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 neureceptors other than dopamine D$_2$ receptors, in particular 5-HT$_{1A}$ receptors, has been suggested to reduce extrapyramidal side-effects (Balsara et al., 1979; Hicks, 1990; Korsgaard et al., 1985). Fast dissociation
from dopamine D₂ 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 D₂ 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 D₂ receptor occupancy by clozapine in patients with schizophrenia using [123I]epidepride (Pilowsky et al., 1997), [3H]BrFLB 457 (Xiberas et al., 2001) and [3F]allypride (Gründler et al., 2006; Kessler et al., 2006). Limbic and cortical selectivity was also reported in other second-generation antipsychotics, e.g. risperidone using [3H]BrFLB 457 (Xiberas et al., 2001) and [123I]epidepride (Bressan et al., 2003), olanzapine using [3H]BrFLB 457 (Xiberas et al., 2001), and quetiapine using [3F]allypride (Kessler et al., 2006) in patients with schizophrenia. On the other hand, no differences in occupancy of dopamine D₂ 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 D₂ receptors were quite different (Hall et al., 1994), were determined by [11C]raclopride and [11C]FLB 457, respectively. In addition, limbic and cortical selectivity was not supported using [3F]allypride with olanzapine in patients with schizophrenia taking clozapine (Talvik et al., 2001) or 9-hydroxyrisperidone (paliperidone) (Arakawa et al., 2008). In these studies, binding to receptors in striatal and extrastriatal regions, in which densities of dopamine D₂ receptors were quite different (Hall et al., 1994), were determined by [11C]raclopride and [11C]FLB 457, respectively. In addition, limbic and cortical selectivity was not supported using [3F]allypride with olanzapine in patients with schizophrenia taking clozapine (Talvik et al., 2001) or 9-hydroxyrisperidone (paliperidone) (Arakawa et al., 2008).

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 68Ge–68Ga 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 [11C]raclopride and [11C]FLB 457 were performed sequentially. After intravenous rapid bolus injection of [11C]raclopride dynamic PET scanning was performed for 60 min. One hour after the end of [11C]raclopride PET measurement, dynamic PET scanning was performed for 90 min after intravenous rapid bolus injection of [11C]FLB 457. The frame sequence consisted of twelve 20-s frames, sixteen 1-min frames, and ten 4-min frames for [11C]raclopride, and nine 20-s frames, five 1-min frames, four 2-min frames, eleven 4-min frames, and six 5-min frames for [11C]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 [11C]raclopride.
and \(^{11}C\)FLB 457, respectively. The specific radioactivity was 114–297 GBq/\(\mu\)mol and 149–214 GBq/\(\mu\)mol in baseline studies, and 86–241 GBq/\(\mu\)mol and 141–230 GBq/\(\mu\)mol 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 (LC–MS/MS) method. The plasma concentrations of risperidone and 9-hydroxy-risperidone were 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 T1-weighted gradient echo sequence produced a gapless series of thin transverse sections (TE 9.2 ms; TR 21 ms; flip angle 30\(^\circ\); field of view 256 mm; acquisition matrix 256 \(\times\) 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:

\[
C_i(t) = R_i C_r(t) + |k_2 - R_i k_t|/(1 + BP_{ND}) \times C_r(t) \otimes \exp \{-k_t/(1 + BP_{ND})\},
\]

where \(C_i\) is the radioactivity concentration in a brain region, \(C_r(t)\) is the radioactivity concentration in the reference region, \(R_i\) is the ratio of \(k_2/K_i'\) (\(K_i\), influx rate constant for the brain region; \(K_i'\), 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\(_{ND}\), \(R_i\), and \(k_2\)) were estimated by nonlinear least-squares curve fitting. The cerebellum was used as a reference region. Dopamine D\(_2\) receptor occupancy by risperidone was calculated as follows:

\[
\text{Occupancy (\%)} = \frac{100 \times (\text{BP}_{ND, \text{baseline}} - \text{BP}_{ND, \text{drug}})}{\text{BP}_{ND, \text{baseline}}},
\]

where BP\(_{ND, \text{baseline}}\) is BP\(_{ND}\) in the baseline study, and BP\(_{ND, \text{drug}}\) 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):

\[
\text{Occupancy (\%)} = 100 \times C/(ED_{50} + C),
\]

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 T1 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 $BPND$ 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 $BPND$ 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 $BPND$ 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 $3 \text{ ml/ml}$ and $BPND$ of $0.1–0.5$ in five steps as $V_T = V_{ND}(1 + BPND)$ (Ito et al., 2001). $V_T$ in the target region was also calculated with $V_{ND} = 3 \text{ ml/ml}$ and $BPND = 3$. $V_T$ in the drug challenge study for both the target and reference regions was calculated with $BPND$ 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:

$$\text{Occupancy (\%)} = \frac{100 \times ((\text{DVR}_{baseline} - 1) - (\text{DVR}_{drug} - 1))}{(\text{DVR}_{baseline} - 1)},$$

(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 $BPND$ values and dopamine $D_2$ receptor occupancy are shown in Tables 1 and 2. The ranges of dopamine $D_2$ receptor occupancy are $71–76\%$ and $56–60\%$ for the striatum and extra-striatum 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 extra-striatal 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 $BPND$ 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 extra-striatal 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 $17.5 \pm 5.2 \text{ ng/ml}$ and $14.5 \pm 4.2 \text{ ng/ml}$ (mean $\pm$ S.D.), respectively. The $ED_{50}$ values were $5.1–6.4 \text{ ng/ml}$ for the striatum and $9.0–10.9 \text{ ng/ml}$ 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>
<thead>
<tr>
<th>Region</th>
<th>Baseline</th>
<th>Drug challenge</th>
<th>Occupancy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caudate head</td>
<td>$2.64 \pm 0.26$</td>
<td>$0.65 \pm 0.16$</td>
<td>$76 \pm 4$</td>
</tr>
<tr>
<td>Putamen</td>
<td>$3.41 \pm 0.38$</td>
<td>$0.98 \pm 0.24$</td>
<td>$71 \pm 4$</td>
</tr>
</tbody>
</table>

Values are mean $\pm$ S.D.
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 D₂ 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 [⁸⁸Br]FLB 457 (Xiberras et al., 2001) and [¹²⁴I]epidepride (Bressan et al., 2003).

In the present study, dopamine D₂ receptor occupancy in the striatum was higher than that in the cerebral cortices. The ED₅₀ values were also lower in the striatum than in the cerebral cortices corresponding with previous reports that ED₅₀ 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 [¹¹C]raclopride and [¹¹C]FLB 457, respectively. A simulation study showed that non-negligible specific binding in the cerebellum could cause an underestimation of 8% in dopamine D₂ receptor occupancy measured by [¹¹C]FLB 457 PET when BP_ND in the

**Table 2.** Extrastratatal binding potential (BP_ND) values and dopamine D₂ receptor occupancy in [¹¹C]FLB 457 PET studies

<table>
<thead>
<tr>
<th>Region</th>
<th>BP_ND</th>
<th>Drug challenge</th>
<th>Occupancy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midbrain</td>
<td>1.57±0.46</td>
<td>0.82±0.21</td>
<td>44±20</td>
</tr>
<tr>
<td>Thalamus</td>
<td>3.40±0.37</td>
<td>1.41±0.17</td>
<td>58±5</td>
</tr>
<tr>
<td>Parahippocampal gyrus</td>
<td>2.52±0.88</td>
<td>1.00±0.20</td>
<td>57±14</td>
</tr>
<tr>
<td>Anterior cingulate</td>
<td>1.27±0.12</td>
<td>0.51±0.09</td>
<td>59±9</td>
</tr>
<tr>
<td>Frontal cortex</td>
<td>1.11±0.23</td>
<td>0.46±0.09</td>
<td>58±11</td>
</tr>
<tr>
<td>Temporal cortex</td>
<td>1.95±0.39</td>
<td>0.76±0.18</td>
<td>60±8</td>
</tr>
<tr>
<td>Parietal cortex</td>
<td>1.32±0.42</td>
<td>0.57±0.17</td>
<td>56±9</td>
</tr>
</tbody>
</table>

Values are mean±s.d.

![Figure 1. Average images of binding potential at baseline condition and after administration of risperidone, dopamine D₂ receptor occupancy for [¹¹C]raclopride, and T₁-weighted images. In the striatum, no obvious regional differences in dopamine D₂ receptor occupancy were observed.](image-url)
cerebellum was 0.3 (Ito et al., 2001) and assumed occupancy was 70%. This indicates that the occupancies of dopamine D\textsubscript{2} receptors in both the striatum and extrastriatum may not have differed. In the present study, [\textsuperscript{11}C]FLB 457 PET studies were begun 2 h after the start of [\textsuperscript{11}C]raclopride PET studies, and therefore, the sum of the plasma concentrations of risperidone and 9-hydroxy-risperidone was slightly lower during [\textsuperscript{11}C]FLB 457 studies (14.5 ± 4.2 ng/ml) than during [\textsuperscript{11}C]raclopride studies (17.5 ± 5.2 ng/ml). When ED\textsubscript{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\textsubscript{2} receptor occupancy, respectively [eqn (3)]. This might be able to partially explain higher dopamine D\textsubscript{2} receptor occupancy in the [\textsuperscript{11}C]raclopride studies than in the [\textsuperscript{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\textsubscript{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 [\textsuperscript{11}C]raclopride and [\textsuperscript{11}C]FLB 457 studies on the occupancies of dopamine D\textsubscript{2} receptors might be very small.

Several mechanisms for the limbic and cortical selectivity in dopamine D\textsubscript{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\textsubscript{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; Xiberras 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 [^{11}C]raclopride 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.

References


Dopamine \(D_2\) receptor occupancy by antipsychotics

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


