radiotracer for measuring extrastriatal dopamine D_2 receptors [10]. The receptor occupancy in the extrastriatum was compared with that in the striatum by olanzapine previously measured using [^{11}C]raclopride [13].

Methods

Subjects and study protocol

Ten patients, aged 23–47 years (36.2 ± 9.0, mean ± SD), diagnosed with schizophrenia according to DSM-IV criteria, participated in this study (Table 1). After complete explanation of the study, written informed consent was obtained from all patients. Exclusion criteria were current or past substance abuse, organic brain disease or epilepsy. Subjects with severe liver or renal dysfunction, or having undergone electroconvulsive therapy within 90 days prior to this study were also excluded. The patients had been taking fixed dosages of olanzapine for more than 2 weeks before this study. Doses of olanzapine were 5 mg/day in two patients, 7.5 mg/day in two patients, 10 mg/day in three patients, 15 mg/day in one patient and 20 mg/day in two patients. The duration between PET scan and the last administration of olanzapine was between 2 and 20 h. Clinical symptoms were assessed by positive and negative symptom scale (PANSS). This study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Chiba, Japan.

PET procedure

A PET scanner system, ECAT EXACT HR+ (CTI-Siemens, Knoxville, TN, USA), was used for all subjects. A head fixation device was used to minimize head movement. Before the dynamic scan, a transmission scan for attenuation correction was performed using a ^{68}Ge–^{68}Ga source. The dynamic PET scan was then performed for 90 min after intravenous bolus injection of 197.0–238.0 MBq (217.5 ± 13.9 MBq, mean ± SD) of [^{11}C]FLB 457. The specific radioactivity of [^{11}C]FLB 457 was 85.8–339.9 MBq/nmol (188.0 ± 79.1 MBq/nmol, mean ± SD); the injected mass of FLB 457 was 0.24–0.90 μg (0.64 ± 0.20 μg, mean ± SD). Venous blood samples were taken before and after PET scanning to measure the plasma concentration of olanzapine. The average values of plasma concentration before and after PET scanning were used. The drug concentration of one patient (No. 8) could not be determined because of a technical error. Magnetic resonance images of the brain were acquired with 1.5 T MRI, Gyroscan NT (Philips Medical Systems, Best, Netherlands). T1-weighted images of 1-mm slices were obtained.

Data analysis

All emission scan data were reconstructed with a Hanning filter. Regions of interest (ROIs) were defined for the temporal cortex as for the extrastriatal region and cerebellar cortex [3, 34]. ROIs were drawn manually on PET images with reference to individual MR images. The values of ROIs for right and left sides were averaged. Binding potential (BP_{ND}) of dopamine D_2 receptor was calculated using a three-parameter simplified reference tissue model [18]. The cerebellum was used as reference tissue because of its negligible density of dopamine D_2 receptors [28].

Receptor occupancy of antipsychotic drug is expressed as follows: Occupancy (%) = $(BP_{base} - BP_{drug})/BP_{base} \times 100$, where BP_{base} is BP_{ND} in the drug-free state and BP_{drug} is BP_{ND} after administration of the drug. In this study,

Table 1 Patient characteristics, plasma concentration of olanzapine, and dopamine D_2 receptor occupancy

No.	Age (years)	Sex	Duration of illness (years)	PANSS	Dose (mg/day)	Duration of fixed dose (months)	Other medication	Plasma concentration (ng/ml)	Receptor occupancy (%)
1	41	M	6.5	50	5	14	–	20.1	61.6
2	45	M	8	38	5	25	BZ	12.7	72.2
3	30	F	12	49	7.5	13	–	25.9	65.6
4	45	F	4	95	7.5	0.5	BZ, AP	25.5	76.9
5	23	M	0.8	50	10	7	–	48.5	69.7
6	41	M	17	44	10	30	BZ	21.8	61.1
7	47	M	27	92	10	3	–	44.5	81.8
8	32	M	17	75	15	16	BZ	ND	67.9
9	23	M	5	101	20	0.5	BZ	61.0	79.5
10	37	F	11	92	20	3	BZ	115.4	85.8

BZ benzodiazepine, *AP* anti-parkinsonian drug, *ND* not determined

mean BP_{ND} of age-matched ten normal male subjects (age range 21–49; 36.2 ± 9.1 years, mean ± SD) measured by the same procedure as for the patients was used as BP_{base} because of the lack of individual baseline BP_{ND}.

The relationship between receptor occupancy and dose (or plasma concentration) of antipsychotic drug can be expressed as follows:

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

where D is the dose of olanzapine and ED_{50} is the dose required to induce 50% occupancy [1, 13, 31]. In this study, maximum occupancy was fixed at 100%, the same as previous occupancy studies with olanzapine [13].

Measurement of plasma concentration of olanzapine

Plasma concentrations of olanzapine were determined using a validated high-performance liquid chromatography (HPLC) method (JCL Bioassay Corporation., Hyogo, Japan).

Statistical analysis

Correlations between dopamine D_2 receptor occupancy in the temporal cortex and daily dose, plasma concentration, age, duration of illness and PANSS (total or sub scores) were assessed using Pearson's correlation coefficient.

Results

Dopamine D_2 receptor occupancy in the temporal cortex ranged from 61.1 to 85.8% (Table 1). Plasma concentration of olanzapine ranged from 12.7 to 115.4 ng/ml. ED_{50} was 3.4 mg/day for the daily dose (Fig. 1) and 10.5 ng/ml for the plasma concentration (Fig. 2). The PANSS score ranged from 38 to 101. Average PANSS scores of all patients were 68.6 ± 24.7.

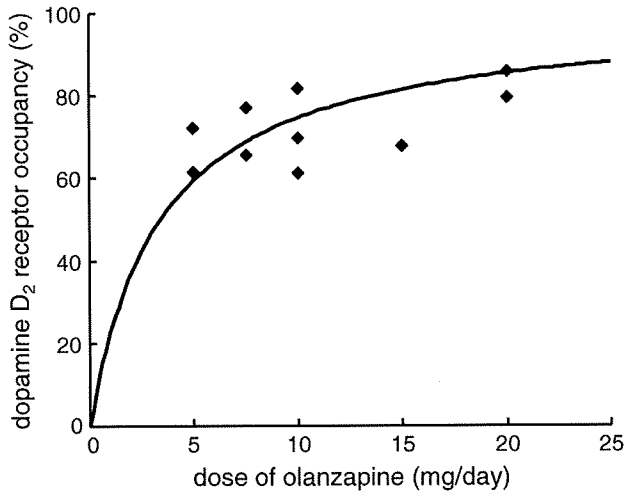

Fig. 1 Relationship between dopamine D_2 receptor occupancy and daily dose of olanzapine

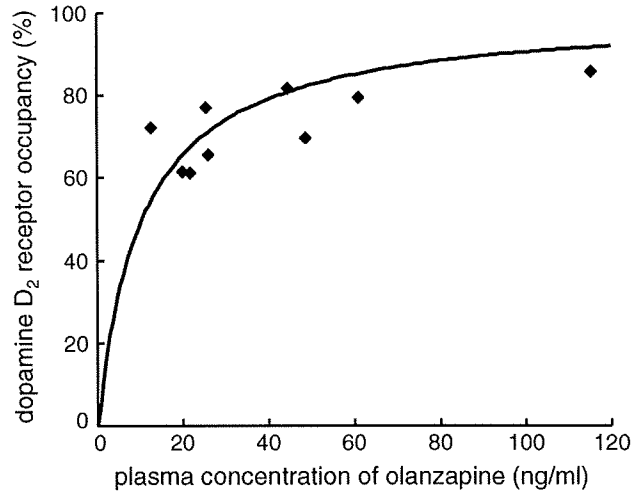

Fig. 2 Relationship between dopamine D_2 receptor occupancy and plasma concentration of olanzapine

A positive correlation was observed between dopamine D_2 receptor occupancy in the temporal cortex and plasma concentration ($r = 0.72$, $P = 0.029$), but not daily dose within this dose range ($r = 0.57$, $P = 0.082$). A positive correlation was also observed with total PANSS scores ($r = 0.80$, $P = 0.0054$), positive scores ($r = 0.78$, $P = 0.0074$), negative scores ($r = 0.68$, $P = 0.032$), and general scores ($r = 0.78$, $P = 0.0072$). No correlations were observed between dopamine D_2 receptor occupancy in the temporal cortex and age ($P = 0.85$) or duration of illness ($P = 0.81$).

Discussion

Although the measured occupancy value was above 50% with 5–20 mg/day of olanzapine, the calculated ED_{50} value from the present result in the temporal cortex was 3.4 mg/day for the daily dose and 10.5 ng/ml for the plasma concentration. The previously reported ED_{50} of olanzapine in the striatum was 4.5 mg/day for the daily dose and 10.3 ng/ml for the plasma concentration [13]. ED_{50} of plasma concentration in the extrastriatum of the present study was similar to that reported in the striatum, meaning that there was no noteworthy regional difference in dopamine D_2 receptor occupancy by olanzapine between the striatum and extrastriatum. Based on 70–80% of dopamine D_2 receptor occupancy [8, 14, 20], the optimal daily dose of olanzapine would be about 8–14 mg/day. This estimated dose was in fairly good agreement with the current clinical dose (5–20 mg/day in Japan).

According to electrophysiological measurement, the effect of olanzapine was reported preferentially in the ventral tegmental area (A10) [27], and olanzapine was reported to increase c-fos expression to a greater degree in the nucleus accumbens than in the dorsolateral striatum [24]. These findings suggested that olanzapine had preferentially different regional effects for extrastriatal regions. The concept of 'limbic selectivity', i.e., differences in dopamine D_2 receptor occupancy between the striatum and extrastriatum, has been discussed. Although there are several reports about 'limbic selectivity' of second-generation antipsychotics, such as clozapine [9, 17, 23, 34], risperidone [5, 34], quetipaine [17, 26] and amisulpride [4, 34], it has also been reported that there is no limbic selectivity with second-generation antipsychotics such as clozapine [32] and risperidone (and paliperidone) [1, 11, 35].

Contradictory results of limbic selectivity have also been reported for olanzapine. Two studies showed higher occupancy in the temporal cortex than in the striatum using [^{123}I]epidepride SPECT (82.8 ± 4.2% in the temporal cortex and 41.3 ± 17.9% in the striatum) [3] and [^{76}Br]FLB 457 PET (83.6 ± 10.5% in the temporal cortex and 45.1 ± 20.9% in the striatum) [34]. On the other hand, no significant difference in occupancy between the temporal cortex (67.5 ± 7.1%) and striatum (70.9 ± 6.9%) was reported using [^{18}F]fallypride PET [16]. Regional differences in occupancies were calculated from the area under the time-activity curve ratio in [^{123}I]epidepride SPECT and [^{76}Br]FLB 457 PET [3, 34]. A previous study reported that the ratio method underestimated striatal occupancy using high-affinity radioligand such as [^{123}I]epidepride or [^{11}C]FLB 457 (probably also [^{76}Br]FLB 457) because radioligand bindings did not reach equilibrium due to the high density of dopamine D_2 receptors in the striatum [21]. In addition, because none of the studies concerning regional difference of occupancy by olanzapine presented plasma concentrations [3, 16, 34], ED_{50} of the extrastriatum could not be compared with the present study.

Differences of occupancy or EC_{50} values in the same brain region (e.g. striatum) were reported using different radioligands ("Discussion" in [19]). As commented above, this difference may be caused using different affinity radioligands at high-density receptor regions [21]. In this study, the dopamine D_2 receptor bindings in the temporal cortex were measured using [^{11}C]FLB 457 because the dopamine D_2 receptor density of the temporal cortex is very low compared with that of the striatum (B_{max} = 0.4 and 16.6 pmol/g tissue, respectively) [15]. Recently, the absence of regional difference between striatal and extrastriatal occupancy of risperidone was reported using [^{11}C]raclopride and [^{11}C]FLB 457 by precise methods [11]. These results suggest that optimal radioligands are necessary for different brain regions with different receptor densities.

The significant positive correlation between temporal dopamine D_2 receptor occupancy and PANSS suggests that higher doses tend to be used for severe symptoms of schizophrenia. However, as this was an open study and the number of patients was limited, further studies (such as randomized controlled trials) are needed.

In the present study, the mean BP_{ND} value of age-matched healthy subjects was used as value of the drug-free state. Although previous studies showed no difference in BP_{ND} values of the temporal cortex between normal subjects and patients with schizophrenia [29, 33] or between the sexes [12], individual differences in BP_{ND} values may lead to potential error in the estimation of dopamine D_2 receptor occupancy [8]. Moreover, there is a possibility of upregulation of dopamine D_2 receptor by neuroleptic treatment [25]. When BP_{base} changes by ±15%, the estimated occupancy ranges from 41 to 57% for an assumed occupancy of 50%. The effect of displaceable binding of [^{11}C]FLB 457 in the cerebellum may also lead to an underestimation of receptor occupancy [2, 22].

Although the time point of the scan following the last drug administration was different among the scans, plasma concentration was measured and the reported time-course of occupancy of olanzapine fitted well with the occupancy simulated by plasma concentration [30].

In conclusion, dopamine D_2 receptor occupancy ranged from 61.1 to 85.8% in the temporal cortex of patients with schizophrenia taking 5–20 mg/day of olanzapine. The ED_{50} values were 3.4 mg/day for dose and 10.5 ng/ml for plasma concentration of olanzapine, in fairly good agreement with the reported values in the striatum using [^{11}C]raclopride. 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.

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Conflict of interest statement All authors reported no conflict of interest.

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ORIGINAL INVESTIGATION

Dopamine D_2 receptor occupancy by perospirone: a positron emission tomography study in patients with schizophrenia and healthy subjects

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Abstract
Rationale Perospirone is a novel second-generation antipsychotic drug with high affinity to dopamine D_2 receptor and short half-life of plasma concentration. There has been no investigation of dopamine D_2 receptor occupancy in patients with schizophrenia and the time course of occupancy by antipsychotics with perospirone-like properties.
Objective We investigated dopamine D_2 receptor occupancy by perospirone in patients with schizophrenia and the time course of occupancy in healthy subjects.
Materials and methods Six patients with schizophrenia taking 16–48 mg/day of perospirone participated. Positron emission tomography (PET) scans using [^{11}C]FLB457 were performed on each subject, and dopamine D_2 receptor occupancies were calculated. Moreover, baseline and three serial PET using [^{11}C]raclopride were performed at 1.5, 8, and 25.5 h after administration of a single dose of 16 mg of perospirone on four healthy male subjects, and occupancy was calculated for each scan.
Results Dopamine D_2 receptor occupancy in the temporal cortex of patients ranged from 39.6% to 83.8%. Especially, occupancy in two patients who took 16 mg of perospirone 2.5 h before PET was over 70%. Mean occupancy in the striatum of healthy subjects was 74.8% at 1.5 h, 60.1% at 8 h, and 31.9% at 25.5 h after administration.
Conclusion Sixteen milligrams of perospirone caused over 70% dopamine D_2 receptor occupancy near its peak level, and then occupancy dropped to about half after 22 h. The time courses of receptor occupancy and plasma concentration were quite different. This single dosage may be sufficient for the treatment of schizophrenia and might be useful as a new dosing schedule choice.

Keywords Dopamine D_2 receptor occupancy · Perospirone · Positron emission tomography · Schizophrenia · Time course

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Introduction

Perospirone is a novel second-generation antipsychotic drug used in Japan (Onrust and McClellan 2001). This drug shows high affinity to dopamine D_2 receptor (K_i= 1.77 nM) and serotonin 5-HT_2 receptor (K_i=0.06 nM; Takahashi et al. 1998), and its plasma concentration has a short half-life ($T_{1/2}$=1.9 h; Yasui-Furukori et al. 2004). A previous positron emission tomography (PET) study using [^{11}C]raclopride and [^{11}C]NMSP in healthy subjects with single 8 mg of perospirone showed blockage of both dopamine D_2 receptor and serotonin 5-HT_2 receptor (Sekine et al. 2006), but the optimal dose of perospirone in patients with schizophrenia has not been investigated.

Kapur et al. (2000b) reported that transient high dopamine D_2 receptor occupancy by quetiapine showed clinical effects for patients with schizophrenia. They suggested that this transient occupancy was related to "atypical" features of second-generation antipsychotics

with low affinity for dopamine D_2 receptor (Kapur and Seeman 2001). Plasma pharmacokinetics and affinity for receptor were considered to affect the time course of receptor occupancy (Kapur and Seeman 2001; Takano et al. 2004). However, the time course of receptor occupancy by antipsychotics with high affinity for dopamine D_2 receptor and a short half-life of plasma concentration has not been investigated.

In this study, we investigated dopamine D_2 receptor occupancy by several doses of perospirone in patients with schizophrenia. Moreover, we investigated the time course of dopamine D_2 receptor occupancy by perospirone with serial PET scanning in healthy subjects.

Materials and methods

This study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Chiba, Japan. After complete explanation of this study, written informed consent was obtained from all subjects.

Patient study

Subjects and study protocol

Six patients aged 26–44 years (34.9±7.1, mean ± SD), diagnosed with schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders-IV criteria, participated in this study (Table 1). Exclusion criteria were current or past substance abuse, brain tumor or vascular disease, and history of severe head injury or epilepsy. Subjects with severe liver or renal dysfunction, or having undergone electroconvulsive therapy within 90 days prior to this study were also excluded. The patients had been taking fixed dosages of perospirone for more than 2 weeks before this study. Doses of perospirone were 16 mg/day in one patient, 24 mg/day in two patients, and 48 mg/day in three patients. The interval between the last administration of perospirone and PET scan was from 2.5 to 17.5 h. Clinical symptoms were assessed by positive and negative symptom scale (PANSS). Venous blood samples were taken before and after PET scanning to measure the plasma concentration of perospirone and ID-15036, an active metabolite of perospirone (hydroxyperospirone). The average values of pre- and post-PET scanning were used.

PET procedure

A PET scanner system, ECAT EXACT HR+ (CTI-Siemens, Knoxville, TN, USA), was used for all subjects. A head fixation device was used to minimize head movement. Before the dynamic scan, a transmission scan for attenuation correction was performed using a ^{68}Ge-^{68}Ga source. The dynamic PET scan was performed for 90 min after intravenous bolus injection of 204.0–225.0 MBq (218.5± 7.7 MBq, mean ± SD) of [^{11}C]FLB 457. The specific radioactivity of [^{11}C]FLB 457 was 129.6–219.4 MBq/nmol (175.4±34.3 MBq/nmol, mean ± SD). Magnetic resonance images of the brain were acquired with 1.5 Tesla magnetic resonance imaging (MRI), Gyroscan NT (Philips Medical Systems, Best, Netherlands). T1-weighted images at 1-mm slices were obtained.

Data analysis

All emission scan data were reconstructed with a Hanning filter. Regions-of-interest (ROIs) were defined for the temporal cortex and cerebellar cortex. ROIs were drawn manually on PET images with reference to the individual MR images. The values of ROIs for right and left sides were averaged. Binding potential (BP_{ND}), defined as the specific binding compared to nondisplaceable uptake, of dopamine D_2 receptor in the temporal cortex was calculated using a three-parameter simplified reference tissue model (SRTM; Innis et al. 2007; Lammertsma and Hume 1996). The cerebellum was used as reference tissue because of its negligible density of dopamine D_2 receptors (Suhara et al. 1999).

Table 1 Patient characteristics, plasma concentration, and dopamine D_2 receptor occupancy

Number	Age (year)	Sex	PANSS	Dose (mg/day)	Interval: last dose–PET (h)	Last dose (mg)	Plasma concentration		Receptor occupancy (%)
							Perospirone (ng/ml)	ID-15036 (ng/ml)	
1	38	M	59	16	2.5	16	4.5	23.3	83.8
2	30	F	69	24	7.5	8	0.6	3.05	61.8
3	44	F	62	24	9.0	8	0	0.75	39.6
4	26	M	81	48	2.5	8	1.25	8.45	60.8
5	30	F	46	48	2.5	16	0.25	8.35	70.1
6	42	F	80	48	17.5	32	0.85	2.1	65.0

Receptor occupancy of perospirone is expressed as follows: Occupancy(%) = $(BP_{baseline} - BP_{drug})/BP_{baseline} \times 100$, where $BP_{baseline}$ is BP_{ND} in the drug-free state, and BP_{drug} is BP_{ND} after administration of the drug. Mean BP_{ND} of age-matched ten normal male subjects (age range 25–43 years; 34.8±6.7 years, mean ± SD) measured by the same procedure as for the patients was used as BP_{base} because of the lack of individual baseline BP_{ND}.

The relationship between receptor occupancy and plasma concentration of antipsychotic drug can be expressed as follows: Occupancy(%) = $C/(C + EC_{50}) \times 100$, where C is the plasma concentration of perospirone or ID-15036, and EC_{50} is the concentration required to induce 50% occupancy.

Measurement of plasma concentration of perospirone

Plasma concentrations of perospirone and ID-15036 were determined using a validated high performance liquid chromatography method (Yasui-Furukori et al. 2003; MP-Technopharma Corporation, Fukuoka, Japan). The lower limit of quantification was 0.1 ng/ml for both perospirone and ID-15036.

Healthy subject study

Subjects and study protocol

Four healthy male subjects aged 22–32 years (26.8±4.1, mean ± SD) participated in the other part of this study. None had a history of psychiatric, neurological, or somatic disorders. None had taken any medication for at least 2 weeks prior to this study. The baseline PET scan was performed within 2 weeks before taking perospirone. All subjects took a single dose of 16 mg of perospirone, and then three serial PET scans were performed at 1.5, 8, and 25.5 h after its administration. Venous blood samples were taken 11 times, at 0.5, 1.0, 1.5, 2.5, 3.5, 5.0, 6.5, 8.0, 9.0, 25.5, and 26.5 h after perospirone administration, to measure the plasma concentrations of perospirone and ID-15036.

PET procedure

A PET scanner system, ECAT EXACT HR+, was used for all subjects. A head fixation device was used to minimize head movement. Before the dynamic scan, a transmission scan for attenuation correction was performed using a ^{68}Ge-^{68}Ga source. The dynamic PET scan was performed for 60 min after intravenous bolus injection of 179.6–246.8 MBq (217.0±16.5 MBq, mean ± SD) of [^{11}C] raclopride. The specific radioactivity of [^{11}C]raclopride was 138.0–320.9 MBq/nmol (235.4±65.8 MBq/nmol, mean ± SD). T1-weighted images at 1-mm slices of the brain were acquired with 1.5 Tesla MRI, Gyroscan NT.

Data analysis

All emission scan data were reconstructed with a Hanning filter. ROIs were defined for the striatum and cerebellar cortex and were drawn manually on the PET images with reference to individual MR images. The values of ROIs for right and left sides were averaged. BP_{ND} of dopamine D_2 receptor in the striatum was calculated using SRTM. The cerebellum was used as reference tissue. Receptor occupancy was calculated using the individual BP_{ND} values of baseline and drug administration.

Results

Patient study

Dopamine D_2 receptor occupancy of patients with schizophrenia in the temporal cortex ranged from 39.6% to 83.8% (Table 1). Plasma concentrations of perospirone and ID-15036 ranged from 0 to 4.5 and 0.75 to 23.3 ng/ml, respectively. The plasma concentrations of perospirone and ID-15036 were fitted curvilinearly to the dopamine D_2 receptor occupancy (Fig. 1a, b). Estimated EC_{50} values of perospirone and ID-15036 were 0.31 and 1.90 ng/ml, respectively. The total PANSS score ranged from 46 to 81, and the average score of all patients was 66.2±13.4.

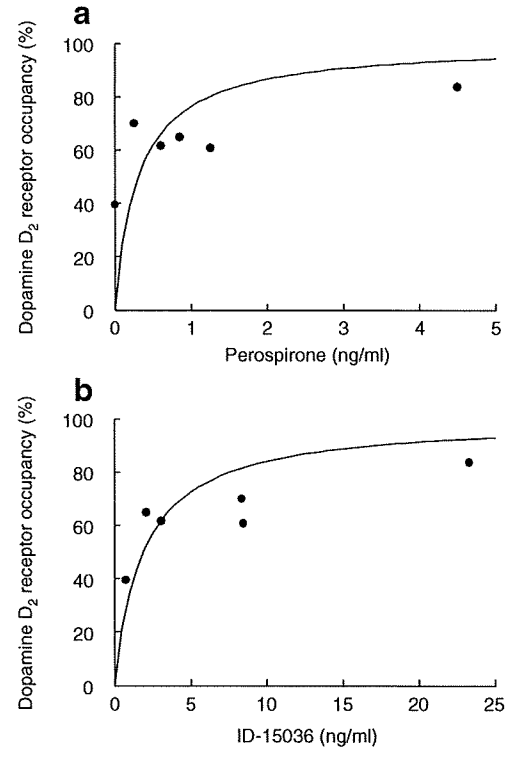

Fig. 1 Relationship between dopamine D_2 receptor occupancy and perospirone (**a**) and ID-15036 (**b**) in the patients study

Healthy subject study

Mean dopamine D_2 receptor occupancies in the striatum were 74.8±8.0% at 1.5 h, 60.1±5.6% at 8 h, and 31.9±6.4% at 25.5 h after administration of 16 mg of perospirone in healthy subjects (Fig. 2). The mean plasma concentrations of both perospirone and ID-15036 reached a peak at 1 h after administration, then rapidly decreased, and were not detectable at 25.5 h after (Fig. 3a, b). Estimated half-lives of plasma concentrations of perospirone and ID-15036 were 2.2 and 1.9 h, respectively. No subject complained of severe side effects such as extrapyramidal symptoms or sleepiness.

Discussion

Clinical dose of perospirone

A previous study reported that dopamine D_2 receptor occupancy using [^{11}C]raclopride was 44.4% with 8 mg of perospirone at 1 h post-administration (Sekine et al. 2006). PET studies have suggested that more than 70% dopamine D_2 receptor occupancy is necessary for antipsychotic effect and that 80% occupancy causes extrapyramidal symptoms (Farde et al. 1992; Kapur et al. 2000a; Nordstrom et al. 1993). Two patients (numbers 1 and 5) administered perospirone at 16 mg 2.5 h before PET scanning showed over 70% occupancy. On the other hand, one patient (number 4) taking 8 mg did not reach 70% occupancy in spite of a short interval between the last administration and PET scan. In healthy subjects, a peak of about 75% occupancy was also obtained with 16 mg of perospirone. Although some patients could be maintained at less than 70% occupancy, 16 mg of perospirone seems to be the necessary dose for achieving antipsychotic effect. The plasma concentrations of perospirone and ID-15036 inducing 70% occupancy (EC_{70}) were 0.72 and 4.43 ng/ml, respectively. Side effects could not be evaluated in this study because some patients were taking benzodiazepines or anti-Parkinson drugs, and plasma prolactin levels were not measured.

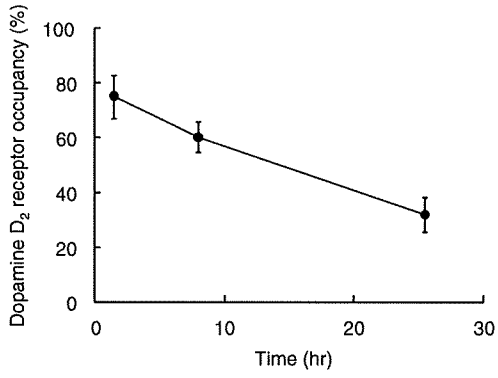

Fig. 2 Time course of mean dopamine D_2 receptor occupancy in healthy subject study. *Bars* represent standard deviation of mean

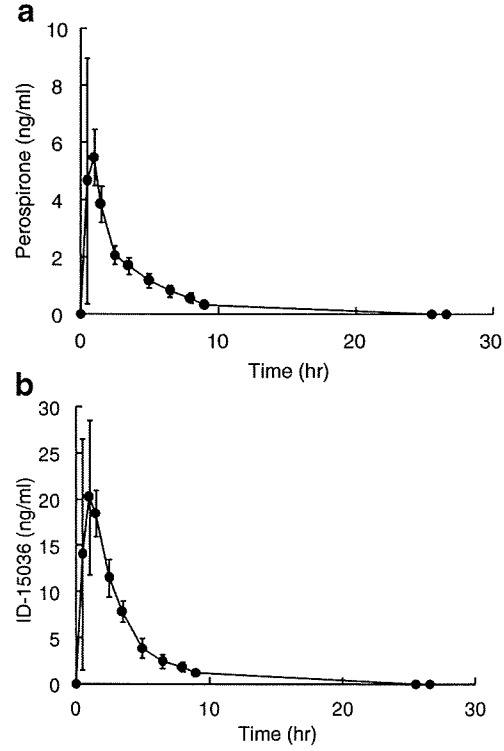

Fig. 3 Time course of mean plasma concentrations of perospirone (**a**) and ID-15036 (**b**) in healthy subjects study. *Bars* represent standard deviation of mean

Pharmacokinetics and contributions to receptor occupancy of perospirone and ID-15036

In healthy subjects, plasma concentrations of perospirone and ID-15036 peaked at 1 h after administration, with the half-lives of plasma concentrations being 2.2 and 1.9 h, respectively. The plasma concentration of ID-15036 was fourfold that of perospirone. These results were in good agreement with the previous study showing that the T_{max} values were 0.8 (perospirone) and 1.1 h (ID-15036), and $T_{1/2}$ was 1.9 h (perospirone; Yasui-Furukori et al. 2004). As ID-15036 has affinity for the dopamine D_2 receptor (K_i= 5.84 nM) and blocks the dopamine D_2 receptor of the in vivo rat brain (Takahashi et al. 1998), both perospirone and ID-15036 contributed to dopamine D_2 receptor occupancy, and the plasma concentrations of both were fitted to the occupancy curve.

Effects of affinity and pharmacokinetics of antipsychotics on time course of receptor occupancy

Dopamine D_2 receptor occupancy was about 75% at 1.5 h after perospirone administration and then showed a rela-

tively rapid decline. After 25.5 h, about 30% occupancy remained, although plasma concentrations of perospirone and ID-15036 were not detectable. The time to reach half of the peak occupancy of 75% was 22 h. The time courses of receptor occupancy and plasma concentration were quite different. In comparison, risperidone and olanzapine showed sustained occupancy; about 80% occupancy 5 or 6 h after administration decreased to only 70% after 24 h (Takano et al. 2004; Tauscher et al. 2002). On the other hand, quetiapine showed transient occupancy; 64% occupancy after 2 h decreased to 0% after 24 h (Kapur et al. 2000b). Some factors such as the time course of plasma concentration of antipsychotics or affinity for dopamine D_2 receptor were considered to affect the time course of receptor occupancy (Kapur and Seeman 2001; Takano et al. 2004). For example, high affinity and long half-life of plasma concentration (e.g., risperidone (K_i=1.1 nM, $T_{1/2}$= 17.8 h) and olanzapine (K_i=5.1 nM, $T_{1/2}$=19.5 h)) expressed sustained occupancy, and low affinity and short half-life of plasma concentration (e.g., quetiapine (K_i= 122 nM, $T_{1/2}$=3.2 h)) expressed transient occupancy (Gefvert et al. 1998; Seeman 2002; Takano et al. 2004; Tauscher et al. 2002). Perospirone has high affinity for dopamine D_2 receptor and a short half-life of plasma concentration (Takahashi et al. 1998; Yasui-Furukori et al. 2004). These features may cause relatively rapid decrease in occupancy, from 75% at 1.5 h of perospirone administration to 32% after 25.5 h, but the occupancy did not completely disappear within a day. In patients taking 32 mg perospirone (number 6), dopamine D_2 receptor occupancy was 65% at 17.5 h after, supporting an intermediate time course between sustained and transient occupancy.

Possibility of new dosing schedule with perospirone

There are several opinions concerning the dosing schedule of antipsychotics. A recent clinical study reported that extended antipsychotic dosing (every second or third day) was effective and decreased side effects for chronic patients with schizophrenia (Remington et al. 2005). An animal study reported that transient antipsychotic medication was more effective for amphetamine-induced behavioral abnormality than continuous one (Samaha et al. 2008). These findings indicate that sustained occupancy might not necessarily be required for antipsychotic therapy of schizophrenia. In prodromal episode-based intervention, antipsychotic drugs were used occasionally, and long antipsychotic-free periods were sometimes inserted. However, some studies reported that intermittent medication increased the relapse rate in schizophrenia (Gaebel et al. 2002; Herz et al. 1991; Schooler et al. 1997). Because perospirone shows an intermediate time course between sustained and transient occupancy, its single administration may become a new dosing schedule choice for an antipsychotic drug. Indeed, the administration of perospirone once a day indicated antipsychotic effects and preventions from relapse for chronic patients with schizophrenia (Kusumi et al. 2008). Four patients in the present study (numbers 1, 4, 5, and 6) taking 16 mg or more at least once a day were maintained for more than 6 months. Further study of relationships between clinical response and receptor occupancy of various dosing schedules in patients with schizophrenia will be needed.

Regional difference of dopamine D_2 receptor occupancy

Regional differences of dopamine D_2 receptor occupancy between the striatum and extrastriatum in some second-generation antipsychotic drugs have been discussed (Arakawa et al. 2008; Ito et al. 2009; Pilowsky et al. 1997; Talvik et al. 2001). In the present study, the mean occupancy of four healthy subject and two patients (number 1 and 5) in a short interval between the administration of 16 mg of perospirone and PET scanning seemed to differ very little (75.1% in the striatum with [^{11}C]raclopride and 77.0% in the temporal cortex with [^{11}C]FLB 457). It is suggested that there were no regional differences of dopamine D_2 receptor occupancy between the striatum and extrastriatum with perospirone despite the subjects, study protocols, and radioligands being different.

Conclusion

Sixteen milligrams of perospirone caused over 70% dopamine D_2 receptor occupancy near its peak level, then becoming about half after 22 h. The time courses of receptor occupancy and plasma concentration were quite different. This single dosage may be sufficient for the treatment of schizophrenia and might be useful as a new dosing schedule choice.

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ARTICLE

CINP

Peripheral benzodiazepine receptors in patients with chronic schizophrenia: a PET study with [^{11}C]DAA1106

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Abstract

Inflammatory/immunological process and glial contribution are suggested in the pathophysiology of schizophrenia. We investigated peripheral benzodiazepine receptors in brains of patients with chronic schizophrenia, which were reported to be located on mitochondria of glial cells, using [^{11}C]DAA1106 with positron emission tomography. Fourteen patients and 14 age- and sex-matched normal controls participated in this study. PET data were analysed by two-tissue compartment model with metabolite-corrected plasma input. Clinical symptoms were assessed using the Positive and Negative Syndrome Scale. There was no significant difference between [^{11}C]DAA1106 binding of the cortical regions of normal controls and patients with schizophrenia, whereas the patients showed a positive correlation between cortical [^{11}C]DAA1106 binding and positive symptom scores. There was also a positive correlation between [^{11}C]DAA1106 binding and duration of illness. Although the correlations need to be interpreted very cautiously, involvement of glial reaction process in the pathophysiology of positive symptoms or progressive change of schizophrenia might be suggested.

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Key words: Microglia, peripheral benzodiazepine receptor, positive symptoms, schizophrenia.

Introduction

An accumulating body of evidence has suggested that the pathophysiology of schizophrenia could be related to the dysregulation of the inflammatory response system, such as increased levels of *in vivo* IL-1RA, sIL-2R, and IL-6 (Lin *et al.* 1998; Nawa & Takei, 2006; Potvin *et al.* 2008; Zhang *et al.* 2004). Microglia has been regarded as a mediator of neuroinflammation via the release of pro-inflammatory cytokines, nitric oxide (NO) and reactive oxygen species (ROS) in the central nervous system (CNS). Peripheral benzodiazepine receptor (PBR) was reported to reflect neuronal injury and inflammatory lesions in the brain by increased expression of the number of binding sites in glial cells including activated microglia and reactive astrocytes as visualized *in vivo* using PET with [^{11}C]PK11195 (Shah *et al.* 1994). Recent reports demonstrated that [^{11}C]PK11195 binding was increased in patients with acute-onset schizophrenia (van Berckel *et al.* 2008) and in patients with schizophrenia during psychosis (Doorduin *et al.* 2009). However, the affinity (Chaki *et al.* 1999) and permeability of the blood–brain barrier was low for PK11195, reportedly a substrate of efflux transporter P-glycoprotein (Jakubikova *et al.* 2002; Vaalburg *et al.* 2005). Low uptake of [^{11}C]PK11195 in the brain could hamper stable quantitative analysis.

(*N*-5-fluoro-2-phenoxyphenyl)-*N*-(2,5-dimethoxylbenzyl) acetamide (DAA1106) is a potent and selective ligand for PBR with high affinity (Chaki *et al.* 1999; Okuyama *et al.* 1999). [^{11}C]DAA1106 is accumulated at high levels in the mouse brain (Zhang *et al.* 2003), and the radioactivity of [^{11}C]DAA1106 at 30 min after injection was reported to be four times higher than that of [^{11}C]PK11195 in the monkey brain (Maeda *et al.* 2004). A quantitative analysis method for [^{11}C]DAA1106 binding in the human brain has been well established with the two-tissue compartment model (Ikoma *et al.* 2007). [^{11}C]DAA1106 was

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Table 1. Demographic and clinical characteristics of the patients with schizophrenia

Subject	Age (yr), sex	PANSS				Duration of illness (yr)	Duration of drug treatment (yr)	Haloperidol equivalent (mg)	Main antipsychotics
		Positive	Negative	General	Total				
1	29, F	12	12	25	49	11	9	3	Olanzapine
2	34, F	17	12	33	62	7	5	6	Risperidone
3	37, F	14	23	27	64	0.5	0.5	3	Olanzapine
4	43, F	21	27	49	97	22	19	17	Risperidone
5	46, F	16	15	34	65	33	21	10	Nemonapride
6	49, F	24	20	33	77	23	16	19.4	Haloperidol
7	42, M	15	22	27	64	4	4	4	Olanzapine
8	43, M	15	26	33	74	26	23	9	Haloperidol
9	44, M	22	25	40	87	22	22	8.5	Olanzapine
10	44, M	16	26	37	79	4	4	14	Haloperidol
11	46, M	29	26	56	111	26	26	3.5	Olanzapine
12	46, M	16	16	25	57	24	24	4	Risperidone
13	52, M	24	35	58	117	18	17	16.5	Olanzapine
14	59, M	27	24	47	87	43	39	10.3	Mosapramine
		19.1±5.3	22.1±6.5	37.4±11.1	77.9±20.1	18.8±12.2	16.4±10.8	9.2±5.7	

PANSS, Positive and Negative Syndrome Scale; F, female; M, male.
Haloperidol (1 mg) was equivalent to chlorpromazine (50 mg).

demonstrated to be useful in the study of neurodegerative disorders such as Alzheimer's disease (Yasuno *et al.* 2008).

In this study, we investigated PBR binding in patients with chronic schizophrenia using [^{11}C]DAA1106 to evaluate whether glial reaction was involved in the pathophysiology of schizophrenia.

Materials and methods

Subjects

Fourteen patients with schizophrenia [six females, eight males; 43.9±7.4 yr (mean±S.D.)] and 14 normal control subjects (five females, nine males; 42.5±9.0 yr) were enrolled in this study. Patients were recruited from the outpatient and in-patient units of Nippon Medical School Hospital, Asai Hospital and Sobu Hospital, located in Tokyo and Chiba prefecture in Japan. The patients were diagnosed as having schizophrenia and treated by attending physicians at each hospital, and their diagnoses were re-evaluated with structured interviews at our PET centre. All 14 patients were diagnosed with schizophrenia according to DSM-IV criteria. Exclusion criteria were current or past substance, cannabis or alcohol abuse, mood disorders, and organic brain disease. The patients' demographic and clinical data are shown in Table 1. None of the patients had taken benzodiazepines within more than 1 month prior to PET measurements. Psychopathology was assessed by the Positive and Negative Syndrome Scale (PANSS; Kay *et al.* 1987). PANSS was completed by three experienced psychiatrists on the same day as the PET measurements. They reviewed the ratings after the interviews, and disagreements were resolved by consensus; the consensus ratings were used in this study. The symptom scores were calculated as total scores, positive symptom, negative symptom, and general symptom subscores of PANSS. The total PANSS score ranged from 49 to 117 (78.6±20.7). The mean positive symptom score was 19.1±5.3, negative symptom score was 22.1±6.5, and general symptom score was 37.4±11.1.

The normal control subjects were recruited from the surrounding community. Based on psychiatric screening interviews, they were free of current and past psychiatric or major medical disease, and had no relatives with neuropsychiatric disorders.

This study complied with the current laws of Japan, and was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Chiba, Japan. Written informed consent was obtained from all subjects.

Radiochemistry

[^{11}C]DAA1106 was prepared as described in detail previously (Ikoma *et al.* 2007; Zhang *et al.* 2003). The precursor was supplied by Taisho Pharmaceutical Co. (Japan).

PET data acquisition

PET scans were performed with ECAT EXACT HR+ (CTI-Siemens, USA), which provides 63 planes and a 15.5-cm axial field of view (FOV). A 10-min transmission scan with a ^{68}Ge–^{68}Ga source was followed by a 90-min dynamic scan (20s × 9, 60s × 5, 120s × 4, 240s × 11, and 300s × 6) with a bolus injection of 261–411 (369 ± 27) MBq of [^{11}C]DAA1106. Specific radioactivity was 15.4–220.7 GBq/μmol at the time of the injection. There was no significant difference in injected radioactivity and specific radioactivity between patients and normal controls (373 ± 20 MBq and 60.3 ± 44.4 GBq/μmol for patients, and 366 ± 32 MBq and 98.4 ± 70.7 GBq/μmol for normal controls). Radioactivity was measured in three-dimensional mode, and the data were reconstructed with a Hanning filter with a cut-off frequency of 0.4 (full width half maximum = 7.5 mm).

Arterial blood sampling

To obtain the arterial input function, an automated blood sampling system was used for continuous (counts/s) blood radioactivity measurements during the first 12 min of PET measurement. At the same time, arterial blood samples were taken manually and their radioactivity concentration was measured 13 times during the initial 3 min after the injection, eight times during the next 17 min, and once every 10 min until the end of the scan. To analyse the metabolite fraction in the plasma, arterial blood samples were taken 10 times during PET measurements. The parent ligand, separated from the total radioactive compound, was measured as previously described (Ikoma *et al.* 2007). The mean time-course of the fraction of the parent ligand is shown in Fig. 1. There was a significant group × time interaction using repeated-measures ANOVA with Greenhouse–Geisser correction ($F_{3.4,81.1} = 4.92$, $p = 0.002$), although one subject from each group was excluded for the statistical analysis due to one missing data-point.

MR imaging

T1-weighted magnetic resonance imaging (MRI) of the brain was performed with Philips Intera 1.5 T (Philips Medical Systems, The Netherlands). T1-weighted images of the brain were obtained from all subjects. The scan parameters were 1-mm-thick 3D T1 images with a transverse plane [repetition time (TR)/echo time (TE) 22/9.2 ms, flip angle 30°, matrix 128 × 128, FOV 256 × 256). Voxel size of the magnetic resonance images was 1 mm × 1 mm × 1 mm.

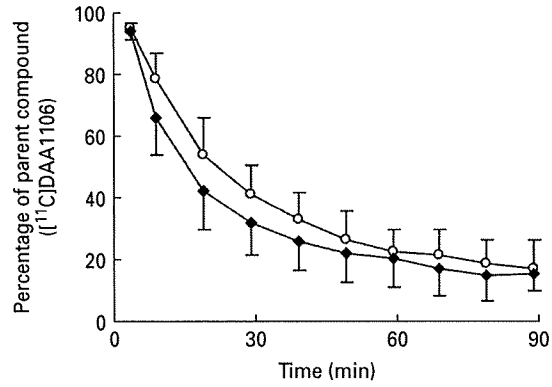

Fig. 1. Mean time-course of the percentage of parent compound ([^{11}C]DAA1106) after venous injection of [^{11}C]DAA1106 between normal controls (–○–) and patients (–◆–) with schizophrenia.

Data analysis

Eleven regions of interest (ROIs) (medial frontal cortex, dorsolateral frontal cortex, medial temporal cortex, lateral temporal cortex, parietal cortex, occipital cortex, thalamus, striatum, cerebellum, anterior cingulate cortex, and posterior cingulate cortex) were delineated on the co-registered PET/MRI images. In addition to each regional ROI, eight cortical ROIs (medial frontal cortex, dorsolateral frontal cortex, medial temporal cortex, lateral temporal cortex, parietal cortex, occipital cortex, anterior cingulate cortex, and posterior cingulate cortex) were also summed up as total cortical regions.

Regional time–activity data were analysed with two-tissue compartment model (2-TC) with the metabolite-corrected plasma input function, a model demonstrated to estimate binding potential (BP_{ND}) most reliably for [^{11}C]DAA1106 (Ikoma *et al.* 2007). Rate constants were estimated with weighted least squares and the Marquardt optimizer. For each region, k_1, k_2, k_3, k_4 and blood volume were estimated by 2-TC. BP_{ND} was calculated as k_3/k_4 in this analysis. Data analysis was performed with PMOD 2.65 (PMOD Technologies, Switzerland).

Statistical analysis

Regional ROIs

Statistical analysis of the difference of regional BP_{ND} for each ROI (for total 11 ROIs) between patients and normal controls was performed by repeated-measures ANOVA ($p < 0.05$ was considered significant). When any interaction was found, *post-hoc* Bonferroni correction was used for multiple comparisons.

Table 2. Significant correlation between PANSS scores and regional [^{11}C]DAA1106 binding

PANSS scores	Region	*p* value
Positive symptom	Medial frontal cortex	0.002*
	Dorsolateral frontal cortex	0.022
	Medial temporal cortex	0.003*
	Lateral temporal cortex	0.013
	Parietal cortex	0.005
	Occipital cortex	0.001*
	Cerebellum	0.022
	Striatum	0.010
Negative symptom	None	
General symptom	Medial frontal cortex	0.018
	Medial temporal cortex	0.027
	Occipital cortex	0.038
Total score	Medial frontal cortex	0.012
	Medial temporal cortex	0.029
	Parietal cortex	0.044
	Occipital cortex	0.017

PANSS, Positive and Negative Syndrome Scale.
* $p < 0.0045$ (0.05/11).

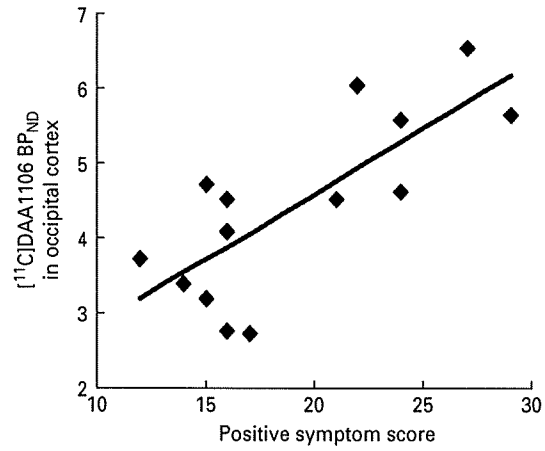

Fig. 2. Positive correlation between [^{11}C]DAA1106 BP_{ND} in the occipital cortex and positive symptom scores in the Positive and Negative Syndrome Scale.

Correlation between regional BP_{ND} values and PANSS scores were analysed with Pearson's correlation method ($p < 0.05$ was considered significant).

Correlation between regional BP_{ND} values and duration of illness, duration of drug treatment, and chlorpromazine equivalent doses (Inagaki *et al.* 1999) were analysed with Pearson's correlation method ($p < 0.05$ was considered significant).

Changes in regional BP_{ND} values with age were analysed with Pearson's correlation method for patients and normal controls, respectively ($p < 0.05$ was considered significant).

Total cortical regions

For analysing differences in total cortical regions between patients and normal controls, Student's *t* test was used ($p < 0.05$ was considered significant).

Correlations between BP_{ND} values in total cortical regions and PANSS scores were analysed with Pearson's correlation method ($p < 0.05$ was considered significant).

Correlation between BP_{ND} values in total cortical regions and duration of illness, duration of drug treatment, and chlorpromazine-equivalent doses (Inagaki *et al.* 1999) were analysed with Pearson's correlation method ($p < 0.05$ was considered significant).

Changes in BP_{ND} values in total cortical regions with age were analysed with Pearson's correlation method for patients and normal controls, respectively ($p < 0.05$ was considered significant).

Results

Regional ROIs

Comparison of regional BP_{ND} values for [^{11}C]DAA1106 between the patients with schizophrenia and normal controls by two-way repeated ANOVA with Greenhouse–Geisser correction showed no significant group × region interaction ($F_{1.7,44.4} = 0.542$, $p = 0.558$).

For the correlation analysis between BP_{ND} values in regional ROIs and positive symptom scores in the patient group, significant correlations were found in regions such as the medial frontal cortex, medial temporal cortex and occipital cortex (Table 2) (Fig. 2). No correlation was found between BP_{ND} values of each region and negative symptoms. Those three regions showed trends of positive correlation with general symptoms and total score (Table 2). There was no significant correlation between regional BP_{ND} and the duration of illness.

There was no significant change of regional BP_{ND} values with age in normal controls, whereas significant changes in BP_{ND} values with age in the patients with schizophrenia were observed in the occipital cortex ($p = 0.014$), lateral temporal cortex ($p = 0.023$), parietal cortex ($p = 0.023$), medial temporal cortex ($p = 0.031$), and medial frontal cortex ($p = 0.036$).

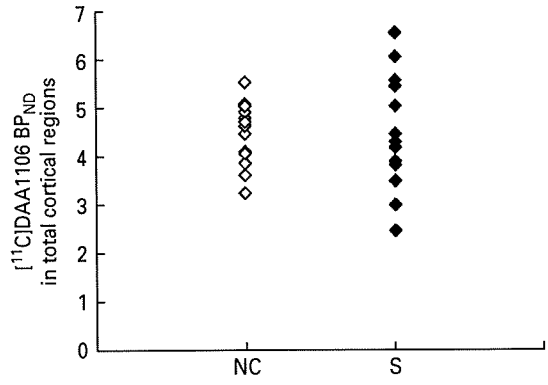

Fig. 3. Comparison of [^{11}C]DAA1106 BP_{ND} of total cortical regions between normal controls (NC) and patients with schizophrenia (S).

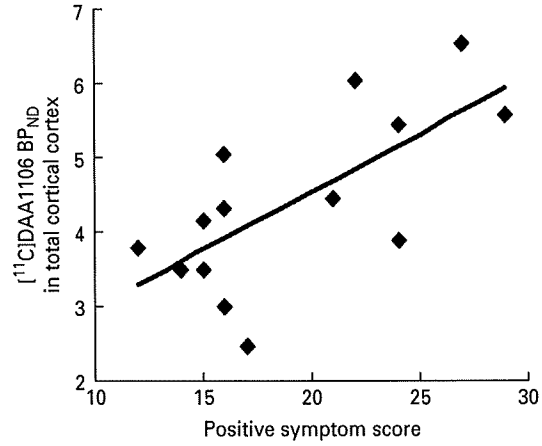

Fig. 4. Positive correlation between [^{11}C]DAA1106 BP_{ND} in the total cortical region and positive symptom scores in the Positive and Negative Syndrome Scale.

Total cortical regions

There was no significant difference of BP_{ND} values in total cortical regions between patients with schizophrenia and normal controls (Fig. 3). Significant correlation was found with the positive symptom scores ($p=0.006$) (Fig. 4). There was no significant correlation with other symptom scores (negative, general, and total symptom scores). Total cortical regions were correlated with duration of illness ($p=0.020$) (Fig. 5) and duration of drug treatment ($p=0.023$). BP_{ND} of total cortical regions was not correlated with chlorpromazine-equivalent doses.

There was no significant change of BP_{ND} values in total cortical regions with age in normal controls, but significant changes of BP_{ND} values with age were observed in total cortical regions of the patients with schizophrenia ($p=0.018$).

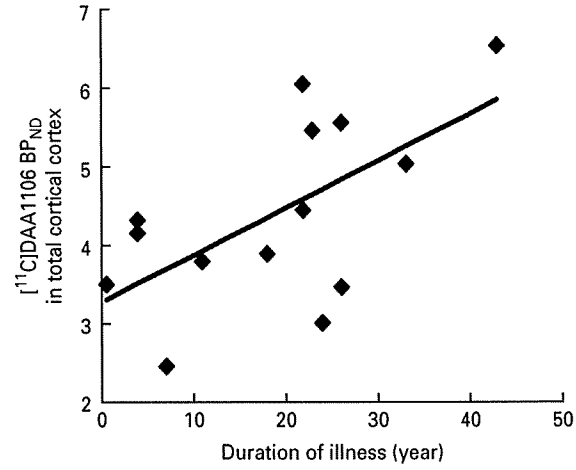

Fig. 5. Positive correlation between [^{11}C]DAA1106 BP_{ND} in the total cortical region and duration of illness.

Discussion

In this study, [^{11}C]DAA1106 binding, which was considered to correspond to the density of PBR, was not different between the patients with chronic schizophrenia and normal controls. A recent study demonstrated that [^{11}C]PK11195 binding increased in total grey matter in patients with acute-onset schizophrenia (van Berckel *et al.* 2008). Another recent study reported that [^{11}C]PK11195 binding in the hippocampus was significantly increased in patients with schizophrenia during acute psychosis, while there was no significant difference in other regions compared with normal controls (Doorduin *et al.* 2009). To understand the difference in the results between the present study and the two [^{11}C]PK11195 studies, several factors, such as the use of different radioligands and different patient groups, should be taken into consideration. Although PK11195 fully displaced the [^{3}H]DAA1106 binding (Chaki *et al.* 1999), a high concentration of PK11195 was required for this displacement. This suggested that the binding domain for DAA1106 contains an extra component that does not interact efficiently with PK11195 (Chaki *et al.* 1999). The mean age of patients with schizophrenia enrolled in the present study was higher (44 yr in 14 patients) than those in the two [^{11}C]PK11195 studies (24 yr in 10 patients, and 31 yr in seven patients). Most of the patients in the present study were at the chronic stage.

Within the patient group, [^{11}C]DAA1106 binding had a significant correlation with the positive symptom score of PANSS, a finding that might be in line

with those recent findings with [^{11}C]PK11195. The present results might indicate that the activated neuroimmune system was related to the pathophysiology of schizophrenia at the chronic stage.

In previous MRI volumetric research in schizophrenia, volume reduction in the brain has been reported in patients with chronic schizophrenia (Shenton *et al.* 2001). However, in the present study, there was no significant difference in the volume of ROIs by ANOVA, and total cortical ROI by Student's *t* test between the patients and normal controls (data not shown). Thus, the insignificance of the difference of [^{11}C]DAA1106 binding between the patients and normal controls is not related to the partial volume effect due to brain atrophy.

In this study, normal controls showed no age effects on [^{11}C]DAA1106 binding in any region. This is in line with the report with [^{11}C]PK11195 binding except the thalamus, where [^{11}C]PK11195 binding was reported to increase with age (Cagnin *et al.* 2001). This might be due to different radioligands or different age ranges between the two studies (24–55 yr in this study and 32–80 yr in the [^{11}C]PK11195 study). On the other hand, [^{11}C]DAA1106 binding was found to increase with age in patients with schizophrenia. Schizophrenia has been considered to be progressive in functional disability and morphological changes (Lieberman *et al.* 2001; Mathalon *et al.* 2001; Saijo *et al.* 2001). The present results of the positive correlation among [^{11}C]DAA1106 binding, duration of illness, and age might suggest that the progressive change occurs at the glial reaction level.

A recent meta-analysis showed that some cytokines such as IL-1RA, sIL-2R, and IL-6 are increased in schizophrenia (Potvin *et al.* 2008). PBR has been considered to modulate the release of pro-inflammatory cytokines in the CNS. PBR was reported to modulate the release of the inflammatory molecules NO and tumour necrosis factor-alpha (TNF-α) (Wilms *et al.* 2003). A PBR ligand, PK11195, has been reported to inhibit lipopolysaccharide-induced expressions of COX-2 and TNF-α in human microglia (Choi *et al.* 2002). Immunomodulatory drugs such as cyclooxygenase-2 (COX-2) inihibitors have been reported to show beneficial effects in schizophrenia (Muller & Schwarz, 2008). The combination of risperidone and COX-2 inhibitor has been reported to show superiority over risperidone alone in positive symptoms and PANSS total scores (Akhondzadeh *et al.* 2007). On the other hand, cytokines such as IL-2 and IL-6 are reported to increase after olanzapine and clozapine treatment (Kluge *et al.* 2009). The present results of PBR binding in the patients with schizophrenia might be in accord with the previous reports of cytokines.

A recent report demonstrated that PBR expression was not confined to microglia but was inducible in nervous tissue cells of neuroepithelial origin (Ji *et al.* 2008). Thus, PBR binding might also arise from astrocytes and other non-microglial elements. Schizophrenia patients with high S100B serum concentration, considered to indicate astrocyte activation, were reported to have cognitive dysfunction compared with patients with low S100B serum concentration (Pedersen *et al.* 2008). DAA1106 binding in patients with schizophrenia might also be related to the change in PBR on astrocytes.

In a post-mortem study, a subgroup of the patients with schizophrenia who committed suicide had increased microglial densities, although microglial HLA-DR expression in the patients with schizophrenia was not different from normal controls (Steiner *et al.* 2008). Microglial activation has been suggested to be interpretable as a consequence of presuicidal stress (Avital *et al.* 2001; Lehmann *et al.* 2002).

Although BP_{ND} of total cortical regions was not correlated with chlorpromazine-equivalent doses in the present study, some antipsychotics were reported to have anti-inflammatory effects (Kato *et al.* 2007; Kowalski *et al.* 2003, 2004; Labuzek *et al.* 2005; Zheng *et al.* 2008). The effect of antipsychotics on DAA1106 binding remains to be studied.

There are several confounding factors in the present study. First, the number of subjects was relatively small. Further larger-scale studies will be needed to confirm the present results. Second, all the patients were under different kinds of antipsychotic treatment. Further study is needed with drug-naive patients and patients under well-controlled drug treatment. Third, the PANSS scores of patients were higher as the duration of the illness was longer and age increased. This might reflect a possible subgroup of treatment-resistant patients.

In conclusion, we found no significant differences in PBR binding between the brains of patients with schizophrenia and those of normal control subjects, unlike recent reports with [^{11}C]PK11195 (van Berckel *et al.* 2008; Doorduin *et al.* 2009). Nevertheless, PBR binding in the patients with schizophrenia was correlated with positive symptoms, disease duration and age. The present results suggest that the glial reaction process might be involved in the pathophysiology of schizophrenia. Although the correlations should be interpreted with caution, these results at least suggest that additional studies are warranted in order to determine whether baseline

differences exist between patients with schizophrenia and healthy subjects, as well as to reveal the biological meanings of the correlations with disease parameters.

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Statement of Interest

None.

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Decreased binding of [^{11}C]NNC112 and [^{11}C]SCH23390 in patients with chronic schizophrenia

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ABSTRACT

Aims: Abnormality of cognitive function in schizophrenia has been suggested to be related to dopamine D_1 receptor. However, the results of previous positron emission tomography (PET) studies of dopamine D_1 receptor in schizophrenia were not consistent.
Main methods: In this study, six patients with schizophrenia in severe residual phase with chronic antipsychotic treatment and twelve healthy age-matched controls participated. Two different radioligands, [^{11}C]NNC112 and [^{11}C]SCH23390, for dopamine D_1 receptor were used on the same subjects. Binding of the ligands was measured by PET, and statistical analysis was performed using one-way analysis of covariate (ANCOVA) with age as covariate.
Key findings: Good correlations between binding potential values (BP_{ND}) and age were observed in all regions of interest (ROIs) with both ligands. ANCOVA with age as covariate of BP_{ND} values of all ROIs revealed that the patient group showed significantly lower BP_{ND} value compared with the control group in both ligands.
Significance: In patients with chronic schizophrenia in severe residual phase with chronic antipsychotic treatment, the binding potential values of both ligands were significantly lower in the striatum and cortical regions than those of healthy controls.

Introduction

Schizophrenia is a chronic illness characterized by positive, negative, cognitive and affective symptoms (Schultz and Andreasen 1999). Although a positive symptom is characteristic of schizophrenia in the acute phase, the characteristic symptoms in the severe residual phase are negative symptom and cognitive dysfunction. The dopamine hypothesis is widely accepted for the pathophysiology of schizophrenia. Regarding dopamine receptors, the density of dopamine D_1 receptor in the cortical region is several times higher than that of dopamine D_2 receptor (Lidow et al. 1998). Abnormality of cognitive function in schizophrenia has been suggested to be related to dopamine function in the prefrontal cortex (Sawaguchi and Goldman-Rakic 1991). Dopamine D_1 receptor plays important roles in cognitive function such as working memory (Goldman-Rakic, 2000). One postmortem study has reported low dopamine D_1 receptors in the striatum in patients with schizophrenia (Hess et al. 1987), but no significant change has been reported in other studies (Seeman et al. 1987; Czudek and Reynolds 1988; Knable et al. 1994). In vivo PET studies reported decreased (Okubo et al. 1997), unaltered (Karlsson et al. 2002), and increased (Abi-Dargham et al. 2002) binding of D_1 receptor in patients with schizophrenia compared with control subjects. Those results were possibly influenced by parameters of the particular patient populations including duration of illness, symptoms and medications. In addition, differences in radioligand [^{11}C]SCH23390 (Okubo et al. 1997; Karlsson et al. 2002) and [^{11}C]NNC112 (Abi-Dargham et al. 2002) were suggested to account for inconsistent PET findings. Furthermore, subjects were medication-free or -naïve patients with schizophrenia in the prodromal, acute or active phase, and the duration of untreated illness may have influenced the difference in dopamine D_1 receptor binding in previous human PET studies.

The purpose of the present study was to compare the dopamine D_1 receptor binding of chronic patients with schizophrenia in severe residual phase with chronic antipsychotic treatment to that of healthy controls in the striatum and extrastriatal regions using both [^{11}C]SCH23390 and [^{11}C]NNC112 in the same subjects.

Materials and methods

Subjects

Six patients with schizophrenia, 1 female and 5 males aged 46.5 ± 8.2 years (mean ± SD), participated in this study (Table 1). All patients

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