchi M, Suhara T. The role of extrastriatal dopamine D2 receptors in schizophrenia. Biological Psychiatry 2006;59:919–28.

Talbot PS, Frankle WG, Hwang DR, Huang Y, Suckow RF, Slifstein M, et al. Effects of reduced endogenous 5-HT on the in vivo binding of the serotonin transporter radioligand 11C-DASB in healthy humans. Synapse 2005;55:164–75.

Talvik M, Nordstrom AL, Olsson H, Halldin C, Farde L. Decreased thalamic D2/D3 receptor binding in drug-naive patients with schizophrenia: a PET study with [11C]FLB 457. The International Journal of Neuropsychopharmacology 2003;6:361–70.

Talvik M, Nordstrom AL, Okubo Y, Olsson H, Borg J, Halldin C, et al. Dopamine D2 receptor binding in drug-naive patients with schizophrenia examined with raclopride-C11 and positron emission tomography. Psychiatry Research 2006;148:165–73.

Wilson AA, Ginovart N, Schmidt M, Meyer JH, Threlkeld PG, Houle S. Novel radiotracers for imaging the serotonin transporter by positron emission tomography: synthesis, radiosynthesis, and in vitro and ex vivo evaluation of 11C-labeled 2-(phenylthio)araalkylamines. Journal of Medicinal Chemistry 2000;43:3103–10.

Yang YK, Yu L, Yeh TL, Chiu NT, Chen PS, Lee IH. Associated alterations of striatal dopamine D2/D3 receptor and transporter binding in drug-naive patients with schizophrenia: a dual-isotope SPECT study. The American Journal of Psychiatry 2004;161:1496–8.

Yasuno F, Suhara T, Okubo Y, Sudo Y, Inoue M, Ichimiya T, et al. Low dopamine d2 receptor binding in subregions of the thalamus in schizophrenia. The American Journal of Psychiatry 2004;161:1016–22.

International Journal of Neuropsychopharmacology (2009), **12**, 667–675. Copyright © 2008 CINP
doi:10.1017/S1461145708009577

ARTICLE

CINP

No regional difference in dopamine D_2 receptor occupancy by the second-generation antipsychotic drug risperidone in humans: a positron emission tomography study

Hiroshi Ito[1], Ryosuke Arakawa[1], Hidehiko Takahashi[1], Harumasa Takano[1], Masaki Okumura[1], Tatsui Otsuka[1], Yoko Ikoma[2], Miho Shidahara[2] and Tetsuya Suhara[1]

[1] *Clinical Neuroimaging Team, Molecular Neuroimaging Group, Molecular Imaging Center, National Institute of Radiological Sciences, Chiba, Japan*

[2] *Image Analysis Team, Biophysics Group, Molecular Imaging Center, National Institute of Radiological Sciences, Chiba, Japan*

Abstract

The effects of antipsychotic drugs have generally been considered to be mediated by blockade of dopamine D_2 receptors. The concept of limbic and cortical selectivity of second-generation antipsychotics, i.e. higher dopamine D_2 receptor occupancy in the cerebral cortices than in the striatum, has been suggested to explain their clinical efficacy with lower incidence of extrapyramidal side-effects. In this study, regional distribution of dopamine D_2 receptor occupancy by risperidone was determined in order to elucidate the limbic and cortical selectivity of second-generation antipsychotics. Striatal and extrastriatal dopamine D_2 receptor binding at baseline and after oral administration of 2 mg risperidone were measured in ten healthy men by positron emission tomography (PET) using different tracers with different affinity for the receptors, [^{11}C]raclopride and [^{11}C]FLB 457, respectively. Striatal and extrastriatal occupancies of dopamine D_2 receptors were calculated for each brain region. Occupancies of dopamine D_2 receptors were about 70% and 60% in the striatum and extrastriatum, respectively. A simulation study showed that non-negligible specific binding in the reference region (cerebellum), could cause systemic underestimation of occupancy in [^{11}C]FLB 457 PET studies, indicating that occupancies in both the striatum and extrastriatum may not have differed. Among the extrastriatal regions including limbic and neocortical regions, no significant regional differences in dopamine D_2 receptor occupancy were observed. Thus, limbic and cortical selectivity was not observed by one of the second-generation antipsychotics, risperidone.

Received 24 April 2008; Reviewed 13 June 2008; Revised 2 September 2008; Accepted 10 September 2008; First published online 23 October 2008

Key words: Antipsychotics, dopamine D_2 receptor, occupancy, PET, risperidone.

Introduction

The effects of antipsychotic drugs have been widely considered to be mediated by blockade of dopamine D_2 receptors (Carlsson and Lindqvist, 1963; Creese et al., 1976; Seeman et al., 1976). This hypothesis has been supported by positron emission tomography (PET) studies to determine dopamine D_2 receptor occupancy in patients with schizophrenia treated with typical antipsychotics, so-called first-generation antipsychotics, e.g. haloperidol (Baron et al., 1989; Farde et al., 1988). Atypical antipsychotics, so-called second-generation antipsychotics, e.g. clozapine, risperidone, and olanzapine, which show lower risk of drug-induced extrapyramidal side-effects than first-generation antipsychotics (Gerlach, 1991; Meltzer et al., 1989), have been broadly used in the treatment of schizophrenia in recent years. To explain the clinical properties of second-generation antipsychotics, several hypotheses have been proposed. Blockade of neuroreceptors other than dopamine D_2 receptors, in particular 5-HT_{2A} receptors, has been suggested to reduce extrapyramidal side-effects (Balsara et al., 1979; Hicks, 1990; Korsgaard et al., 1985). Fast dissociation

Address for correspondence: H. Ito, M.D., Ph.D., Clinical Neuroimaging Team, Molecular Neuroimaging Group, Molecular Imaging Center, National Institute of Radiological Sciences, 4-9-1 Anagawa, Inage-ku, Chiba 263-8555, Japan.
Tel.: (+81) 43-206-4702 *Fax*: (+81) 43-253-0396
E-mail: hito@nirs.go.jp

from dopamine D_2 receptors has been suggested to explain the lower incidence of extrapyramidal side-effects in some second-generation antipsychotics (Kapur and Seeman, 2001). The concept of limbic and cortical selectivity of second-generation antipsychotics, i.e. higher dopamine D_2 receptor occupancy in the cerebral cortices than in the striatum, has also been suggested to explain their clinical efficacy with few extrapyramidal side-effects (Pilowsky et al., 1997).

Limbic and cortical selectivity was originally observed in dopamine D_2 receptor occupancy by clozapine in patients with schizophrenia using [^{123}I]epidepride (Pilowsky et al., 1997), [^{76}Br]FLB 457 (Xiberas et al., 2001) and [^{18}F]fallypride (Grunder et al., 2006; Kessler et al., 2006). Limbic and cortical selectivity was also reported in other second-generation antipsychotics, e.g. risperidone using [^{76}Br]FLB 457 (Xiberas et al., 2001) and [^{123}I]epidepride (Bressan et al., 2003), olanzapine using [^{76}Br]FLB 457 (Xiberas et al., 2001), and quetiapine using [^{18}F]fallypride (Kessler et al., 2006) in patients with schizophrenia. On the other hand, no differences in occupancy of dopamine D_2 receptors between the cerebral cortices and striatum were observed in patients with schizophrenia taking clozapine (Talvik et al., 2001) or 9-hydroxy-risperidone (paliperidone) (Arakawa et al., 2008). In those studies, binding to receptors in striatal and extrastriatal regions, in which densities of dopamine D_2 receptors were quite different (Hall et al., 1994), were determined by [^{11}C]raclopride and [^{11}C]FLB 457, respectively. In addition, limbic and cortical selectivity was not supported using [^{18}F]fallypride with olanzapine in patients with schizophrenia (Kessler et al., 2005) and with clozapine and risperidone in animals (Mukherjee et al., 2001). However, in most studies concerning the regional selectivity of dopamine D_2 receptor occupancy in patients with schizophrenia, baseline binding to receptors for the calculation of occupancy were binding of other healthy subjects, not the binding of the neuroleptic naive state of the same patients.

In the present study, to elucidate the regional difference in dopamine D_2 receptor occupancy by second-generation antipsychotics, regional occupancy by risperidone was determined in healthy human subjects. Striatal and extrastriatal dopamine D_2 receptor binding at baseline and after oral administration of drug were measured in the same subjects by PET. Because dopamine D_2 receptor density is quite different between the striatal and extrastriatal regions (Hall et al., 1994, 1996), striatal and extrastriatal dopamine D_2 receptor binding were measured by different tracers with different affinity for the receptors, [^{11}C]raclopride and [^{11}C]FLB 457, respectively (Farde et al., 1995; Suhara et al., 1999).

Materials and methods

Subjects

The study was approved by the Ethics and Radiation Safety Committees of the National Institute of Radiological Sciences, Chiba, Japan. Ten healthy men [20–37 yr, 26.9 ± 5.6 (mean ± S.D.)] were recruited and written informed consent was obtained. The subjects were free of somatic, neurological or psychiatric disorders on the basis of their medical history and magnetic resonance (MR) imaging of the brain. They had no history of current or previous drug abuse.

PET procedures

All PET studies were performed with a Siemens ECAT Exact HR+ system, which provides 63 sections with an axial field of view of 15.5 cm (Brix et al., 1997). The intrinsic spatial resolution was 4.3 mm in-plane and 4.2 mm full-width at half maximum (FWHM) axially. With a Hanning filter (cut-off frequency: 0.4 cycle/pixel), the reconstructed in-plane resolution was 7.5 mm FWHM. Data were acquired in three-dimensional mode. Scatter was corrected (Watson et al., 1996). A 10-min transmission scan using a ^{68}Ge–^{68}Ga line source was performed for correction of attenuation. A head fixation device with thermoplastic attachments for individual fit minimized head movement during PET measurements.

PET studies were performed under resting condition (baseline study) and oral administration of risperidone (drug challenge study) on separate days. The interval between the two studies was 7 d in six subjects, 21 d in two subjects, 28 d in one subject, and 4 months in one subject. In each study, both PET scans with [^{11}C]raclopride and [^{11}C]FLB 457 were performed sequentially. After intravenous rapid bolus injection of [^{11}C]raclopride dynamic PET scanning was performed for 60 min. One hour after the end of [^{11}C]raclopride PET measurement, dynamic PET scanning was performed for 90 min after intravenous rapid bolus injection of [^{11}C]FLB 457. The frame sequence consisted of twelve 20-s frames, sixteen 1-min frames, and ten 4-min frames for [^{11}C]raclopride, and nine 20-s frames, five 1-min frames, four 2-min frames, eleven 4-min frames, and six 5-min frames for [^{11}C]FLB 457. The radioactivity injected was 190–238 MBq and 195–263 MBq in baseline studies, and 187–233 MBq and 188–234 MBq in drug challenge studies for [^{11}C]raclopride

and [^{11}C]FLB 457, respectively. The specific radioactivity was 114–297 GBq/μmol and 149–GBq/μmol in baseline studies, and 86–241 GBq/μmol and 141–230 GBq/μmol in drug challenge studies for [^{11}C]raclopride and [^{11}C]FLB 457, respectively. The injected mass of raclopride and FLB 457 was 0.74–1.82 nmol and 0.87–1.37 nmol in baseline studies, and 0.87–2.66 nmol and 0.98–1.61 nmol in drug challenge studies, respectively.

In the drug challenge study, 2 mg risperidone was orally administered at 2 h before the start of PET scanning with [^{11}C]raclopride. To estimate the plasma concentration of risperidone and its active metabolite (9-hydroxy-risperidone), venous blood samplings were performed at the start and end of each PET scanning. The plasma concentrations of risperidone and 9-hydroxy-risperidone were determined by a validated liquid chromatography coupled to mass spectrometry/mass spectrometry (LC–MS/MS) method. Since risperidone and 9-hydroxy-risperidone have similar binding profiles to neuroreceptors (Leysen et al., 1994), the sum of their plasma concentrations was used as the plasma concentration of antipsychotic drug in the present study.

All MR imaging studies were performed with a 1.5-T MR scanner (Philips Medical Systems, Best, The Netherlands). Three-dimensional volumetric acquisition of a T_1-weighted gradient echo sequence produced a gapless series of thin transverse sections (TE 9.2 ms; TR 21 ms; flip angle 30°; field of view 256 mm; acquisition matrix 256 × 256; slice thickness 1 mm).

Regions of interest (ROIs)

The MR images were co-registered to each of summation images of all frames of dynamic PET scans for a subject with the statistical parametric mapping (SPM2) system (Friston et al., 1990). ROIs were drawn on co-registered MR images and transferred to the PET images. ROIs were defined for the cerebellar cortex, midbrain, thalamus, caudate head, putamen, parahippocampal gyrus including amygdala, anterior part of the cingulate gyrus, frontal cortex, temporal cortex, and parietal cortex. Each ROI was drawn in three adjacent sections and data were pooled to obtain the average radioactivity concentration for the whole volume of interest. To obtain regional time–activity curves, regional radioactivity was calculated for each frame, corrected for decay, and plotted vs. time.

Calculation of dopamine D_2 receptor occupancy

For both PET studies with [^{11}C]raclopride and [^{11}C]FLB 457, the binding potential (BP_{ND}) was calculated by the reference tissue model method (Lammertsma et al., 1996; Lammertsma and Hume, 1996). With this method, the time–activity curve in the brain region is described by that in the reference region with no specific binding, assuming that both regions have the same level of non-displaceable radioligand binding:

$$C_i(t) = R_1 C_r(t) + \{k_2 - R_1 k_2/(1 + BP_{ND})\} \times C_r(t) \otimes \exp\{-k_2 t/(1 + BP_{ND})\}, \quad (1)$$

where C_i is the radioactivity concentration in a brain region, $C_r(t)$ is the radioactivity concentration in the reference region, R_1 is the ratio of K_1/K_1' (K_1, influx rate constant for the brain region; K_1', influx rate constant for the reference region), k_2 is the efflux rate constant for the brain region, and $\otimes$ denotes the convolution integral. In this analysis, three parameters (BP_{ND}, R_1, and k_2) were estimated by nonlinear least-squares curve fitting. The cerebellum was used as reference region. Dopamine D_2 receptor occupancy by risperidone was calculated as follows:

$$\text{Occupancy}\,(\%) = 100 \times (BP_{ND,\,baseline} - BP_{ND,\,drug})/BP_{ND,\,baseline}, \quad (2)$$

where $BP_{ND,\,baseline}$ is BP_{ND} in the baseline study, and $BP_{ND,\,drug}$ is BP_{ND} in the drug challenge study.

The relation between the plasma concentration of antipsychotic drug and dopamine D_2 receptor occupancy can be expressed as follows (Kapur and Remington, 1996; Takano et al., 2004):

$$\text{Occupancy}\,(\%) = 100 \times C/(ED_{50} + C), \quad (3)$$

where C is the sum of plasma concentrations of risperidone and 9-hydroxy-risperidone, and ED_{50} is the plasma concentration required to induce 50% occupancy.

Anatomic standardization

The analysis using ROI does not allow evaluation of data throughout the brain. For visualization of regional differences in dopamine D_2 receptor occupancy, inter-subject averaging of occupancy images, which requires transformation of brain images of individual subjects into a standard brain shape and size in three dimensions (anatomical standardization), was performed (Fox et al., 1988). BP_{ND} images of [^{11}C]raclopride and [^{11}C]FLB 457 were calculated on a voxel-by-voxel basis by the reference tissue model (Lammertsma et al., 1996; Lammertsma and Hume, 1996) with the basis function method (Gunn et al., 1997). Images of dopamine D_2 receptor occupancy were also calculated on a voxel-by-voxel basis. All MR

images that were co-registered to the PET images were transformed into the standard brain size and shape by linear and nonlinear parameters with SPM2 (Friston et al., 1990). The brain templates used in SPM2 for the anatomical standardization were T_1 templates for MR images. All PET images were also transformed into the standard brain size and shape by the use of same parameters as MR images. Thus, brain images of all subjects had the same anatomical format. Average images for BP_{ND} and dopamine D_2 receptor occupancy were calculated on a voxel-by-voxel basis.

Simulation study

Although specific [^{11}C]FLB 457 binding in the cerebellum was not supported statistically in previous studies (Olsson et al., 1999; Suhara et al., 1999), the BP_{ND} value for the cerebellum has been reported to be small but not zero (Ito et al., 2001). It has recently been reported that a non-negligible density of dopamine D_2 receptors in the cerebellum led to the underestimation of BP_{ND} in a brain region as well as errors in dopamine D_2 receptor occupancy in [^{11}C]FLB 457 PET studies (Asselin et al., 2007). To estimate such errors in the occupancy of receptors calculated by methods using data of the reference region, i.e. cerebellum, in a [^{11}C]FLB 457 PET study, a simulation study was performed.

For the baseline study, the total distribution volume V_T in the reference region was calculated from the distribution volume for non-displaceable binding (V_{ND}) of 3 ml/ml and BP_{ND} of 0.1–0.5 in five steps as $V_T = V_{ND}(1 + BP_{ND})$ (Ito et al., 2001). V_T in the target region was also calculated with $V_{ND} = 3$ ml/ml and $BP_{ND} = 3$. V_T in the drug challenge study for both the target and reference regions was calculated with BP_{ND} that was varied with occupancy of 0–100% and equal across regions. From the total distribution volume ratio (DVR) of the target region to the reference region, the estimated dopamine D_2 receptor occupancy was calculated as follows:

$$\text{Occupancy (\%)} = \frac{100 \times \{(DVR_{baseline} - 1) - (DVR_{drug} - 1)\}}{(DVR_{baseline} - 1)}, \quad (4)$$

These estimated occupancy values were compared with the assumed values which were occupancy values varied in the target brain region without consideration of specific binding in the cerebellum.

Results

Striatal and extrastriatal BP_{ND} values and dopamine D_2 receptor occupancy are shown in Tables 1 and 2.

Table 1. Striatal binding potential (BP_{ND}) values and dopamine D_2 receptor occupancy in [^{11}C]raclopride PET studies

Region	BP_{ND}		Occupancy (%)
	Baseline	Drug challenge	
Caudate head	2.64±0.26	0.65±0.16	76±4
Putamen	3.41±0.38	0.98±0.24	71±4

Values are mean±S.D.

The ranges of dopamine D_2 receptor occupancy are 71–76% and 56–60% for the striatum and extrastriatum without the midbrain, respectively. No drug-induced extrapyramidal side-effects were observed in any of subjects. Although direct comparisons of dopamine D_2 receptor occupancy between striatal and extrastriatal regions may not be appropriate due to systematic errors in occupancy for [^{11}C]FLB 457 studies as mentioned below, dopamine D_2 receptor occupancy in the caudate head was significantly higher than that in midbrain, thalamus, anterior cingulate, and parietal cortex after correction of multiple comparisons ($p < 0.05$). Dopamine D_2 receptor occupancy in the putamen was significantly higher than that in the thalamus. No significant differences in the radioactivity injected, specific radioactivity, and injected mass were observed between baseline and drug challenge studies for both [^{11}C]raclopride and [^{11}C]FLB 457.

Average images of BP_{ND} at baseline condition and after administration of risperidone, and dopamine D_2 receptor occupancy for [^{11}C]raclopride and [^{11}C]FLB 457 are shown in Figures 1 and 2. The visualization of regional differences in dopamine D_2 receptor occupancy throughout the brain was allowed by inter-subject averaging of images. Among extrastriatal regions, no obvious regional differences in dopamine D_2 receptor occupancy were observed. In the striatum, no obvious regional differences in occupancy were also observed.

The sum of the plasma concentrations of risperidone and 9-hydroxy-risperidone during [^{11}C]raclopride and [^{11}C]FLB 457 PET studies, averaged between the start and end of each scanning, was 17.5±5.2 ng/ml and 14.5±4.2 ng/ml (mean±S.D.), respectively. The ED_{50} values were 5.1–6.4 ng/ml for the striatum and 9.0–10.9 ng/ml for the cerebral cortical regions.

Relation between the assumed and estimated dopamine D_2 receptor occupancy for [^{11}C]FLB 457 in simulation studies is shown in Figure 3. Systematic

Table 2. Extrastriatal binding potential (BP_{ND}) values and dopamine D_2 receptor occupancy in [^{11}C]FLB 457 PET studies

Region	BP_{ND}		Occupancy (%)
	Baseline	Drug challenge	
Midbrain	1.57±0.46	0.82±0.21	44±20
Thalamus	3.40±0.37	1.41±0.17	58±5
Parahippocampal gyrus	2.52±0.88	1.00±0.20	57±14
Anterior cingulate	1.27±0.12	0.51±0.09	59±9
Frontal cortex	1.11±0.23	0.46±0.09	58±11
Temporal cortex	1.95±0.39	0.76±0.18	60±8
Parietal cortex	1.32±0.42	0.57±0.17	56±9

Values are mean±S.D.

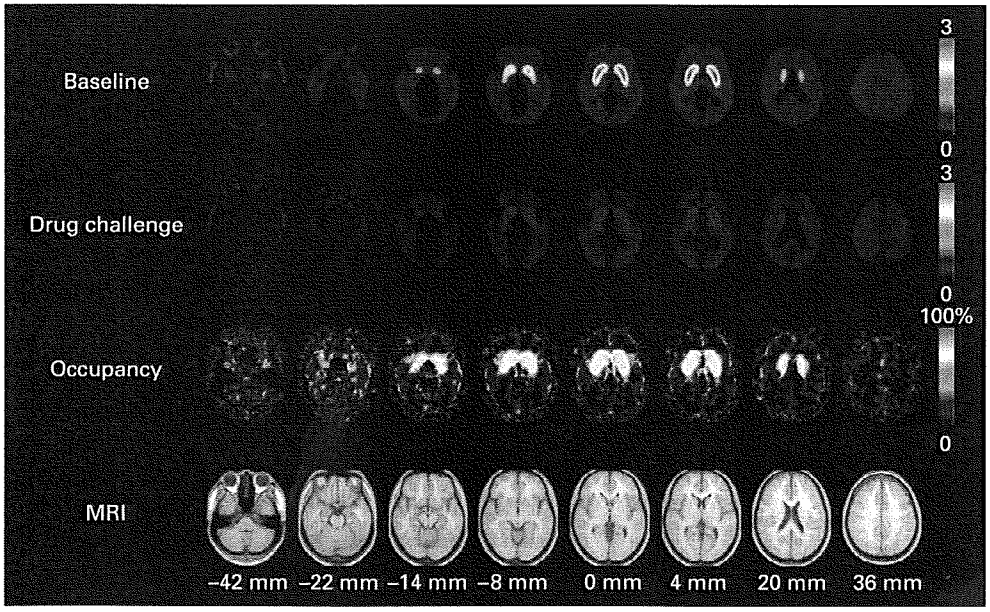

Figure 1. Average images of binding potential at baseline condition and after administration of risperidone, dopamine D_2 receptor occupancy for [^{11}C]raclopride, and T_1-weighted images. In the striatum, no obvious regional differences in dopamine D_2 receptor occupancy were observed.

underestimation in estimated occupancy was caused by specific binding in the reference region.

Discussion

The concept of limbic and cortical selectivity of second-generation antipsychotics, namely, higher dopamine D_2 receptor occupancy in the cerebral cortices than in the striatum, has been suggested (Pilowsky et al., 1997), and limbic and cortical selectivity was reported in risperidone using [^{76}Br]FLB 457 (Xiberas et al., 2001) and [^{123}I]epidepride (Bressan et al., 2003). In the present study, dopamine D_2 receptor occupancy in the striatum was higher than that in the cerebral cortices. The ED_{50} values were also lower in the striatum than in the cerebral cortices corresponding with previous reports that ED_{50} of risperidone was 6.87 ng/ml in the striatum (Nyberg et al., 1999) and 7.43 ng/ml in the cerebral cortices (Yasuno et al., 2001) measured using [^{11}C]raclopride and [^{11}C]FLB 457, respectively. A simulation study showed that non-negligible specific binding in the cerebellum could cause an underestimation of 8% in dopamine D_2 receptor occupancy measured by [^{11}C]FLB 457 PET when BP_{ND} in the

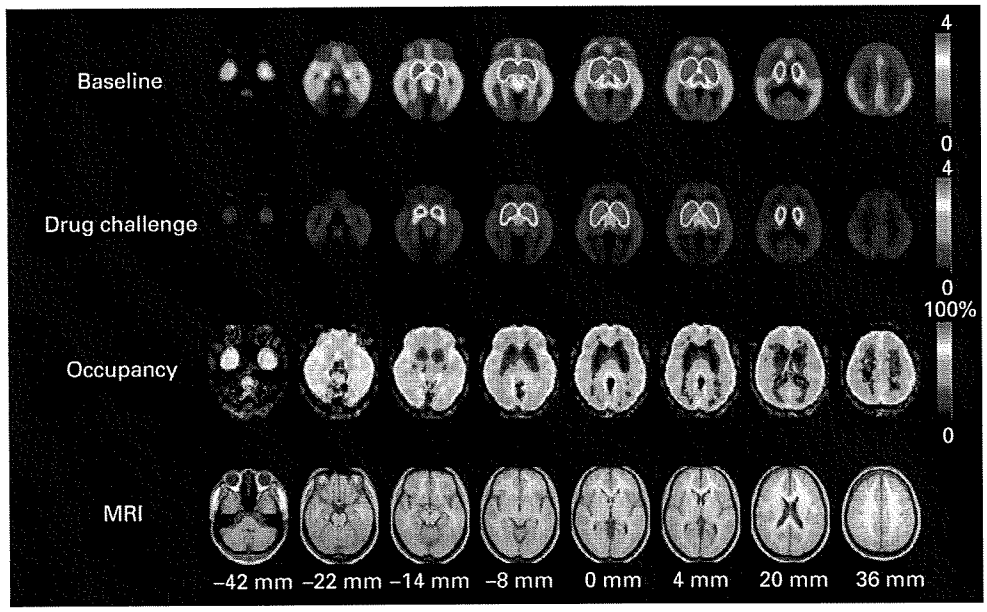

Figure 2. Average images of binding potential at baseline condition and after administration of risperidone, dopamine D_2 receptor occupancy for [^{11}C]FLB 457, and T_1-weighted images. Among extrastriatal regions, no obvious regional differences in dopamine D_2 receptor occupancy were observed.

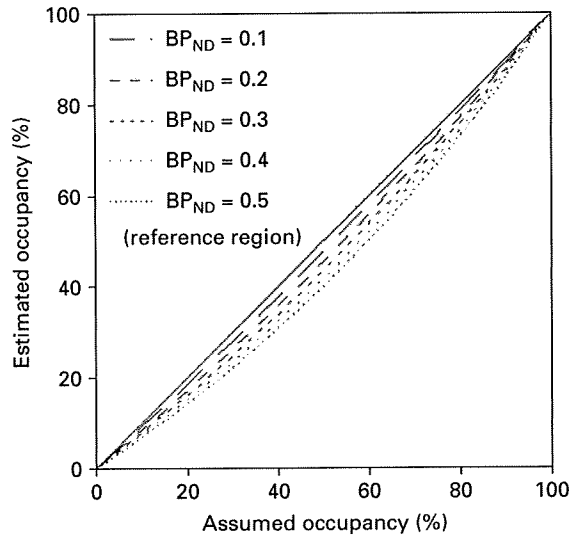

Figure 3. Relation between the assumed and estimated occupancies of dopamine D_2 receptors for [^{11}C]FLB 457 in simulation studies. Binding potential (BP_{ND}) in the reference region was varied from 0.1 to 0.5. Systematic underestimation in estimated occupancy was caused by specific binding in the reference region.

cerebellum was 0.3 (Ito et al., 2001) and assumed occupancy was 70%. This indicates that the occupancies of dopamine D_2 receptors in both the striatum and extrastriatum may not have differed. In the present study, [^{11}C]FLB 457 PET studies were begun 2 h after the start of [^{11}C]raclopride PET studies, and therefore, the sum of the plasma concentrations of risperidone and 9-hydroxy-risperidone was slightly lower during [^{11}C]FLB 457 studies (14.5 ± 4.2 ng/ml) than during [^{11}C]raclopride studies (17.5 ± 5.2 ng/ml). When ED_{50} is 6 ng/ml, 17.5 and 14.5 ng/ml of the sum of plasma concentrations of risperidone and 9-hydroxy-risperidone reveal 74% and 71% of dopamine D_2 receptor occupancy, respectively [eqn (3)]. This might be able to partially explain higher dopamine D_2 receptor occupancy in the [^{11}C]raclopride studies than in the [^{11}C]FLB 457 studies. In addition, it has been reported that the half-life of the sum of plasma concentrations of risperidone and 9-hydroxy-risperidone was about 18 h, and that high dopamine D_2 receptor occupancy was sustained (Takano et al., 2004), indicating that the effects of differences in plasma concentrations of risperidone and 9-hydroxy-risperidone between [^{11}C]raclopride and [^{11}C]FLB 457 studies on the occupancies of dopamine D_2 receptors might be very small.

Several mechanisms for the limbic and cortical selectivity in dopamine D_2 receptor occupancy by the second-generation antipsychotic risperidone have been proposed (Bressan et al., 2003). One possible mechanism was that risperidone also bound to dopamine D_3 receptors (Arnt and Skarsfeldt, 1998), which were highly expressed in limbic regions (Joyce, 2001).

However, the occupancies of dopamine D_2 receptors by risperidone in both the striatum and extrastriatum may not have differed in the present study. Because dopamine D_2 receptor density is quite different between the striatal and extrastriatal regions (Hall et al., 1994, 1996), it should be appropriate to determine striatal and extrastriatal binding by different tracers with different affinity for receptors whereas both striatal and extrastriatal binding were determined by same tracer in previous reports supporting limbic and cortical selectivity of risperidone (Bressan et al., 2003; Xiberas et al., 2001). The dissociation constant K_D, indicating affinity for receptors in the living human brain was quite different between [^{11}C]raclopride and [^{11}C]FLB 457, i.e. about 10 nM with the former (Farde et al., 1995) and 1 nM with the latter (Suhara et al., 1999). Talvik and colleagues stated that a simple ratio approach using a high-affinity radioligand such as [^{123}I]epidepride without validation of equilibrium conditions might yield an underestimation of D_2 receptor occupancy in the striatum in comparison with the D_2 receptor occupancy in the extrastriatal regions (Talvik et al., 2001). Although non-negligible specific binding in the cerebellum and differences in plasma concentrations of risperidone and 9-hydroxy-risperidone between studies cause systematic errors in occupancy, the use of two tracers with different affinities, [^{11}C]raclopride and [^{11}C]FLB 457, must be superior compared with the use of one tracer to determine the occupancy in both the striatum and extrastriatum. Erlandsson et al. (2003) reported that too short a data acquisition time in [^{11}C]FLB 457 PET studies could cause an underestimation of occupancy in extrastriatal regions. However, the accuracy of estimation of extrastriatal BP_{ND} and occupancy in [^{11}C]FLB 457 studies with a data acquisition time of over 60 min was confirmed (Ito et al., 2001; Olsson and Farde, 2001; Olsson et al., 1999; Sudo et al., 2001). The accuracy of estimation of striatal BP_{ND} using [^{11}C]raclopride was also confirmed (Ito et al., 1998; Lammertsma et al., 1996). Although direct comparisons of dopamine D_2 receptor occupancy between striatal and extrastriatal regions determined by different tracers may not be appropriate due to systematic errors in occupancy for [^{11}C]FLB 457 studies as mentioned above (Kessler and Meltzer, 2002), limbic and cortical selectivity of risperidone was not supported in the present study with healthy subjects.

Among extrastriatal regions including limbic and neocortical regions, no significant regional differences in dopamine D_2 receptor occupancy by risperidone were observed. In the striatum, no obvious regional differences in occupancy were also observed. Although the density of dopamine D_2 receptors varies in these regions (Ito et al., 2008), dopamine D_2 receptor occupancy by antipsychotics is independent of receptor density. These data indicate that the concentrations of risperidone and 9-hydroxy-risperidone in tissue may be uniform throughout the brain. If the dissociation constant of antipsychotic drug to dopamine D_2 receptors would regionally change in patients, the occupancy by antipsychotic drug would be regionally changed. However, to our knowledge, there are no reports about regional changes in dissociation constant of antipsychotic drugs in patients.

Second-generation antipsychotics have been suggested to have clinical efficacy with few extrapyramidal side-effects compared with first-generation antipsychotics (Balsara et al., 1979; Hicks, 1990; Kapur and Seeman, 2001; Korsgaard et al., 1985; Pilowsky et al., 1997). However, a recent randomized controlled trial has shown no differences in the effects on the quality of life between first- and second-generation antipsychotics (Jones et al., 2006). For antipsychotic therapy with less extrapyramidal side-effects, the determination of adequate clinical dosage of antipsychotics by measuring dopamine D_2 receptor occupancy using PET may be important whether for first- or second-generation antipsychotics (Farde et al., 1992; Takano et al., 2006).

In conclusion, striatal and extrastriatal occupancies of dopamine D_2 receptors after oral administration of a second-generation antipsychotic drug, risperidone, were measured in healthy subjects by PET with [^{11}C]raclopride and [^{11}C]FLB 457, respectively. Higher dopamine D_2 receptor occupancy in the cerebral cortices than in the striatum was not observed, and the concept of limbic and cortical selectivity of the second-generation antipsychotic drug risperidone was not supported in the present study.

Acknowledgments

This study was supported in part by a Grant-in-Aid for Molecular Imaging Program from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japanese Government and a Grant-in-Aid for Scientific Research (C) (No. 18591372) from the Japan Society for the Promotion of Science. We thank Mr Katsuyuki Tanimoto, Mr Takahiro Shiraishi, Mr Akira Ando, and Mr Toshio Miyamoto for their assistance in performing the PET experiments at the National Institute of Radiological Sciences. We also thank Ms. Yoshiko Fukushima of the National Institute of Radiological Sciences for her help as clinical research coordinator.

Statement of Interest

None.

References

Arakawa R, Ito H, Takano A, Takahashi H, Morimoto T, Sassa T, Ohta K, Kato M, Okubo Y, Suhara T (2008). Dose-finding study of paliperidone ER based on striatal and extrastriatal dopamine D_2 receptor occupancy in patients with schizophrenia. *Psychopharmacology 197*, 229–235.

Arnt J, Skarsfeldt T (1998). Do novel antipsychotics have similar pharmacological characteristics? A review of the evidence. *Neuropsychopharmacology 18*, 63–101.

Asselin MC, Montgomery AJ, Grasby PM, Hume SP (2007). Quantification of PET studies with the very high-affinity dopamine D_2/D_3 receptor ligand [^{11}C]FLB 457: re-evaluation of the validity of using a cerebellar reference region. *Journal of Cerebral Blood Flow and Metabolism 27*, 378–392.

Balsara JJ, Jadhav JH, Chandorkar AG (1979). Effect of drugs influencing central serotonergic mechanisms on haloperidol-induced catalepsy. *Psychopharmacology 62*, 67–69.

Baron JC, Martinot JL, Cambon H, Boulenger JP, Poirier MF, Caillard V, Blin J, Huret JD, Loc'h C, Maziere B (1989). Striatal dopamine receptor occupancy during and following withdrawal from neuroleptic treatment: correlative evaluation by positron emission tomography and plasma prolactin levels. *Psychopharmacology 99*, 463–472.

Bressan RA, Erlandsson K, Jones HM, Mulligan RS, Ell PJ, Pilowsky LS (2003). Optimizing limbic selective D_2/D_3 receptor occupancy by risperidone: a [^{123}I]-epidepride SPET study. *Journal of Clinical Psychopharmacology 23*, 5–14.

Brix G, Zaers J, Adam LE, Bellemann ME, Ostertag H, Trojan H, Haberkorn U, Doll J, Oberdorfer F, Lorenz WJ (1997). Performance evaluation of a whole-body PET scanner using the NEMA protocol. *Journal of Nuclear Medicine 38*, 1614–1623.

Carlsson A, Lindqvist M (1963). Effect of chlorpromazine or haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain. *Acta Pharmacologica et Toxicologica 20*, 140–144.

Creese I, Burt DR, Snyder SH (1976). Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. *Science 192*, 481–483.

Erlandsson K, Bressan RA, Mulligan RS, Ell PJ, Cunningham VJ, Pilowsky LS (2003). Analysis of D_2 dopamine receptor occupancy with quantitative SPET using the high-affinity ligand [^{123}I]epidepride: resolving conflicting findings. *NeuroImage 19*, 1205–1214.

Farde L, Hall H, Pauli S, Halldin C (1995). Variability in D_2-dopamine receptor density and affinity: a PET study with [^{11}C]raclopride in man. *Synapse 20*, 200–208.

Farde L, Nordstrom AL, Wiesel FA, Pauli S, Halldin C, Sedvall G (1992). Positron emission tomographic analysis of central D_1 and D_2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. Relation to extrapyramidal side effects. *Archives of General Psychiatry 49*, 538–544.

Farde L, Wiesel FA, Halldin C, Sedvall G (1988). Central D_2-dopamine receptor occupancy in schizophrenic patients treated with antipsychotic drugs. *Archives of General Psychiatry 45*, 71–76.

Fox PT, Mintun MA, Reiman EM, Raichle ME (1988). Enhanced detection of focal brain responses using intersubject averaging and change-distribution analysis of subtracted PET images. *Journal of Cerebral Blood Flow and Metabolism 8*, 642–653.

Friston KJ, Frith CD, Liddle PF, Dolan RJ, Lammertsma AA, Frackowiak RS (1990). The relationship between global and local changes in PET scans. *Journal of Cerebral Blood Flow and Metabolism 10*, 458–466.

Gerlach J (1991). New antipsychotics: classification, efficacy, and adverse effects. *Schizophrenia bulletin 17*, 289–309.

Grunder G, Landvogt C, Vernaleken I, Buchholz HG, Ondracek J, Siessmeier T, Hartter S, Schreckenberger M, Stoeter P, Hiemke C, et al. (2006). The striatal and extrastriatal D_2/D_3 receptor-binding profile of clozapine in patients with schizophrenia. *Neuropsychopharmacology 31*, 1027–1035.

Gunn RN, Lammertsma AA, Hume SP, Cunningham VJ (1997). Parametric imaging of ligand-receptor binding in PET using a simplified reference region model. *NeuroImage 6*, 279–287.

Hall H, Farde L, Halldin C, Hurd YL, Pauli S, Sedvall G (1996). Autoradiographic localization of extrastriatal D_2-dopamine receptors in the human brain using [^{125}I]epidepride. *Synapse 23*, 115–123.

Hall H, Sedvall G, Magnusson O, Kopp J, Halldin C, Farde L (1994). Distribution of D_1- and D_2-dopamine receptors, and dopamine and its metabolites in the human brain. *Neuropsychopharmacology 11*, 245–256.

Hicks PB (1990). The effect of serotonergic agents on haloperidol-induced catalepsy. *Life Sciences 47*, 1609–1615.

Ito H, Hietala J, Blomqvist G, Halldin C, Farde L (1998). Comparison of the transient equilibrium and continuous infusion method for quantitative PET analysis of [^{11}C]raclopride binding. *Journal of Cerebral Blood Flow and Metabolism 18*, 941–950.

Ito H, Sudo Y, Suhara T, Okubo Y, Halldin C, Farde L (2001). Error analysis for quantification of [^{11}C]FLB 457 binding to extrastriatal D_2 dopamine receptors in the human brain. *NeuroImage 13*, 531–539.

Ito H, Takahashi H, Arakawa R, Takano H, Suhara T (2008). Normal database of dopaminergic neurotransmission system in human brain measured by positron emission tomography. *NeuroImage 39*, 555–565.

Jones PB, Barnes TR, Davies L, Dunn G, Lloyd H, Hayhurst KP, Murray RM, Markwick A, Lewis SW (2006). Randomized controlled trial of the effect on Quality of Life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic

Drugs in Schizophrenia Study (CUtLASS 1). *Archives of General Psychiatry 63*, 1079–1087.

Joyce JN (2001). Dopamine D_3 receptor as a therapeutic target for antipsychotic and antiparkinsonian drugs. *Pharmacology & Therapeutics 90*, 231–259.

Kapur S, Remington G (1996). Serotonin-dopamine interaction and its relevance to schizophrenia. *American Journal of Psychiatry 153*, 466–476.

Kapur S, Seeman P (2001). Does fast dissociation from the dopamine D_2 receptor explain the action of atypical antipsychotics? A new hypothesis. *American Journal of Psychiatry 158*, 360–369.

Kessler RM, Ansari MS, Riccardi P, Li R, Jayathilake K, Dawant B, Meltzer HY (2005). Occupancy of striatal and extrastriatal dopamine D_2/D_3 receptors by olanzapine and haloperidol. *Neuropsychopharmacology 30*, 2283–2289.

Kessler RM, Ansari MS, Riccardi P, Li R, Jayathilake K, Dawant B, Meltzer HY (2006). Occupancy of striatal and extrastriatal dopamine D_2 receptors by clozapine and quetiapine. *Neuropsychopharmacology 31*, 1991–2001.

Kessler RM, Meltzer HY (2002). Regional selectivity in clozapine treatment? *American Journal of Psychiatry 159*, 1064–1065.

Korsgaard S, Gerlach J, Christensson E (1985). Behavioral aspects of serotonin-dopamine interaction in the monkey. *European Journal of Pharmacology 118*, 245–252.

Lammertsma AA, Bench CJ, Hume SP, Osman S, Gunn K, Brooks DJ, Frackowiak RS (1996). Comparison of methods for analysis of clinical [^{11}C]raclopride studies. *Journal of Cerebral Blood Flow and Metabolism 16*, 42–52.

Lammertsma AA, Hume SP (1996). Simplified reference tissue model for PET receptor studies. *NeuroImage 4*, 153–158.

Leysen JE, Janssen PM, Megens AA, Schotte A (1994). Risperidone: a novel antipsychotic with balanced serotonin-dopamine antagonism, receptor occupancy profile, and pharmacologic activity. *Journal of Clinical Psychiatry 55* (Suppl.), 5–12.

Meltzer HY, Matsubara S, Lee JC (1989). The ratios of serotonin2 and dopamine2 affinities differentiate atypical and typical antipsychotic drugs. *Psychopharmacology Bulletin 25*, 390–392.

Mukherjee J, Christian BT, Narayanan TK, Shi B, Mantil J (2001). Evaluation of dopamine D_2 receptor occupancy by clozapine, risperidone, and haloperidol in vivo in the rodent and nonhuman primate brain using ^{18}F-fallypride. *Neuropsychopharmacology 25*, 476–488.

Nyberg S, Eriksson B, Oxenstierna G, Halldin C, Farde L (1999). Suggested minimal effective dose of risperidone based on PET-measured D_2 and 5-HT_{2A} receptor occupancy in schizophrenic patients. *American Journal of Psychiatry 156*, 869–875.

Olsson H, Farde L (2001). Potentials and pitfalls using high affinity radioligands in PET and SPET determinations on regional drug induced D_2 receptor occupancy-a simulation study based on experimental data. *NeuroImage 14*, 936–945.

Olsson H, Halldin C, Swahn CG, Farde L (1999). Quantification of [^{11}C]FLB 457 binding to extrastriatal dopamine receptors in the human brain. *Journal of Cerebral Blood Flow and Metabolism 19*, 1164–1173.

Pilowsky LS, Mulligan RS, Acton PD, Ell PJ, Costa DC, Kerwin RW (1997). Limbic selectivity of clozapine. *Lancet 350*, 490–491.

Seeman P, Lee T, Chau-Wong M, Wong K (1976). Antipsychotic drug doses and neuroleptic/dopamine receptors. *Nature 261*, 717–719.

Sudo Y, Suhara T, Inoue M, Ito H, Suzuki K, Saijo T, Halldin C, Farde L (2001). Reproducibility of [^{11}C]FLB 457 binding in extrastriatal regions. *Nuclear Medicine Communications 22*, 1215–1221.

Suhara T, Sudo Y, Okauchi T, Maeda J, Kawabe K, Suzuki K, Okubo Y, Nakashima Y, Ito H, Tanada S, Halldin C, Farde L (1999). Extrastriatal dopamine D_2 receptor density and affinity in the human brain measured by 3D PET. *International Journal of Neuropsychopharmacology 2*, 73–82.

Takano A, Suhara T, Ikoma Y, Yasuno F, Maeda J, Ichimiya T, Sudo Y, Inoue M, Okubo Y (2004). Estimation of the time-course of dopamine D_2 receptor occupancy in living human brain from plasma pharmacokinetics of antipsychotics. *International Journal of Neuropsychopharmacology 7*, 19–26.

Takano A, Suhara T, Yasuno F, Suzuki K, Takahashi H, Morimoto T, Lee YJ, Kusuhara H, Sugiyama Y, Okubo Y (2006). The antipsychotic sultopride is overdosed – a PET study of drug-induced receptor occupancy in comparison with sulpiride. *International Journal of Neuropsychopharmacology 9*, 539–545.

Talvik M, Nordstrom AL, Nyberg S, Olsson H, Halldin C, Farde L (2001). No support for regional selectivity in clozapine-treated patients: a PET study with [^{11}C]raclopride and [^{11}C]FLB 457. *American Journal of Psychiatry 158*, 926–930.

Watson CC, Newport D, Casey ME (1996). A single scatter simulation technique for scatter correction in 3D PET. In: Grangeat P, Amans JL (Eds), *Three-dimensional Image Reconstruction in Radiology and Nuclear Medicine* (pp. 255–268). Dordrecht, The Netherlands: Kluwer Academic Publishers.

Xiberas X, Martinot JL, Mallet L, Artiges E, Loc HC, Maziere B, Paillere-Martinot ML (2001). Extrastriatal and striatal D_2 dopamine receptor blockade with haloperidol or new antipsychotic drugs in patients with schizophrenia. *British Journal of Psychiatry 179*, 503–508.

Yasuno F, Suhara T, Okubo Y, Sudo Y, Inoue M, Ichimiya T, Tanada S (2001). Dose relationship of limbic-cortical D_2 dopamine receptor occupancy with risperidone. *Psychopharmacology 154*, 112–114.

Eur Arch Psychiatry Clin Neurosci (2010) 260:345–350
DOI 10.1007/s00406-009-0082-5

ORIGINAL PAPER

Extrastriatal dopamine D_2 receptor occupancy in olanzapine-treated patients with schizophrenia

Ryosuke Arakawa · Hiroshi Ito · Masaki Okumura · Akihiro Takano · Hidehiko Takahashi · Harumasa Takano · Yoshiro Okubo · Tetsuya Suhara

Received: 18 September 2008 / Accepted: 9 October 2009 / Published online: 23 October 2009

Abstract Olanzapine is described as a multi-acting receptor-targeted antipsychotic agent. Although regional differences of dopamine D_2 receptor occupancy, i.e., limbic selectivity, were reported for olanzapine, contradictory results were also reported. We measured dopamine D_2 receptor occupancy of olanzapine in extrastriatal regions in patients with schizophrenia using positron-emission tomography with [^{11}C]FLB457 and the plasma concentrations of olanzapine. Ten patients with schizophrenia taking 5–20 mg/day of olanzapine participated. Dopamine D_2 receptor occupancy in the temporal cortex ranged from 61.1 to 85.8%, and plasma concentration was from 12.7 to 115.4 ng/ml. The ED_{50} value was 3.4 mg/day for dose and 10.5 ng/ml for plasma concentration. The ED_{50} values obtained in this study were quite similar to those previously reported in the striatum. In conclusion, although the subjects and methods were different from previous striatal occupancy studies, these results suggest that limbic occupancy by olanzapine may not be so different from that in the striatum.

Keywords Dopamine D_2 receptor occupancy · Extrastriatum · Olanzapine · Positron-emission tomography · Schizophrenia

R. Arakawa · H. Ito · M. Okumura · A. Takano · H. Takahashi · H. Takano · T. Suhara (✉)
Molecular Neuroimaging Group, Molecular Imaging Center, National Institute of Radiological Sciences, 4-9-1, Anagawa, Inage-ku, Chiba 263-8555, Japan
e-mail: suhara@nirs.go.jp

R. Arakawa · M. Okumura · Y. Okubo
Department of Neuropsychiatry, Nippon Medical School, 1-1-5, Sendagi, Bunkyo-ku, Tokyo, Japan

Introduction

Olanzapine is a second-generation antipsychotic drug that is widely used in the treatment of schizophrenia [7]. Most second-generation antipsychotic drugs, such as clozapine, risperidone, olanzapine and quetiapine, have high affinity for several kinds of neuroreceptors in addition to dopamine D_2 receptors [6]. Olanzapine has high affinity for dopamine D_2 receptors (Ki = 11 nM) as well as for other receptors, i.e., serotonin 5-HT_{2A} (4 nM), 5-HT_{2C} (11 nM), muscarine m_1–m_5 (1.9–25 nM), adrenaline α_1 (19 nM) and histamine H_1 (7 nM) receptors [6]. The pharmacological profile is similar to that of clozapine, described as a multi-acting receptor-targeted antipsychotic agent. The difference in occupancy of dopamine D_2 receptors with clozapine between striatal and extrastriatal regions has been reported as 'limbic selectivity' [23]. This feature was considered one of the reasons for the low risk of extrapyramidal symptoms and a possible effect for negative symptoms [23].

Some animal studies reported greater effects on dopamine D_2 receptors by olanzapine in the extrastriatum than in the striatum [24, 27]. In human studies, higher occupancy in the temporal cortex than in the striatum was also reported for olanzapine [3, 34]. On the other hand, in another human study using olanzapine, no difference in dopamine D_2 receptor occupancies between the striatum and extrastriatum was also reported [16]. In those studies, occupancies in the striatum and extrastriatum were measured from the same data, despite their quite different receptor densities [15].

In the present study, dopamine D_2 receptor occupancy in extrastriatal regions by olanzapine was measured in patients with schizophrenia using positron-emission tomography (PET) with [^{11}C]FLB 457, an optimized