Striatal and extra-striatal D_2/D_3 dopamine receptor occupancy by quetiapine *in vivo*

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

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Background Selective action at limbic cortical dopamine D_2-like receptors could mediate atypical antipsychotic efficacy with few extrapyramidal side-effects.

Aims To test the hypothesis that quetiapine has 'limbic selective' D_2/D_3 receptor occupancy *in vivo*.

Method The high-affinity D_2/D_3 ligand [^{123}I]-epidepride and single photon emission tomography were used to estimate D_2/D_3 specific binding and an index of relative percentage D_2/D_3 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 D_2/D_3 receptor occupancy by quetiapine was 32.0% (14.6) 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 D_2/D_3 blockade similar to clozapine and significantly higher than typical antipsychotics.

Conclusions Preliminary data suggest that limbic selective D_2/D_3 receptor blockade is important for atypical drug action.

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Dopamine D_2 receptor blockade is thought to mediate antipsychotic action. Clozapine has a superior therapeutic profile, with modest occupancy of striatal dopamine D_2/D_3 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 D_2/D_3 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 [^{123}I]-epidepride single photon emission tomography (SPET) to test the hypothesis that quetiapine demonstrates 'limbic selective' D_2/D_3 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 concomitant 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; Andreason, 1981) and Positive Symptoms (SAPS; Andreason, 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

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the subjective and objective Rating Scale for Drug-Induced Akathisia (Barnes, 1989).

Preparation of [^{123}I]-epidepride

[^{123}I]-epidepride, ((S)-N-[(1-ethyl-2-pyrrolidinyl)methyl]-5-iodo-2,3-dimethoxybenzamide) (K_d=23 pM), was obtained from two sources: MAP Medical Technologies (Finland) and by preparation in our laboratory according to the following method. [^{123}I]-epidepride was prepared via oxidative iododestannylation by the addition of chloramine T to a vial containing [^{123}I]-Na (specific radionuclide purity greater than 99.9%) and the tributyltin precursor ((tri-n-butyltin)-N-[(1-ethyl-2-pyrrolidinyl)methyl]-2,3-dimethoxybenzamine), 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). [^{123}I]-epidepride eluted at a retention time equivalent to that for a standard reference sample of epidepride (about 6 minutes). The eluent fraction containing [^{123}I]-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% [^{123}I] in the form of [^{123}I]-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 ^{123}I (135–190 KeV) was used to acquire data.

Subjects received a bolus intravenous injection of approximately 150 MBq of [^{123}I]-epidepride in an antecubital vein. Multi-slice whole brain acquisitions (at 2.5 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).

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 isocontour 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 isocontour 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%.

[^{123}I]-epidepride specific binding to available D_2/D_3 receptors

An approximation of specific [^{123}I]-epidepride binding to D_2/D_3 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 D_2 dopamine receptors (Camps *et al*, 1989) and represents the background uptake (=non-specific binding+free ligand). D_2/D_3 'specific binding' was averaged between the left and right sides for striatal and temporal cortical regions. Figure 1 shows the D_2/D_3 specific binding ratio indices for quetiapine-treated patients and untreated healthy volunteers, in the temporal cortex and striatum respectively.

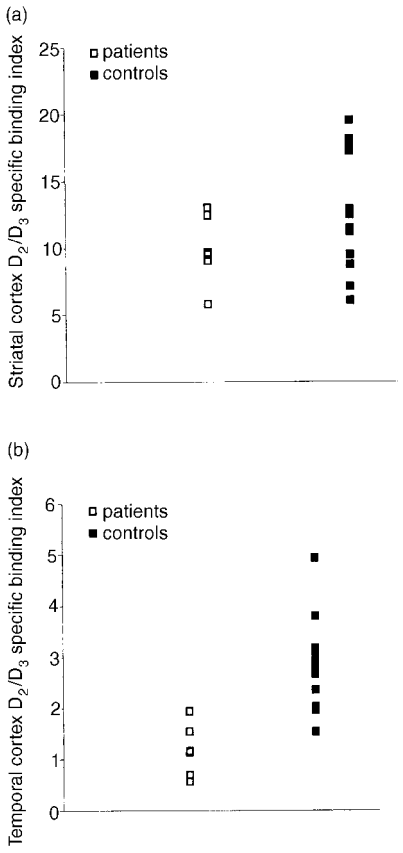

Fig. 1 Scatterplots showing individual (a) striatal and (b) temporal cortical D_2/D_3 specific binding ((total/background)−1) ratio indices for quetiapine-treated patients (n=6) and healthy volunteers (n=14).

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Relative percentage D_2/D_3 receptor occupancy by quetiapine

For unmedicated volunteers, it is assumed that [^{123}I]-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 [^{123}I]-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, $(\text{specific binding ratio})_v$, from 180 minutes onwards by the following equation:

$$1-\frac{(\text{specific binding ratio})_p}{(\text{specific binding ratio})_v}\times 100$$

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

Quetiapine-treated patients			Volunteers		
Case number	Gender	Age (years)	Case number	Gender	Age (years)
1	Male	52	1	Male	34
2	Male	26	2	Male	29
3	Female	40	3	Male	26
4	Male	27	4	Male	48
5	Male	26	5	Male	35
6	Male	26	6	Male	26
			7	Male	48
			8	Male	27
			9	Male	25
			10	Male	47
			11	Male	48
			12	Male	25
			13	Male	22
			14	Male	22
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

Case number	Previous treatment	Quetiapine dose (mg/day)	Prescription duration (days)	Percentage temporal cortical occupancy	Percentage striatal occupancy
1	Pipotiazine palmitate depot 50 mg, monthly	300	34	81	41
2	Trifluoperazine, 30 mg/day; chlorpromazine 100 mg/day; venlafaxine 225 mg/day	400	17	34	16
3	Clozapine: intolerant to initial doses	400	33	61	34
4	Drug free for 8 months	400	33	48	12
5	Sertindole 24 mg/day	500	33	76	49
6	Risperidone 2 mg/day	700	26	62	38
Mean (s.d.)		450	29	60.1 (17.2)	32.0 (14.6)

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Table 3 Clinical scores for patients: initial scores (percentage improvement after 6 weeks of treatment)

Patient case number	BPRS	SAPS	SANS	GAS	MADRS
1	52 (50)	13 (85)	33 (60)	41 (49)	6 (100)
2[1]	37	23	12	50	14
3	52 (4)	48 (13)	36 (53)	35 (−9)	8 (−50)
4	53 (2)	24 (13)	69 (−6)	51 (−12)	20 (−30)
5	62 (5)	47 (17)	31 (0)	50 (−2)	14 (50)
6	59 (36)	38 (76)	51 (63)	35 (43)	19 (58)

1. Case 2 was assessed at the time of the scan, and longitudinal data were not gathered.
BPRS, Brief Psychiatric Rating Scale; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; GAS, Global Assessment Scale; MADRS, Montgomery–Åsberg Depression Rating Scale.

daily dose and striatal relative percentage D_2/D_3 occupancy ($r=-0.011$, $P=0.98$), or temporal cortical relative percentage D_2/D_3 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 D_2/D_3 occupancy.

Relative percentage D_2/D_3 occupancy: comparison with clozapine and typical antipsychotics

Figure 3 shows individual relative percentage D_2/D_3 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 D_2/D_3 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 Bigliani *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 D_2/D_3 occupancy and significantly lower limbic selectivity then 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).

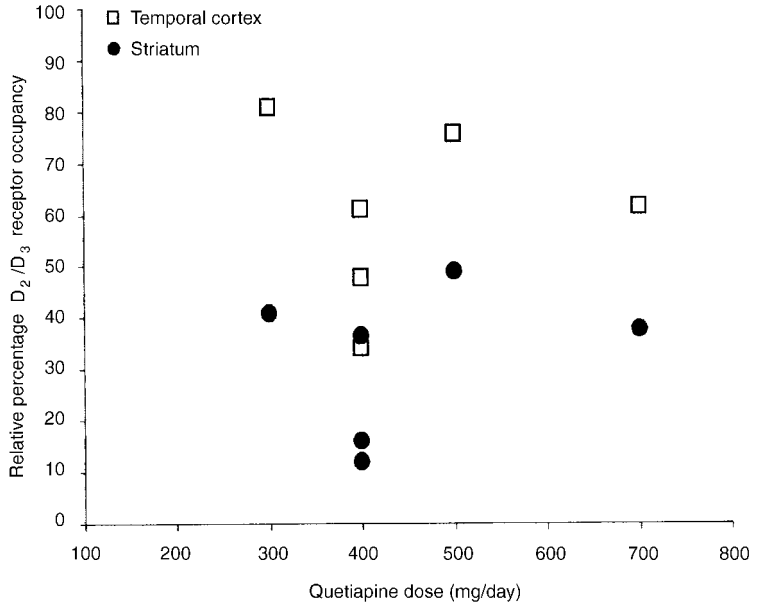

Fig. 2 Relative percentage D_2/D_3 receptor occupancy against dose for each quetiapine-treated patient in the temporal cortex and striatum (right and left averaged).

DISCUSSION

We have performed the first study of quetiapine's effect on extra-striatal D_2/D_3 dopamine receptors with [^{123}I]-epidepride SPET. Quetiapine shows low occupancy of striatal and temporal cortical D_2/D_3 receptors *in vivo* (in keeping with its low *in vitro* affinity for D_2 receptors). The data support the hypothesis that quetiapine has preferential occupancy for temporal cortical D_2/D_3 receptors (so-called D_2/D_3 limbic selectivity) at clinically relevant doses, and shares this property with clozapine (Pilowsky *et al*, 1997; Xiberas *et al*, 1999).

Methodological considerations

We have used a semi-quantitative ratio method (using the cerebellum as a background region with negligible density of D_2/D_3 receptors, i.e. beneath the level of detection of the SPET camera (Shafer & Levant, 1998)) to estimate specific binding of [^{123}I]-epidepride to D_2/D_3 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 D_2/D_3 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 D_2 receptor density is similar in drug naïve patients with schizophrenia and healthy volunteers. There are as yet no *in vivo* studies comparing temporal cortical D_2/D_3

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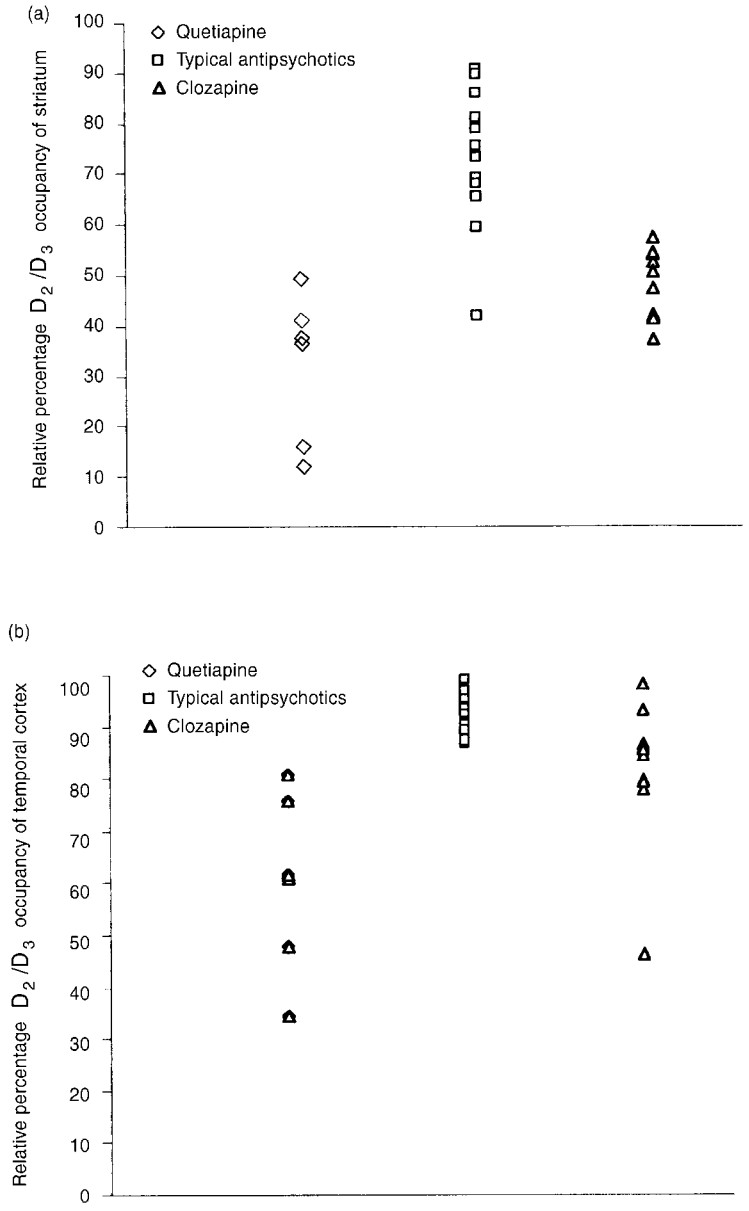

Fig. 3 Scatterplots of individual relative percentage D_2/D_3 receptor occupancy values in the striatum and temporal cortex of patients treated with quetiapine (n=6), clozapine (n=10) and typical antipsychotic drugs (n=12).

Table 4 Mean relative percentage D_2/D_3 occupancy (s.d.) for antipsychotic drugs estimated by [^{123}I]-epidepride single photon emission tomography (P values report results of t-test in each case)

Drug	Temporal cortex	Striatum	Limbic selectivity ratio
Quetiapine	60.1 (17.2)	32.0 (14.6)	1.9
Typical antipsychotics	93.2 (4.0)	80.0 (11.4)	1.18
(Bigliani *et al*, 1999)	$P<0.0001$	$P<0.0001$	$P=0.003$
Clozapine	83.1 (11.4)	49.8 (4.9)	1.67
(Pilowsky *et al*, 1997)	$P=0.006$	$P=0.003$	$P=0.144$

density in untreated patients with schizophrenia and healthy controls. However, a post-mortem study found disorganisation, but no alteration in D_2/D_3 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 [^{123}I]-epidepride behaviour in healthy volunteer studies (Kornhuber *et al*, 1995; Pirker *et al*, 1997). The peak of [^{123}I]-epidepride specific binding to D_2/D_3 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 D_2/D_3 specific binding index over 180- to 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 (Bigliani *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 [^{123}I]-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 D_2/D_3 binding of [^{123}I]-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 D_2/D_3 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% D_2/D_3 receptor occupancy in

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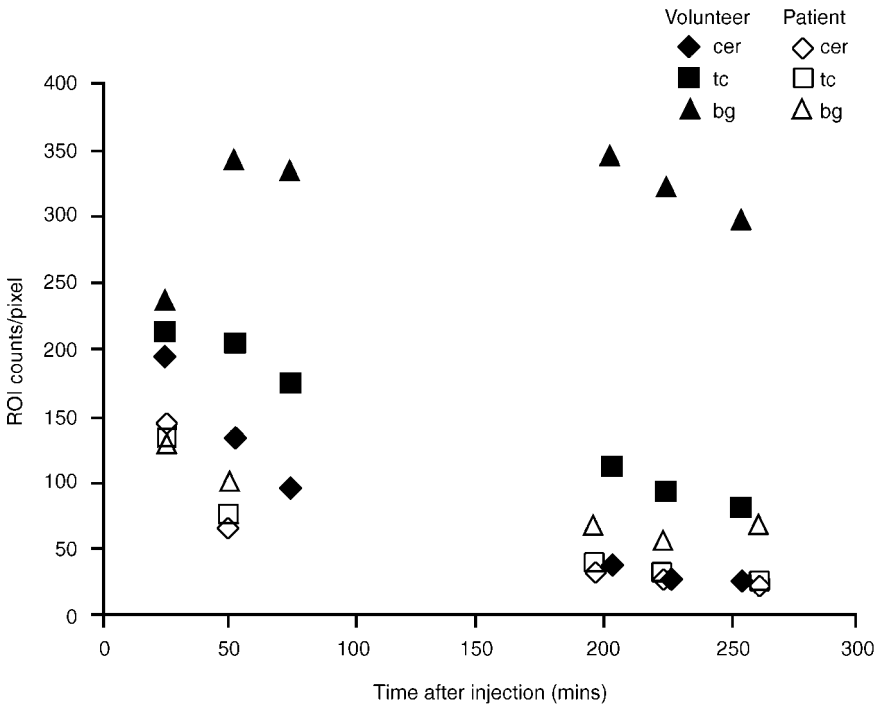

Fig. 4 Total [^{123}I]-epidepride binding over time (after injection) in basal ganglia (BG), temporal cortical (TC) and cerebellar (CER) regions of interest (ROI; mean activity in each region estimated as counts/pixel), in a representative healthy volunteer and patient (treated with fluphenazine decanoate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

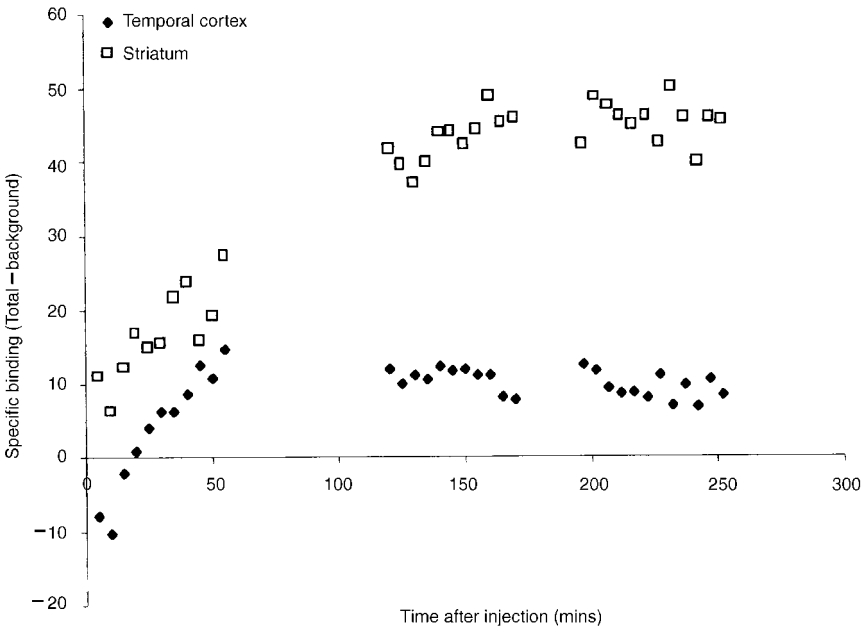

Fig. 5 Time *v.* D_2/D_3 specific binding (total − background activity) curves from a representative patient with schizophrenia scanned on the Picker Prism 3000 triple-headed single photon electron tomography camera, after 3 weeks' quetiapine treatment (dose: 300 mg/day). The peaks of specific activity in striatal and temporal cortical regions occur at about 150 and 50 minutes respectively.

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 Ichise *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 bindng 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.

Striatal percentage D_2/D_3 receptor occupancy by quetiapine

Striatal occupancy of D_2/D_3 receptors was low for quetiapine (mean 32%), which substantiates findings of PET and SPET studies (Kufferle *et al*, 1997; Gefvert *et al*, 1998; Hagberg *et al*, 1998). The variance in our striatal D_2/D_3 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 (Aravintis *et al*, 1997).

We did not find a correlation between quetiapine dose and D_2/D_3 receptor occupancy in the striatum or temporal cortex. The sample was small, the dose range narrow, and the specific binding ratio

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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 ^{11}[C]-raclopride PET to estimate D_2/D_3 occupancy by quetiapine) over a similarly narrow dose range. Clozapine also fails to demonstrate a dose: percentage D_2/D_3 receptor occupancy relationship in the striatum. The variability in measures of striatal D_2/D_3 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 D_2 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 D_2/D_3 receptor occupancy

Quetiapine showed temporal lobe relative percentage D_2/D_3 receptor occupancy values lower than those for clozapine, and far lower than for typical antipsychotic drugs. This is consistent with the relative D_2/D_3 receptor affinities of the three groups of antipsychotic. If temporal lobe or limbic D_2/D_3 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 D_2/D_3 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 D_2/D_3 receptor occupancy reported here might be sufficient to account for the efficacy of quetiapine if the underlying mechanism were D_2/D_3 receptor blockade. There was no correlation between clinical improvement and temporal cortical D_2/D_3 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 D_2/D_3 receptor occupancy (Bigliani *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 D_2 receptors could more easily achieve higher occupancy in regions (such as the temporal cortex) with low receptor density *in vivo*. Quetiapine has lower D_2 affinity than clozapine or typical antipsychotic drugs, so this model could parsimoniously account for its higher limbic selectivity. Seeman & Tallerico (1999) have suggested that antipsychotic drugs with lower D_2 affinity would achieve higher D_2 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 D_2 receptors.

It has also been postulated that limbic selectivity depends on the D_3/D_2 affinity ratio of a drug, with D_3 affinity having greater importance in extrastriatal regions (Scatton *et al*, 1997). Again, quetiapine has a higher D_3/D_2 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 D_2/D_3 blockade by antipsychotic drugs remains unclear and awaits further investigation.

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REFERENCES

Abi-Dargham, A., Kegeles, L., Zea-Ponce, Y., *et al* (1999) Imaging resting phasic dopamine synaptic activity in schizophrenia. *Schizophrenia Research*, **36**, 239.

Alcohol, Drug Abuse, and Mental Health Administration (1974) *Abnormal Involuntary Movements Scale (AIMS)*. Washington, DC: Department of Health, Education and Welfare.

American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders* (4th edn) (DSM–IV). Washington, DC: APA.

Andreason, N. C. (1981) *Scale for the Assessment of Negative Symptoms (SANS)*. Iowa City, IA: University of Iowa.

—— (1984) *Scale for the Assessment of Positive Symptoms (SAPS)*. Iowa City, IA: University of Iowa.

Aravintis, L. A., Miller, B. G. & Seroquel Trial 13 Study Group (1997) Multiple fixed doses of 'Seroquel' (Quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. *Biological Psychiatry*, **42**, 233–246.

Barnes, T. R. E. (1989) A rating scale for drug-induced akathisia. *British Journal of Psychiatry*, **154**, 672–676.

Bigliani, V., Mulligan, R. S., Acton, P. D., *et al* (1999) *In vivo* occupancy of striatal and temporal cortical D_2/D_3 dopamine receptors by typical antipsychotic drugs: [^{123}I]-epidepride single photon emission tomography (SPET) study. *British Journal of Psychiatry*, **175**, 231–238.

Camps, M., Cortes, R., Gueye, B., *et al* (1989) Dopamine receptors in human brain. Autoradiographic distribution of D_2 sites. *Neuroscience*, **28**, 275–290.

Damasio, H. & Damasio, A. R. (1989) *Lesion Analysis in Neuropsychology*. New York: Oxford University Press.

Endicott, J., Spitzer, R. L., Fleiss, J. L., *et al* (1976) The Global Assessment Scale: a procedure for measuring overall severity of psychiatric disturbances. *Archives of General Psychiatry*, **33**, 766–771.

Farde, L., Suhara, T., Nyberg, S., *et al* (1997) A PET study of ^{11}C-FLB-457 binding to extrastriatal D_2 dopamine receptors in healthy subjects and antipsychotic drug-treated patients. *Psychopharmacology*, **133**, 396–404.

Fujita, M., Seibyl, J. P., Verhoeff, N. P. L. G., *et al* (1999) Kinetic and equilibrium analyses of [^{123}I]-epidepride binding to striatal and extrastriatal dopamine D_2 receptors. *Synapse*, **34**, 290–304.

Gefvert, O., Bergstrom, M., Langstrom, B., *et al* (1998) Time course of central nervous dopamine-D_2 and 5-HT_2 receptor blockade and plasma drug concentrations after discontinuation of quetiapine (Seroquel) in patients with schizophrenia. *Psychopharmacology*, **135**, 119–126.

Goldsmith, S. K., Shapiro, R. M. & Joyce, J. N. (1997) Disrupted pattern of D_2 dopamine receptors in the temporal lobe in schizophrenia: a postmortem study. *Archives of General Psychiatry*, **54**, 649–658.

Goldstein, J. (1995) Preclinical pharmacology of new atypical antipsychotics in late stage development. *Experimental Opinion in Investigational Drugs*, **4**, 291–298.

Hagberg, G., Gefvert, O., Bergstrom, M., *et al* (1998) N-[^{11}C]Methylspiperone PET, in contrast to [^{11}C]raclopride, fails to detect D_2 receptor occupancy by an atypical neuroleptic. *Psychiatry Research*, **82**, 147–160.

Ichise, M., Fujita, M., Seibyl, J. P., *et al* (1999) Graphical analysis and simplified quantification of striatal and extrastriatal dopamine D_2 receptor binding with [^{123}I]epidepride SPECT. *Journal of Nuclear Medicine*, **40**, 1902–1912.

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Kornhuber, J., Brucke, T., Angelberger, P., *et al* (1995) SPECT imaging of dopamine receptors with [^{123}I]-epidepride: characteristics of uptake in the human brain. *Journal of Neural Transmission*, **101**, 95–103.

Kufferle, B., Tauscher, J., Asenbaum, S., *et al* (1997) IBZM SPECT imaging of striatal dopamine-2 receptors in psychotic patients treated with the novel antipsychotic substance quetiapine in comparison to clozapine and haloperidol. *Psychopharmacology*, **133**, 323–328.

Laruelle, M., Abi-Dargham, A., Gil, R., *et al* (1999) Increased dopamine transmission in schizophrenia: relationship to illness phase. *Biological Psychiatry*, **46**, 56–72.

Lidow, M. S., Williams, G. V. & Goldman-Rakic, P. S. (1998) The cerebral cortex: a case for a common site of action of antipsychotics. *Trends in Pharmacological Sciences*, **19**, 136–140.

Moghaddam, B., Berridge, C. W., Goldman-Rakic, P. S., *et al* (1993) *In vivo* assessment of basal and drug-induced dopamine release in cortical and subcortical regions of the anesthetized primate. *Synapse*, **13**, 215–222.

Montgomery, S. A. & Åsberg, M. (1979) A new depression scale designed to be sensitive to change. *British Journal of Psychiatry*, **134**, 382–389.

Overall, J. & Gorham, D. E. (1962) The brief psychiatric rating scale. *Psychological Reports*, **10**, 799–812.

Pilowsky, L. S., Mulligan, R. S., Acton, P. D., *et al* (1997) Limbic selectivity of clozapine. *Lancet*, **350**, 490–491.

——, Bigliani, V., Mulligan, R. S., *et al* (1998) Clozapine preferentially occupies limbic cortical D_2/D_3 receptors *in vivo*: a ^{123}I-epidepride SPET (single photon emission tomography). *Journal of Psychopharmacology*, **12** (suppl. A), A53.

Pirker, W., Asenbaum, S., Wenger, S., *et al* (1997) Iodine-123-epidepride-SPECT: studies in Parkinson's disease, multiple system atrophy and Huntington's disease. *Journal of Nuclear Medicine*, **38**, 1711–1717.

Scatton, B., Claustre, Y., Cudennec, A., *et al* (1997) Amisulpride: from animal pharmacology to therapeutic action. *International Journal of Clinical Psychopharmacology*, **12** (suppl. 2), S29–S36.

Schafer, R. A. & Levant, B. (1998) The D_3 dopamine receptor in cellular and organismal function. *Psychopharmacology*, **135**, 1–16.

Seeman, P. & Tallerico, T. (1999) Rapid release of antipsychotic drugs from dopamine D_2 receptors: an explanation for low receptor occupancy and early clinical relapse upon withdrawal of clozapine or quetiapine. *American Journal of Psychiatry*, **156**, 876–884.

Simpson, G. H. & Angus, J. W. S. (1970) A rating scale for extra-pyramidal side effects. *Acta Psychiatrica Scandinavica*, **212** (suppl.), 11–19.

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_2 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:relative 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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Suhara, T., Sudo, Y., Okauchi, T., *et al* (1999) Extrastriatal dopamine D_2 receptor density and affinity in the human brain measured by 3D PET. *International Journal of Neuropsychopharmacology*, **2**, 73–82.

Xiberas, X., Martinot, J. L., Pailliere-Martinot, M. L., *et al* (1999) In vivo interactions of antipsychotic drugs with the extrastriatal D_2 dopamine receptors. *Schizophrenia Research*, **36**, 249.

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