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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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Table 1
Clinical characteristics of patients.

Patient no.	Age (years)	Gender	Diagnosis (DSM-IV)	Dose of sulpiride (mg)	Duration of illness (years)	PANSS			
						Positive	Negative	General	Total
1	32	M	295.30	1200	15	16	21	30	67
2	45	F	295.30	600	28	25	26	49	100
3	47	M	295.30	1200	8	18	23	44	85
4	47	M	295.30	1000	25	23	26	47	96
5	52	M	295.10	1200	5	13	33	46	92
6	56	M	295.60	600	29	20	43	59	122
Mean ± SD	46.5 ± 8.2			966.7 ± 294.4	18.3 ± 10.5	19.2 ± 4.4	28.7 ± 8.1	45.8 ± 9.4	93.7 ± 18.1

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; PANSS, Positive and Negative Scale for Schizophrenia; M, Male; F, Female.

met the criteria of the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) for diagnosis of schizophrenia. The diagnosis was assessed by Structured Clinical Interview for DSM-IV by three psychiatrists. The patients underwent general medical and laboratory evaluation. Organic brain disease was ruled out by CT, T1-weighted magnetic resonance (MR) images, and electroencephalogram.

Prior to this study, they had been prescribed antipsychotics during the periods indicated as 'duration of illness' in Table 1. In chlorpromazine equivalents, daily doses ranged from 200 mg to 606 mg and mean dose was 384 ± 139 mg/day (Inagaki and Inada 2006).

In all patients, the previously used antipsychotic drugs were changed to sulpiride, a selective dopamine D_2/D_3 receptor antagonist without affinity to dopamine D_1 receptor. PET scans were performed after a washout period of at least three weeks after changing to sulpiride. Sulpiride was maintained at the same dosage during the washout period. Because of extrapyramidal side effects, two patients were administered a relatively low dose of sulpiride (600 mg), although there had been no exacerbation of their psychic symptoms. All patients underwent clinical ratings of their psychopathology using the positive and negative syndrome scale (PANSS; Kay et al. 1987), and the following cognitive function tests: Wisconsin Card Sorting Test (Heaton 1981) to evaluate executive function, Stroop test (Cohen and Servan-Schreiber 1992) and *n*-back tasks (2-back minus 0-back using letters as stimulus; Cohen et al. 1994; Owen et al. 2005) to evaluate working memory.

The healthy control sample consisted of 6 females and 6 males, age-matched at 42.8 ± 8.5 years. Based on unstructured psychiatric screening interviews, none had a history of neurological or psychiatric illness. Organic brain disease was ruled out by T1-weighted MRI.

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

PET and MRI procedures

All patients except patient #6 (Table 1) underwent both PET scans using [^{11}C]NNC112 and [^{11}C]SCH23390 on the same day. Patient #6 and twelve healthy controls underwent each of the PET scans with [^{11}C]NNC112 and [^{11}C]SCH23390 within several days. The PET system ECAT EXACT HR+ (CT1-Siemens, Knoxville, TN) was used for all PET studies. The system provides 63 planes with a 15.5 cm axial field of view. After a transmission scan with a ^{68}Ge–^{68}Ga source, a bolus of [^{11}C]NNC112 or [^{11}C]SCH23390 was rapidly injected into the antecubital vein with a 20-ml saline flush. Injected radioactivity and specific radioactivity were 220.5 ± 9.25 MBq and 140.0 ± 64.1 GBq/μmol for patients in the [^{11}C]NNC112 studies, 215.0 ± 14.1 MBq and 152.5 ± 50.6 GBq/μmol for controls in the [^{11}C]NNC112 studies, 200.2 ± 15.9 MBq and 59.7 ± 15.5 GBq/μmol for patients in the [^{11}C]SCH23390 studies, and 220.5 ± 18.1 MBq and 68.6 ± 11.0 GBq/μmol for controls in the [^{11}C]SCH23390 studies, respectively.

Radioactivity in the brain was measured by a series of scans for 90 min for [^{11}C]NNC112 or 60 min for [^{11}C]SCH23390, starting immediately after the injection. During image acquisition, the subjects were instructed to lie quietly with their eyes closed and earplugs in place. Image reconstruction was performed with a Hanning filter with a cut-off frequency of 0.4, a value experientially determined for the purpose of noise reduction, resulting in a final spatial resolution of 7.5 mm FWHM (full width at half maximum).

T1-weighted MR images were acquired on Philips Gyroscan NT, 1.5 T (Philips Medical Systems, Best, The Netherlands). Scan parameters were 1-mm-thick 3D images with a transverse plane (repetition time, TR/echo time, TE 21/9.2 ms, flip angle 30°, matrix 256 × 256, field of view (FOV) 256 × 256), yielding 196 contiguous slices of the head.

PET data analysis

Regions of interest (ROIs) were manually drawn on the transverse slices from each subject's PET summation images referred from MRI images coregistered to the reconstructed PET images. ROIs were set to cover 3 adjacent slices for the striatum including both the caudate nucleus and the putamen, anterior cingulate, cerebellum, temporal cortex and frontal cortex including the superior frontal gyrus, middle frontal gyrus, and inferior frontal gyrus, which roughly corresponds to dorsolateral prefrontal cortex. The sets of ROIs for each section were transferred to the corresponding PET images, and time–activity curves (TACs) were obtained. The TACs of each region were analyzed using a simplified reference tissue model in a least-squares manner, in which the cerebellum was used as reference tissue (Lammertsma and Hume 1996). This procedure produced the binding potential (BP_{ND}; Innis et al. 2007) value.

Statistical analysis

Statistical analysis of the regional BP_{ND} obtained from patients with schizophrenia and healthy control subjects was performed using one-way analysis of covariance (one-way ANCOVA) with age as covariate using SPSS for Windows 16.0.2J (SPSS Inc, Chicago, Illinois, USA 2008), and post hoc Bonferroni correction was used for multiple comparisons. p value $< 0.05/4 = 0.0125$ was considered significant.

Results

Table 1 lists the clinical profiles of the patients. The average duration of illness after schizophrenia diagnosis was 18.3 years. Scores of the two cognitive functional tests are shown in Table 2, and significant group effects were found in each cognitive function test. Because four patients, #2, #3, #5 and #6, were not able to do *n*-back task (2 back), results were not shown in Table 2.

Significant correlations between BP_{ND} and age were observed in patients with [^{11}C]NNC112 (frontal cortex, $r = -0.924$, $p = 0.004$; striatum, $r = -0.981$, $p = 0.001$), controls with [^{11}C]NNC112 (striatum, $r = -0.886$, $p < 0.001$) and controls with [^{11}C]SCH23390 (frontal cortex, $r = -0.757$, $p = 0.004$; striatum, $r = -0.700$, $p = 0.011$). Trend

Table 2
Cognitive task scores of patients.

Patient no.	W-CST			Stroop test	
	Category	PEN	DMS	Error	Time score
1	6	0	0	0	17.4
2	2	9	5	11	46.6
3	1	7	3	1	7.4
4	5	1	1	0	5.4
5	2	14	0	2	68
6	Incapable	Incapable	Incapable	2	75
Mean ± SD	3.2 ± 2.2	6.2 ± 5.8	1.8 ± 2.2	2.7 ± 4.2	36.6 ± 30.8
Controls					
Mean ± SD	4.7 ± 1.6	1.4 ± 2.0	0.8 ± 1.4	0.8 ± 1.2	5.6 ± 4.0

W-CST, Wisconsin card sorting test; PEN, errors of nelson; DMS, difficulty in maintaining set.

level correlations were observed in other regions and patients with [^{11}C]SCH23390.

All BP_{ND} values of both ligands are shown in Fig. 1 and summarized in Table 3. ANCOVA with age as covariate ($df = 1,15$) 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 ([^{11}C]NNC112: temporal cortex, $F = 26.24$, $p < 0.001$; striatum, $F = 60.08$, $p < 0.001$; anterior cingulate cortex, $F = 9.14$, $p = 0.009$; frontal cortex, $F = 42.96$, $p < 0.001$, [^{11}C]SCH23390: temporal cortex, $F = 34.68$, $p < 0.001$; striatum, $F = 25.46$, $p < 0.001$; anterior cingulate cortex, $F = 8.91$, $p = 0.009$; frontal cortex, $F = 37.60$, $p < 0.001$). There was significant correlation between average BP values of [^{11}C]NNC112 weighted by ROI size and that of [^{11}C]SCH23390 ($r = 0.859$; $BP_{NNC} = 0.613\ BP_{SCH} + 0.0414$).

There was no significant correlation between BP_{ND} values and doses of antipsychotic drugs and between BP_{ND} values and PANSS scores for positive symptom, negative symptom, general symptom and total score in any of the brain regions.

Discussion

Both [^{11}C]NNC112 and [^{11}C]SCH23390 bindings in the striatum and cortical regions of patients with schizophrenia in severe residual phase were significantly lower compared with healthy controls. In previous PET studies of patients with schizophrenia who were antipsychotics-naïve or -free, BP of [^{11}C]SCH23390 was decreased (Okubo et al. 1997) or unchanged (Karlsson et al. 2002), and was increased when measured by [^{11}C]NNC112 (Abi-Dargham et al. 2002). Several differences in those studies have been discussed, including those regarding duration of illness, medications, race, severity of symptoms and radioligands. Guo et al. (2003) reported different characteristics of in vivo binding of the two radioligands in rat brain, increased [^{11}C]NNC112 binding and decreased [^{3}H]SCH23390 binding, following subchronic dopamine depletion with reserpine. But the inconsistent results cannot be explained solely by the difference of radiotracers, and demographics of patients might have been contributing factors.

Although [^{11}C]SCH23390 and [^{11}C]NNC112 are selective radioligands for dopamine D_1 receptor, both ligands have some affinity for 5-

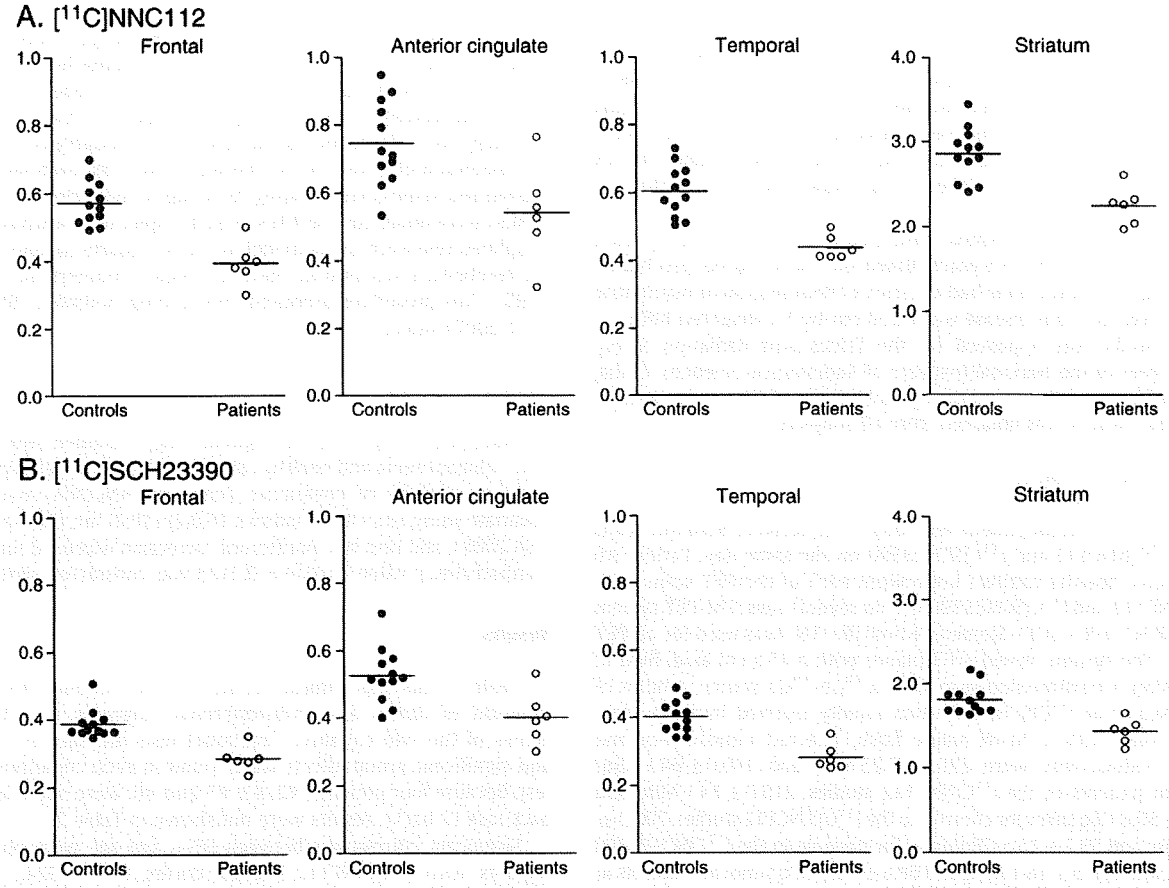

Fig. 1. BP_{ND} values of all subjects in both ligands [^{11}C] NNC112 and [^{11}C]SCH23390. Filled circles represent controls and open circles represent patients. A. BP_{ND} measured by [^{11}C] NNC112; B. BP_{ND} measured by [^{11}C]SCH23390. The horizontal line represents the group mean. In all ROIs, statistically significant differences were observed between patients with schizophrenia and healthy controls (one-way ANCOVA with age as covariate, $p < 0.0125 = 0.05/4$).

Table 3
[^{11}C] NNC112 and [^{11}C]SCH23390 binding potential.

Region	[^{11}C]NNC112				[^{11}C]SCH23390			
	Controls ($n=12$)	Patients ($n=6$)	p value	Reduction (%)	Controls ($n=12$)	Patients ($n=6$)	p value	Reduction (%)
Frontal cortex	0.57 ± 0.064	0.39 ± 0.065	<0.001*	31.2	0.39 ± 0.043	0.28 ± 0.037	<0.001*	26.7
Anterior cingulate	0.75 ± 0.12	0.54 ± 0.14	0.009*	27.2	0.53 ± 0.083	0.40 ± 0.079	0.009*	23.5
Temporal cortex	0.61 ± 0.074	0.44 ± 0.037	<0.001*	27.7	0.40 ± 0.048	0.28 ± 0.038	<0.001*	29.9
Striatum	2.85 ± 0.31	2.25 ± 0.23	<0.001*	21.4	1.83 ± 0.18	1.45 ± 0.15	<0.001*	20.9

Data are mean ± SD.
* $p<0.0125$ (=0.05/4, Bonferroni corrected) ANCOVA with age as covariate ($df=1,15$).

HT_{2A} receptor (Slifstein et al. 2007). However, Okubo et al. (2000) reported no difference in binding in the prefrontal cortex using [^{11}C]N-methylspiperone as ligand for 5-HT2 receptor in the same schizophrenia patients who showed lower binding with [^{11}C]SCH23390 (Okubo et al. 1997) and a non-significant trend towards decreased binding. In this study, all patients were medicated with only sulpiride as antipsychotic drug. Sulpiride is a selective dopamine D_2 antagonist and has negligible affinity to dopamine D_1 receptor in vivo (Farde et al. 1989). All antipsychotics of the patients were changed to sulpiride. Even though sulpiride had no direct affinity to dopamine D_1 receptor, these patients had been receiving long-term chronic antipsychotic treatment. Several studies of primates have reported that chronic administration of dopamine D_2 receptor antagonist decreased the density of dopamine D_1 receptor (Lidow and Goldman-Rakic 1994; Lidow et al. 1997), although one animal study has reported that there was no influence of chronic medication on dopamine D_1 receptor density (Sanci et al. 2002). Hirvonen et al. (2006) reported a widespread reduction of D_1 receptor binding in the brain in patients with schizophrenia, which was associated with antipsychotic medication dose. However, we did not find a correlation between them, possibly due to a lack of variance in antipsychotic dose.

The patients in this study were in a very severe residual phase according to the deficits in the cognitive test scores (Table 2) and the high total scores of PANSS despite the low positive symptom scores (Table 1). Some studies have reported regional structural brain abnormalities of gray matter in the striatum and extrastriatal regions of schizophrenia patients with chronic antipsychotic treatment (Jernigan et al. 1991; Tamagaki et al. 2005). In this study, since we confirmed that there was no significant difference between the volume of each ROI in patients and that of controls, we measured the gray matter volume ratio in each ROI. The results revealed no significant difference between the gray matter volume in patients and that of controls in each ROI (data not shown). The values of reduction in BP_{ND} shown by percentage (Table 3) seemed considerably larger than the reduction of gray matter. However, the effect of brain gray matter reduction cannot also be ruled out.

Our results indicated lower dopamine D_1 receptor binding in schizophrenia patients with chronic antipsychotic treatment measured by different radioligands, [^{11}C]NNC112 and [^{11}C]SCH23390. However, as the small sample size was a distinct limitation of this study, a larger study population will be necessary to more definitively examine the relation between dopamine D_1 receptor binding and factors such as duration of illness and severity of symptoms.

Conflict of interest statement

There are no conflicts of interests.

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