Striatal and extra-striatal D2/D3 dopamine receptor occupancy by quetiapine in vivo

[123I]-epidepride single photon emission tomography (SPET) study

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Background
Selective action at limbic cortical dopamine D2-like receptors could mediate atypical antipsychotic efficacy with few extrapyramidal side-effects.

Aims
To test the hypothesis that quetiapine has ‘limbic selective’ D2/D3 receptor occupancy in vivo.

Method
The high-affinity D2/D3 ligand [123I]-epidepride and single photon emission tomography were used to estimate D2/D3 specific binding and an index of relative percentage D2/D3 occupancy in striatal and temporal cortical regions for quetiapine-treated patients (n=6). Quetiapine, and previously studied typical-antipsychotic- and clozapine-treated patients were compared.

Results
Mean (s.d.) relative percentage D2/D3 receptor occupancy by quetiapine was 32.0% (4.6%) in striatum and 60.1% (17.2%) in temporal cortex (mean daily dose 450 mg; range 300–700 mg/day). Quetiapine treatment resulted in limbic selective D2/D3 blockade similar to clozapine and significantly higher than typical antipsychotics.

Conclusions
Preliminary data suggest that limbic selective D2/D3 receptor blockade is important for atypical drug action.

Declaration of interest
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Dopamine D2 receptor blockade is thought to mediate antipsychotic action. Clozapine has a superior therapeutic profile, with modest occupancy of striatal dopamine D2/D3 receptors. Quetiapine is a new atypical antipsychotic drug. In vitro, it has a broad relative affinity profile similar to clozapine, with lower absolute affinities for most receptor subtypes. Preclinical testing supports limbic selective dopamine antagonism for quetiapine (Goldstein, 1995). Preferential occupancy of temporal cortical D2/D3 receptors has been demonstrated in clozapine-treated patients (Pilowsky et al., 1997). This is not seen in typical-antipsychotic-treated patients (Bigliani et al., 1999) and may contribute to clozapine’s beneficial therapeutic profile. We used [123I]-epidepride single photon emission tomography (SPET) to test the hypothesis that quetiapine demonstrates ‘limbic selective’ D2/D3 dopamine receptor blockade in vivo. Comparisons were made with previously studied typical-antipsychotic- and clozapine-treated patients (Pilowsky et al., 1997, 1998; Bigliani et al., 1999).

METHOD

Subjects
Ethical permission was obtained from the Bethlem and Maudsley National Health Service (NHS) Trust Ethics Committee and the UK Administration of Radioactive Substances Advisory Committee (ARSAC). Patients were recruited from the Bethlem and Maudsley NHS Trust, London, and informed consent was obtained after full explanation of the study.

Patients
The inclusion criteria were: a diagnosis of schizophrenia according to DSM-IV criteria (American Psychiatric Association, 1994); quetiapine treatment was begun following intolerance (extrapyramidal side-effects (EPS) or hyperprolactinaemia) or failure of previous antipsychotic treatment. Exclusion criteria were: other primary psychiatric or physical illness; drug or alcohol dependence syndromes; and comitant use of another antipsychotic drug. Six patients with schizophrenia (five male and one female) took part in the study.

Controls
Healthy control subjects (n=14) were recruited from the community. They completed a general health screening and drug and alcohol misuse checklist. Volunteers with current or previous physical or psychiatric illness or drug or alcohol dependency syndromes were excluded.

Clinical management
Quetiapine treatment began after a 3-day washout period following oral medication. For case 1, quetiapine was started in place of depot after a 4-week inter-injectional period. Initial dose was increased to 300 mg over the first 4 days, then titrated according to clinical need, following the manufacturer’s guidelines.

Clinical assessment
Clinical ratings were performed by a trained psychiatric rater (C.M.E.S.), before quetiapine treatment began, at the time of scanning (except for case 2) and after 6 weeks of treatment. Psychiatric symptoms were assessed using the 24-item Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962) and the Scale for Assessment of Negative (SANS; Andreasen, 1981) and Positive Symptoms (SAPS; Andreasen, 1984). High scores indicate greater symptom severity. Global functioning was assessed by the Global Assessment Scale (GAS; Endicott et al., 1976), a continuous scale from 0 to 100, anchored every 10 points with social and behavioural descriptors, a high score denoting improvement. Depressive symptoms were rated using the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979), a 10-item clinician-rated scale of depressive symptoms (high scores denote greater severity). Motor side-effects were rated using the Simpson and Angus scale (Simpson & Angus, 1970) for Parkinsonian side-effects, the Abnormal Involuntary Movements Scale (AIMS; Alcohol, Drug Abuse and Mental Health Administration, 1974) for tardive dyskinesia, and...
the subjective and objective Rating Scale for Drug-Induced Akathisia (Barnes, 1989).

**Preparation of [¹²³I]-epidepride**

[¹²³I]-epidepride, ((S)-N-[1-ethyl-2-pyroloidinyl]methyl)-5-iodo-2,3-dimethoxybenzamide (Kₚᵣ = 23 PM), was obtained from two sources: MAP Medical Technologies (Finland) and by preparation in our laboratory according to the following method. [¹²³I]-epidepride was prepared via oxidative iododestannylation by the addition of chloramine T to a vial containing [¹²³I]-Na (specific radionuclide purity greater than 99.9%) and the tributyltin precursor (tri-n-butyltin-N-[1-ethyl-2-pyroloidinyl]methyl)-2,3-dimethoxybenzamide, pH <2. The reaction proceeded at room temperature for 3 minutes, and was then quenched with sodium metabisulphite. The reaction mixture was purified by high-performance liquid chromatography (HPLC) using a semi-preparative reverse-phase HPLC column (μ-Bondapack-C-18 (Waters, Millford, MA, USA) 300 × 7.8 mm, 10 mm; mobile phase: acetonitrile/phosphoric acid (0.01 M) 40/60, flow rate 4 ml/minute, wavelength 254 nm). [¹²³I]-epidepride eluted at a retention time equivalent to that for a standard reference sample of epidepride (about 6 minutes). The eluent fraction containing [¹²³I]-epidepride was recovered by loading onto a Baker Bond octadecyl 100 mg column, eluted with ethanol and diluted with 0.9% saline. Radiochemical yield was greater than 90%. Analytical HPLC revealed a radiochemical purity of more than 98% [¹²³I] in the form of [¹²³I]-epidepride and a specific activity >2000 Ci/mmol.

One patient (case 1) was studied with epidepride prepared in our own laboratory, and compared with eight volunteers studied with epidepride prepared in the same way. All other patients were compared with six volunteers studied with epidepride obtained from MAP Medical Technologies (Finland). This approach was taken for methodological consistency, and the overall result was unchanged regardless of whether comparisons were made on this basis or between patient and volunteer groups as a whole.

**SPET image acquisition**

A high-resolution brain-dedicated SME 810 12-detector tomographic scanner (Strichman Medical Equipment, Medfield, MA, USA) linked to a Macintosh computer was used for dynamic SPET. The spatial resolution of the scanner is 7–9 mm full-width at half-maximum, with a slice thickness of 12.5 mm. An energy window optimal for [¹²³I] in an antecubital vein. Multi-slice whole brain acquisitions (at 2.3 minutes per slice) lasting about 25 minutes were performed in all subjects at the time of the injection and 3–4 hours post-injection. All subjects had a minimum of two acquisitions over the whole time period. Slices on planes parallel to the orbito-meatal line were acquired (10 mm inter-slice spacing) from base (including cerebellum) towards vertex (including striatum).

**[¹²³I]-epidepride specific binding to available D₂/D₃ receptors**

An approximation of specific [¹²³I]-epidepride binding to D₂/D₃ receptors was calculated at each time point after 180 minutes using a semi-quantitative method. Ratios were calculated as (striatal or temporal cortical regional density/cerebellar density) – 1, where the striatal or temporal cortical regional density represents the total uptake (=specific binding + non-specific binding + free ligand). Cerebellar regional density is presumed free of D₂ dopamine receptors (Campos et al., 1989) and represents the background uptake (=non-specific binding + free ligand). D₂/D₃ ‘specific’ binding was averaged between the left and right sides for striatal and temporal cortical regions. Figure 1 shows the D₂/D₃ specific binding ratio indices for quetiapine-treated patients and untreated healthy volunteers, in the temporal cortex and striatum respectively.

**Image analysis**

Images were analysed using a customised SME 810 analysis platform. The image display density scale was normalised to the maximum counts within each frame. Irregular regions of interest (ROIs) were drawn around the 50% count maximum isocountur at the right and left temporal poles and cerebellum, on the ‘early’ images (mainly reflecting blood flow delivery of ligand to the brain). The temporal (or so-called ‘limbic cortical’) ROIs incorporated the inferior and medial temporal cortex (these regions also include the entorhinal cortex, hippocampus and amygdala). The right and left striata (incorporating the head of the caudate nucleus and putamen) were visualised best on the ‘late’ images, and ROIs defined on these frames at the 75% count maximum isocountur were mapped to the early images unchanged. Regions were defined in accordance with standard anatomical sections (Damasio & Damasio, 1989). Minor adjustments in ROI placement were made to correct for patient movement during the scans. There was no significant difference in region area between patient and control groups in any of the regions studied. Image analysis was performed on separate occasions by two trained raters (V.B., who was blind to medication and dose status, and C.M.E.S.). Radioactive density was calculated within each region. Interrater reliability for these measures was greater than 90%.

**Fig. 1** Scattersplots showing individual (a) striatal and (b) temporal cortical D₂/D₃ specific binding ((total/background) – 1) ratio indices for quetiapine-treated patients (n = 6) and healthy volunteers (n = 14).

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Relative percentage $D_2/D_3$ receptor occupancy by quetiapine

For unmedicated volunteers, it is assumed that $[125I]$-epidepride binds competitively to all available $D_2/D_3$ receptors, and 0% of the receptors are occupied by ‘cold’ or unlabelled competitor (although it is accepted that endogenous dopamine will occupy a small proportion of receptors). Treatment with unlabelled antipsychotic drugs competitively reduces $D_2/D_3$ receptor availability for binding to $[125I]$-epidepride (the reduction reflecting the degree of receptor occupancy by antipsychotic drugs relative to the drug-free state). The relative percentage $D_2/D_3$ striatal and temporal cortical occupancy by quetiapine was calculated for each patient with reference to volunteers’ mean $D_2/D_3$ specific binding ratio (specific binding ratio)$_a$ from 180 minutes onwards by the following equation:

$$1 - \frac{\text{specific binding ratio}_p}{\text{specific binding ratio}_a} \times 100$$

The interrater reliability for occupancy values was greater than 90%.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 7.5 for Windows.

Analysis of variance (ANOVA) was used to compare $D_2/D_3$ receptor specific binding indices for quetiapine-treated and healthy volunteer groups, and relative percentage $D_2/D_3$ receptor occupancies for typical-antipsychotic- and clozapine-treated groups v. the quetiapine-treated group.

Post hoc unpaired t-tests were used to compare striatal and temporal cortical percentage $D_2/D_3$ occupancy and limbic selectivity ratios between quetiapine-, typical-antipsychotic- and clozapine-treated patient groups. Bonferroni corrections were performed.

Pearson’s correlation was used to explore relationships between dose, clinical change and relative percentage $D_2/D_3$ receptor occupancy by quetiapine in the striatum and temporal cortex.

RESULTS

Sample characteristics and clinical assessment

Six patients with schizophrenia (mean age 32.8 years, range 26–52, s.d.=10.8) and 14 healthy volunteers (mean age 33.0 years, range 22–48, s.d.=10.3) were studied. Tables 1, 2 and 3 show demographic, clinical and treatment details. Baseline EPS scores for all but one patient (case 1) were zero. These patients were drug free, or treated with atypical antipsychotics before the study. No treatment-emergent EPS were seen, and the patient with existing EPS showed complete eradication of Parkinsonian symptoms (case 1: initial scores of 16 on the Simpson and Angus scale, 3 on the AIMS and 10 on the Barnes akathisia scale all fell to 0 within 6 weeks of treatment with quetiapine).

Relative percentage $D_2/D_3$ receptor occupancy in vivo

Figure 2 shows the relative percentage $D_2/D_3$ receptor occupancy in the temporal cortex and striatum, as a function of daily quetiapine dose. Mean percentage $D_2/D_3$ receptor occupancy was 60.1% (s.d.=17.2) in the temporal cortex and 32.0% (s.d.=14.6) in the striatum for a mean quetiapine dose of 450 mg/day (see Table 2 for individual values). There was no relationship between quetiapine

### Table 1 Demographic details: patients and volunteers

<table>
<thead>
<tr>
<th>Quetiapine-treated patients</th>
<th>Volunteers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case number</td>
<td>Gender</td>
</tr>
<tr>
<td>1</td>
<td>Male</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
</tr>
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<td>5</td>
<td>Male</td>
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<tr>
<td>9</td>
<td>Male</td>
</tr>
<tr>
<td>11</td>
<td>Male</td>
</tr>
<tr>
<td>13</td>
<td>Male</td>
</tr>
</tbody>
</table>

Mean (s.d.) 32.8 (10.8) 33.0 (10.3)

### Table 2 Clinical details and striatal and temporal cortical $D_2/D_3$ receptor occupancies for patients treated with quetiapine

<table>
<thead>
<tr>
<th>Case number</th>
<th>Previous treatment</th>
<th>Quetiapine dose (mg/day)</th>
<th>Prescription duration (days)</th>
<th>Percentage temporal cortical occupancy</th>
<th>Percentage striatal occupancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pipotazine palmitate depot 50 mg, monthly</td>
<td>300</td>
<td>34</td>
<td>81</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>Trifluoperazine, 30 mg/day; chlorpromazine 100 mg/day; venlafaxine 225 mg/day</td>
<td>400</td>
<td>17</td>
<td>34</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>Clozapine: intolerant to initial doses</td>
<td>400</td>
<td>33</td>
<td>61</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>Drug free for 8 months</td>
<td>400</td>
<td>33</td>
<td>48</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>Sertindole 24 mg/day</td>
<td>500</td>
<td>33</td>
<td>76</td>
<td>49</td>
</tr>
<tr>
<td>6</td>
<td>Risperidone 2 mg/day</td>
<td>700</td>
<td>26</td>
<td>62</td>
<td>38</td>
</tr>
</tbody>
</table>

Mean (s.d.) 450 29 60.1 (17.2) 32.0 (14.6)
daily dose and striatal relative percentage D₂/D₃ occupancy (r = -0.011, P = 0.98), or temporal cortical relative percentage D₂/D₃ occupancy (r = 0.244, P = 0.64). There were no correlations between change on any of the clinical indices measured and striatal or temporal cortical relative percentage D₂/D₃ occupancy.

### Relative percentage D₂/D₃ occupancy: comparison with clozapine and typical antipsychotics

Figure 3 shows individual relative percentage D₂/D₃ occupancy values in the striatum and temporal cortex for patients treated with quetiapine, clozapine and typical antipsychotics. Table 4 shows mean temporal cortical and striatal relative percentage D₂/D₃ occupancy values and the limbic selectivity indices for patients treated with quetiapine compared with clozapine (values taken from Pilowsky et al., 1997, 1998) and typical antipsychotics (values from Biglani et al., 1999). For the clozapine-treated group: n = 10, mean age = 30.9 years (s.d. = 6.9), mean dose = 445 mg (range 150–750 mg). For the typical-antipsychotic-treated group: n = 12, mean age = 39.6 (s.d. = 10.7), mean dose = 669 mg (s.d. = 516.8) chlorpromazine equivalents per day.

One-way ANOVA showed significant between-group differences for temporal cortical (F = 19.16, P < 0.0001) and striatal occupancy (F = 47.88, P < 0.0001), and limbic selectivity ratios (F = 9.07, P < 0.001). The most significant differences observed were between quetiapine- and typical-antipsychotic-treated patients. Typical-antipsychotic-treated patients had significantly higher striatal percentage D₂/D₃ occupancy and significantly lower limbic selectivity than quetiapine-treated patients. Patients treated with clozapine also showed higher occupancies in the striatum and temporal cortex, but no significant difference in limbic selectivity ratio, compared with the quetiapine-treated group (see Table 4).

### DISCUSSION

We have performed the first study of quetiapine’s effect on extra-striatal D₂/D₃ dopamine receptors with [¹²³I]epidepride SPET. Qutiapine shows low occupancy of striatal and temporal cortical D₂/D₃ receptors in vivo (in keeping with its low in vitro affinity for D₂ receptors). The data support the hypothesis that quetiapine has preferential occupancy for temporal cortical D₂/D₃ receptors (so-called D₂/D₃ limbic selectivity) at clinically relevant doses, and shares this property with clozapine (Pilowsky et al., 1997; Xiberras et al., 1999).

### Methodological considerations

We have used a semi-quantitative ratio method (using the cerebellum as a background region with negligible density of D₂/D₃ receptors, i.e. beneath the level of detection of the SPET camera (Shafer & Levant, 1998)) to estimate specific binding of [¹²³I]epidepride to D₂/D₃ receptors in vivo. This approach does not attain the accuracy of quantitative methods and is vulnerable to confounding factors, including individual differences in regional blood flow and plasma clearance of the ligand. Nevertheless, the ratio method controls for inter-subject differences in percentage injected dose of the radioligand, whole brain uptake, and height and weight. In accordance with other studies, our calculations of relative percentage occupancy of D₂/D₃ receptors are based on comparison with a drug-free healthy volunteer group (Farde et al., 1997; Hagberg et al., 1998). This approach is based on the consensus from positron emission tomography (PET) and SPET studies that in vivo striatal D₂ receptor density is similar in drug naive patients with schizophrenia and healthy volunteers. There are as yet no in vivo studies comparing temporal cortical D₂/D₃...
density in untreated patients with schizophrenia and healthy controls. However, a post-mortem study found disorganisation, but no alteration in D2/D3 receptor density in the temporal cortex and hippocampus of patients with schizophrenia compared to controls (Goldsmith et al., 1997).

The timing of SPET data acquisition was based on our own (and other SPET groups') consistent experience with [123I]-epidepride behaviour in healthy volunteer studies (Kornhuber et al., 1995; Pirker et al., 1997). The peak of [123I]-epidepride specific binding to D2/D3 receptors (total background uptake) occurs 150–180 minutes in the striatum and 60–100 minutes in the temporal cortex after intravenous bolus injection (although considerable variability is evident (Pirker et al., 1997)). Figure 4 illustrates washout from all areas after injection in a healthy volunteer over the time of a representative SPET experiment. No displacement of the cerebellar signal is evident in a typical-antipsychotic-treated patient, implying no measurable specific binding in this region and supporting its utility as a reference region (see also Suhara et al., 1999). Estimation of the D2/D3 specific binding index over 180–240-minute samples around (or after) the peak in total (and specific) binding for striatum and temporal cortex, before washout of radioactivity in the cerebellum, results in unacceptably low count statistics (Biglioni et al., 1999).

After the main sample was collected, the method was further validated on a Picker Prism 3000 triple detector SPET camera (Marconi, Cleveland, OH, USA), capable of rapid acquisition (1 minute acquisition time) of high-resolution whole brain images, providing very detailed SPET time:activity data. A [123I]-epidepride scan (with 5 minute whole brain data acquisition frames commencing immediately after intravenous bolus injection of the tracer) was performed in a 33-year-old patient with schizophrenia when drug naïve and after 3 weeks of quetiapine treatment at 300 mg per day. The curves (Fig. 5) confirm that specific striatal D2/D3 binding of [123I]-epidepride peaks at about 180 minutes after injection, and temporal cortical binding at about 50 minutes after injection in the drug-treated state. This supports our estimation of the D2/D3 specific binding index in both regions after ‘transient equilibrium’. Analysis of this patient’s data by the method used in the present study yields results (53.1% D2/D3 receptor occupancy in

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Fig. 3 Scatterplots of individual relative percentage D2/D3 receptor occupancy values in the striatum and temporal cortex of patients treated with quetiapine (n = 6), clozapine (n = 10) and typical antipsychotic drugs (n = 12).

Table 4 Mean relative percentage D2/D3 occupancy (± s.d.) for antipsychotic drugs estimated by [123I]-epidepride single photon emission tomography (P values report results of t-test in each case)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Temporal cortex</th>
<th>Striatum</th>
<th>Limbic selectivity ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quetiapine</td>
<td>60.1 (17.2)</td>
<td>32.0 (14.6)</td>
<td>1.9</td>
</tr>
<tr>
<td>Typical antipsychotics</td>
<td>93.2 (4.0)</td>
<td>80.0 (11.4)</td>
<td>1.18</td>
</tr>
<tr>
<td>(Biglioni et al., 1999)</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001</td>
<td>P = 0.003</td>
</tr>
<tr>
<td>Clozapine</td>
<td>83.1 (11.4)</td>
<td>49.8 (4.9)</td>
<td>1.67</td>
</tr>
<tr>
<td>(Pilowsky et al., 1997)</td>
<td>P = 0.006</td>
<td>P = 0.003</td>
<td>P = 0.144</td>
</tr>
</tbody>
</table>
the temporal cortex and 15.2% in the striatum) entirely consistent with the main patient group reported in this study. These data further confirm that the finding is not simply due to effects of quetiapine on cerebral blood flow. If limbic selectivity were due to blood flow, it would be clearly evident early in the ‘blood flow’ dominated part of the scan (before 50 minutes post-injection in the temporal cortex). In fact, there is complete overlap in the total:background ratio curves of the drug-naïve and quetiapine-treated states until transient equilibrium is attained. Examination of the cerebellar density:time activity curves in this individual confirmed no displaceable binding or increase in cerebellar perfusion in the drug-treated state.

We accept that the simple ratio technique does not accurately quantify dopaminergic function (Fujita et al., 1999). However, further analysis of the data presented by Iliche et al. (1999) indicates that, while the absolute values of specific binding may be inaccurate, the ratio of binding in the striatum to that in the temporal cortex (the ‘limbic selectivity index’) gives a much better correlation with the full quantitative approach. This is not entirely unexpected, since most of the variability in the simplified ratio methods appears to come from variability in non-specific binding or background. Since this may be uniform in both target regions, it should cancel out to some extent when the limbic selectivity index is determined. Hence, although the absolute measures of specific binding may be only an approximation to available receptor concentration, the relative uptake between the striatum and temporal cortex should provide more quantitative results.

**Fig. 4** Total [123I]-epidepride binding over time (after injection) in basal ganglia (BG), temporal cortical (TC) and cerebellar (CER) regions of interest (ROI; mean activity in each region estimated as counts/pixel), in a representative healthy volunteer and patient (treated with fluphenazine decanoate 75 mg, 2-weekly).

**Fig. 5** Time x D2/D3 specific binding (total—background activity) curves from a representative patient with schizophrenia scanned on the Picker Prism 3000 triple-headed single photon electron tomography camera, after 3 weeks' quetiapine treatment (dose: 300 mg/day). The peaks of specific activity in striatal and temporal cortical regions occur at about 150 and 50 minutes respectively.

**Striatal percentage D2/D3 receptor occupancy by quetiapine**

Striatal occupancy of D2/D3 receptors was low for quetiapine (mean 32%), which substantiates findings of PET and SPECT studies (Kufferle et al., 1997; Gefvert et al., 1998; Hagberg et al., 1998). The variance in our striatal D2/D3 occupancy values concurs with the available literature. This low striatal occupancy is consistent with the very low propensity for quetiapine to produce EPS in clinical trials (Aravinitis et al., 1997).

We did not find a correlation between quetiapine dose and D2/D3 receptor occupancy in the striatum or temporal cortex. The sample was small, the dose range narrow, and the specific binding ratio
method may have contributed to ‘noise’ or variability in the data, which could obscure a genuine dose:occupancy relationship. However, the present finding is in keeping with that of Hagberg et al. (1998), who also did not reveal a striatal dose:occupancy relationship (using 11C-raclopride PET to estimate D2/D3 occupancy by quetiapine) over a similarly narrow dose range. Clozapine also fails to demonstrate a dose: percentage D2/D3 receptor occupancy relationship in the striatum. The variability in measures of striatal D2/D3 occupancy by quetiapine could relate to underlying dopaminergic tone. Seeman & Tallerico (1999) have suggested that quetiapine and clozapine are particularly sensitive to displacement from the D3 receptor by endogenous dopamine in vivo, and Laruelle et al. (1999) have indirectly demonstrated a 50% variance in endogenous dopamine response to amphetamine challenge in patients with schizophrenia.

**Temporal cortex relative percentage D2/D3 receptor occupancy**

Quetiapine showed temporal lobe relative percentage D2/D3 receptor occupancy values lower than those for clozapine, and far lower than for typical antipsychotic drugs. This is consistent with the relative D2/D3 receptor affinities of the three groups of antipsychotic. If temporal lobe or limbic D2/D3 receptor occupancy is important for the efficacy of antipsychotic drugs, there is as yet no consensus on the absolute threshold of occupancy required. It is accepted that the data reported here provide relative measures of D2/D3 receptor occupancy by quetiapine. Clinical trials demonstrate that quetiapine has efficacy equivalent to that of haloperidol and chlorpromazine for positive symptoms of schizophrenia. The levels of temporal cortical D2/D3 receptor occupancy reported here might be sufficient to account for the efficacy of quetiapine if the underlying mechanism were D2/D3 receptor blockade. There was no correlation between clinical improvement and temporal cortical D2/D3 receptor occupancy, but it is difficult to put much weight on this given the small sample size and the sources of variances within the occupancy estimation discussed above. It is also clear that some patients are poorly responsive to antipsychotics, despite higher levels of temporal cortical D2/D3 receptor occupancy (Biligiani et al., 1999), which raises the possibility that other neurochemical systems (such as glutamatergic and serotonergic) could mediate antipsychotic efficacy in these individuals.

**Mechanism of limbic selectivity**

Several possible mechanisms for the limbic-selective dopamine action of atypical antipsychotic drugs have recently been discussed in the literature (Lidow et al., 1998). It has been supposed that drugs with low affinity for D2 receptors could more easily achieve higher occupancy in regions (such as the temporal cortex) with low receptor density in vivo. Quetiapine has lower D2 affinity than clozapine or typical antipsychotics, so this model could parsimoniously account for its higher limbic selectivity. Seeman & Tallerico (1999) have suggested that antipsychotic drugs with lower D2 affinity would achieve higher D2 receptor occupancy in regions with lower levels of endogenous dopamine. Microdialysis studies in the primate suggest that endogenous dopamine levels are lower in cortical than in striatal regions (Moghaddam et al., 1993). This would provide a further mechanism for limbic selectivity, which would be greater for drugs with modest affinity for D2 receptors.

It has also been postulated that limbic selectivity depends on the D2/D3 affinity ratio of a drug, with D2 affinity having greater importance in extrastriatal regions (Scatton et al., 1997). Again, quetiapine has a higher D2/D3 ratio than clozapine or typical antipsychotics, which would be consistent with our findings of a high limbic selectivity ratio for quetiapine. The mechanism underlying limbic selectivity D2/D3 blockade by antipsychotic drugs remains unclear and awaits further investigation.

**ACKNOWLEDGEMENTS**

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**REFERENCES**


CLINICAL IMPLICATIONS

- Quetiapine has a D$_2$/D$_3$ receptor occupancy profile similar to that of clozapine, with low occupancies in the striatum relative to extrastriatal regions. Absolute occupancies are lower for quetiapine than clozapine, in keeping with the lower D$_3$ receptor affinity of quetiapine.

- Compared to typical antipsychotics and in common with clozapine, quetiapine shows marked limbic selective D$_2$/D$_3$ receptor blockade, in keeping with clinical observations of its therapeutic efficacy and placebo-level extrapyramidal side-effects.

- Striatal D$_2$/D$_3$ receptor occupancies showed a mean of 32% for quetiapine. The observed association of antipsychotic efficacy with low striatal percentage D$_2$/D$_3$ occupancy suggests that extrastriatal rather than striatal D$_2$/D$_3$ receptor blockade is of greater relevance to antipsychotic efficacy in schizophrenia.

LIMITATIONS

- The D$_2$/D$_3$ specific binding ratio is a semi-quantitative index that does not provide a fully accurate estimation of receptor density or occupancy. Fully quantitative positron-emission tomography and single photon emission tomography studies would resolve this issue.

- The narrow dose range and inherent variability in semi-quantitative specific binding ratio estimation may have obscured a genuine dose:relation percentage D$_2$/D$_3$ receptor occupancy relationship in the striatum and temporal cortex.

- Large, prospectively ascertained samples of patients on a wide range of quetiapine doses may be necessary to define fully the relationship between dose and relative percentage D$_2$/D$_3$ receptor occupancy in extrastriatal regions.

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