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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:

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

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.

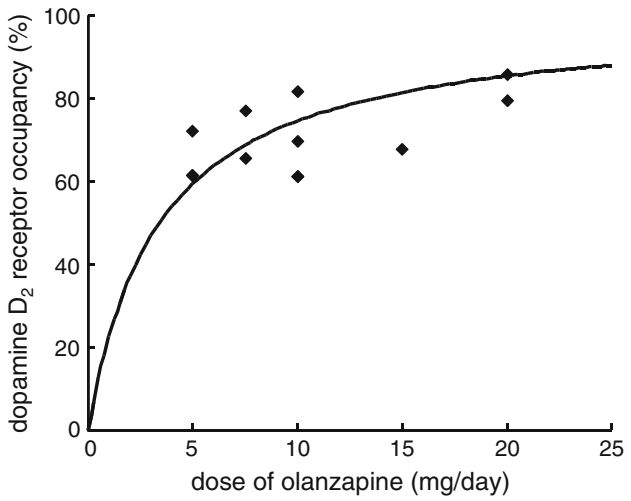

Fig. 1 Relationship between dopamine D_2 receptor occupancy and daily dose of olanzapine

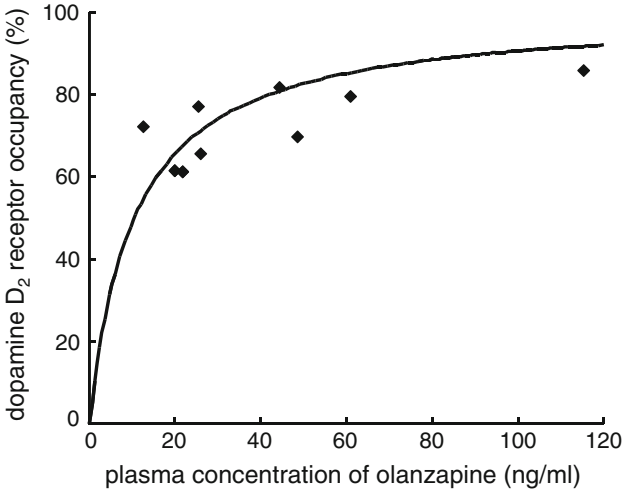

Fig. 2 Relationship between dopamine D_2 receptor occupancy and plasma concentration of olanzapine

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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