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ARTICLE

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

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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.

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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

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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-hydroxyrisperidone (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.

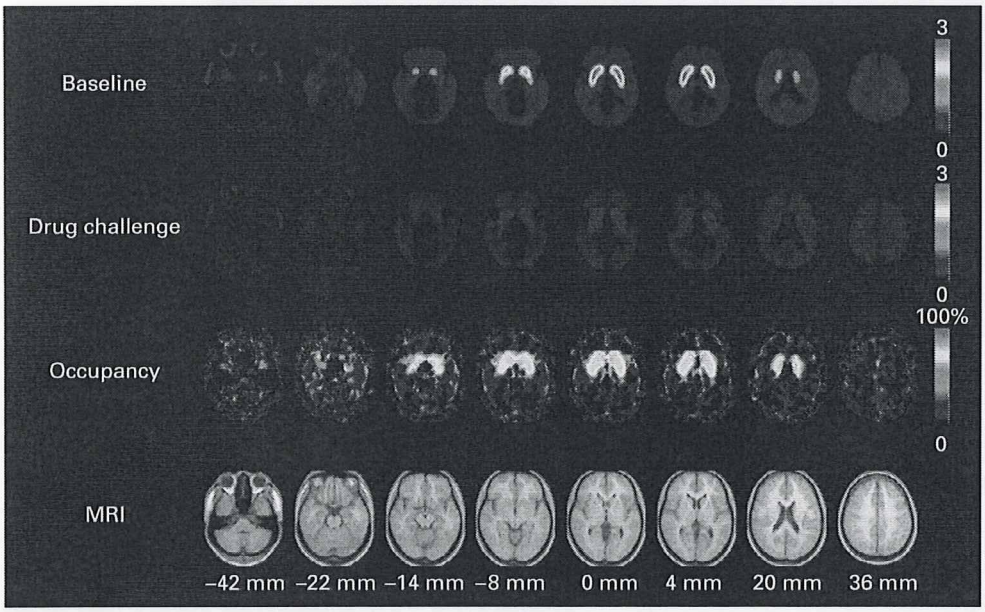

Figure 1. Average images of binding potential at baseline condition and after administration of risperidone, dopamine D_2 receptor occupancy for [^{11}C]raclopride, and T_1-weighted images. In the striatum, no obvious regional differences in dopamine D_2 receptor occupancy were observed.

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

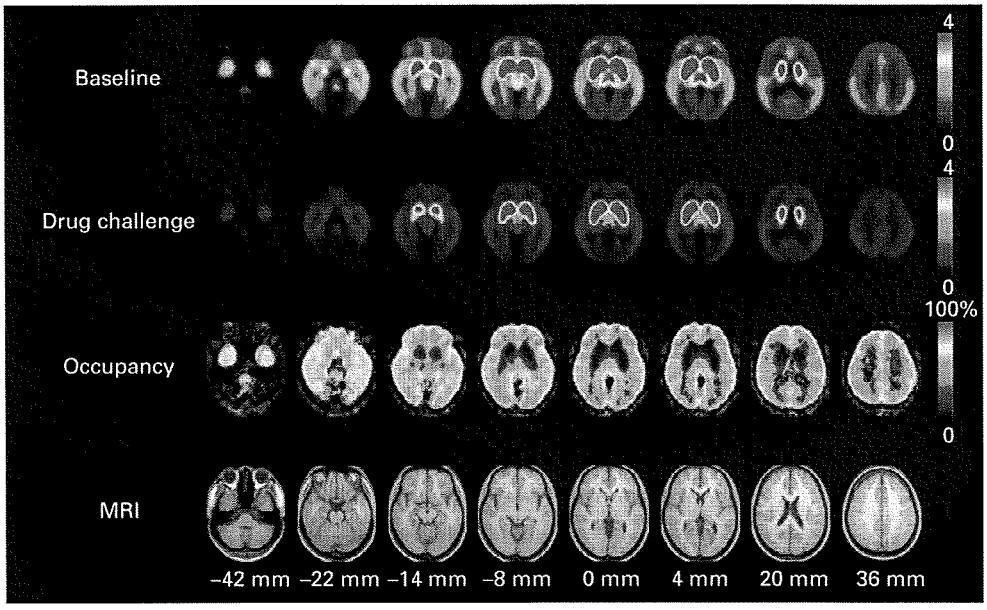

Figure 2. Average images of binding potential at baseline condition and after administration of risperidone, dopamine D_2 receptor occupancy for [^{11}C]FLB 457, and T_1-weighted images. Among extrastriatal regions, no obvious regional differences in dopamine D_2 receptor occupancy were observed.

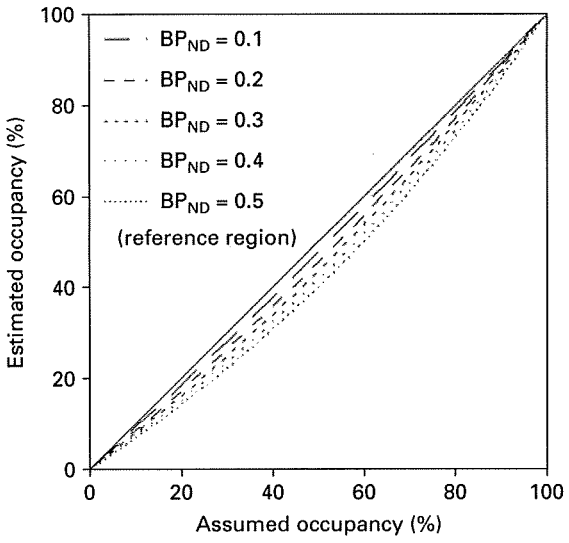

Figure 3. Relation between the assumed and estimated occupancies of dopamine D_2 receptors for [^{11}C]FLB 457 in simulation studies. Binding potential (BP_{ND}) in the reference region was varied from 0.1 to 0.5. Systematic underestimation in estimated occupancy was caused by specific binding in the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

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Statement of Interest

None.

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ORIGINAL PAPER

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

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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

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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

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.

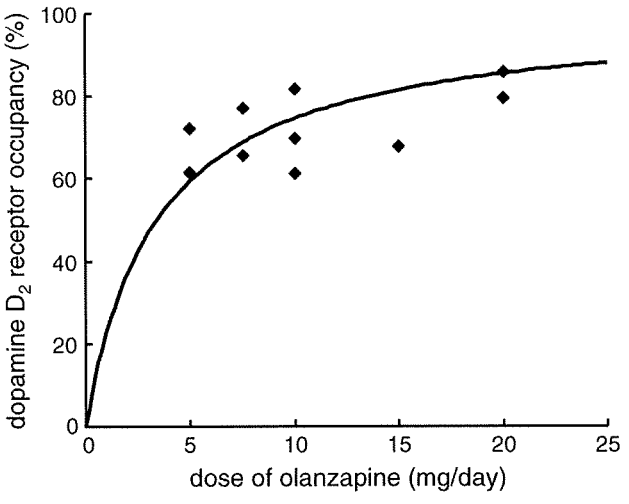

Fig. 1 Relationship between dopamine D_2 receptor occupancy and daily dose of olanzapine

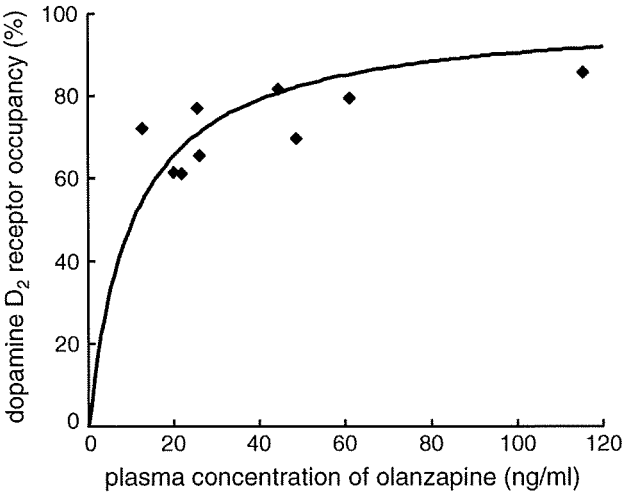

Fig. 2 Relationship between dopamine D_2 receptor occupancy and plasma concentration of olanzapine

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.

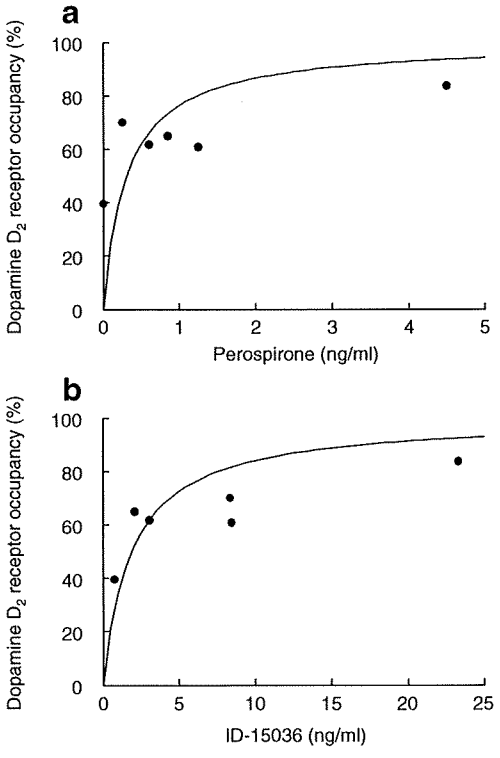

Fig. 1 Relationship between dopamine D_2 receptor occupancy and perospirone (**a**) and ID-15036 (**b**) in the patients study

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

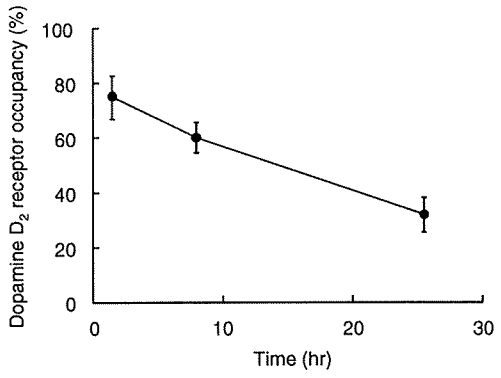

Fig. 2 Time course of mean dopamine D_2 receptor occupancy in healthy subject study. *Bars* represent standard deviation of mean

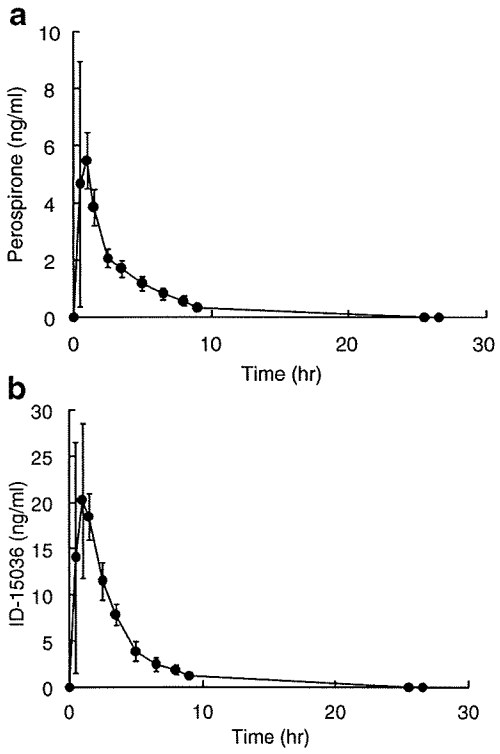

Fig. 3 Time course of mean plasma concentrations of perospirone (**a**) and ID-15036 (**b**) in healthy subjects study. *Bars* represent standard deviation of mean

benzodiazepines or anti-Parkinson drugs, and plasma prolactin levels were not measured.

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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