A Positron Emission Tomography Study of Quetiapine in Schizophrenia

A Preliminary Finding of an Antipsychotic Effect With Only Transiently High Dopamine D₂ Receptor Occupancy

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Background: Quetiapine is a new atypical antipsychotic medication. As such, relatively little has been published regarding its in vivo effects at the dopamine type 2 (D₂) and serotonin type 2a (5-HT₂a) receptor systems. The following study was undertaken to explore these effects across the clinical dose range and relate this information to its clinical profile.

Methods: Twelve patients with schizophrenia were randomly assigned to doses of 150 to 600 mg/d (n = 3, at 150, 300, 450, and 600 mg/d) of quetiapine. After 3 weeks of treatment, D₂ and 5-HT₂a occupancy were measured using positron emission tomography (PET) imaging, 12 to 14 hours after the last dose. Clinical efficacy and adverse effect ratings were obtained at baseline, at the time of PET scanning, and at 12 weeks. Two additional patients were included to examine the effects of the drug 2 to 3 hours after last dose.

Results: Quetiapine was an effective antipsychotic and improved the extrapyramidal symptoms and prolactin level elevation noted at baseline. It achieved these results with minimal (0%-27%) D₂ occupancy 12 hours after the last dose. Study of the additional subjects revealed that quetiapine does give rise to transiently high (58%-64%) D₂ occupancy 2 to 3 hours after a single dose that then decreases to minimal levels in 12 hours.

Conclusions: Quetiapine shows a transiently high D₂ occupancy, which decreases to very low levels by the end of the dosing interval. Quetiapine’s low D₂ occupancy can explain its freedom from extrapyramidal symptoms and prolactin level elevation. The data suggest that transient D₂ occupancy may be sufficient for its antipsychotic effect. Future studies controlling for nonpharmacological effects as well as activities on other receptors will be necessary to confirm this suggestion.
PATIENTS AND METHODS

PATIENTS

This study was approved by the Human Subjects Review Committee of the University of Toronto and all subjects provided written consent prior to participation. Patients were recruited from the inpatient units and outpatient clinics of the Schizophrenia Division of the Centre for Addiction and Mental Health, a university-affiliated psychiatric facility. Patients were included if they were voluntary and competent to consent to treatment and research, aged between 18 and 45 years, and carried a clinical diagnosis of schizophrenia confirmed using a DSM-IV criteria checklist by a trained research rater (C.J.). Patients were excluded if they suffered from a major medical or neurological illness, met DSM-IV criteria for substance abuse in the last 3 months or substance dependence in the last 6 months, or had received a depot antipsychotic medication in the 12 months prior to the study. All patients agreed to abstain from use of alcohol or illicit psychoactive drugs during the 12-week study period; this was monitored clinically, but was not confirmed using any blood or urine tests. Subjects were not involved in any specific non-pharmacological therapies aside from routine clinical care. Patients were allowed access to benzodiazepines and antiparkinsonian medication as deemed clinically necessary; no subjects required antiparkinsonian treatment.

The patients were assigned to treatment, using a random sequence generated by computer, stratified to provide 3 patients at each of the 4 doses: 150 mg/d (75 mg twice daily), 300 mg/d (150 mg twice daily), 450 mg/d (225 mg twice daily) and 600 mg/d (300 mg twice daily). All subjects who completed the PET scans are included in the analysis. Three original subjects discontinued the study before the PET scans (2 of them because of protocol noncompliance and 1 because of inability to complete the PET scan) and were replaced by random assignment. When the initial results showed very low D2 occupancy despite adequate plasma levels, it was decided to recruit 2 additional subjects to investigate the time course of occupancy. Two subjects who were receiving routine clinical treatment with quetiapine, but met all inclusion and exclusion criteria listed above, were recruited for this component. Both the patients had been receiving quetiapine for more than 1 month and were at multiple-dose steady state; one (aged 24 years and male) was receiving 400 mg twice daily; while another (aged 29 years and male) was receiving 450 mg every night.

STUDY DOSING AND CLINICAL ASSESSMENTS

Patients enrolled in the study went through a 1- or 2-day washout and were then titrated to their assigned dose of quetiapine. The 150-mg group achieved their target dose in 3 days, the 300-mg/d group in 4 days, the 450-mg/d group in 6 days, and the 600-mg/d group in 7 days. Patients were then held at their assigned dose for at least a period of 14 days and were scanned between days 21 and 28 of quetiapine treatment. Given the short half-life of quetiapine (approximately 6 hours), all patients should have been at steady state plasma concentrations at the time of the PET scan. After the PET scan, the patients reverted to flexible dosing (150-600 mg/d) and were evaluated with structured ratings for another 8 weeks.

To determine clinical outcome, each of the patients was rated on the Positive and Negative Syndrome Scale (PANSS) and a Clinical Global Impression Scale (CGI) for severity of illness and for improvement with treatment. Adverse effects were rated using the Barnes Akathisia Scale and the Simpson Angus Rating Scale. These scales were administered to all the patients by a single trained rater (C.J.) who has previous experience as well as

RESULTS

CLINICAL CHARACTERISTICS

Twelve patients completed the controlled part of the study. The sample consisted of 9 men and 3 women, with a mean ± SD age of 29.6 ± 6 years (age range, 21-40 years). Ten of the patients were outpatients and 2 were inpatients. The average number of previous admissions was 1 (range, 0-4 admissions). The mean ± SD duration of illness since first psychotic break was 93 ± 76 months.

DRUG LEVELS AND RECEPTOR OCCUPANCY

Patients showed a dose-dependent increase in plasma levels of quetiapine: mean ± SD, 29 ± 4 ng/mL when given 150 mg/d; 50 ± 28 ng/mL when given 300 mg/d; 172 ± 111 when given 450 mg/d; and 201 ± 113 when given 600 mg/d (F1,10 = 10.67, r = 0.71, P = .008). Plasma levels at the time of the [18F]-setoperone scan were about 70% of those at the time of raclopride scan (as would be expected from a drug with 6-hour half-life) and were highly correlated (F1,9 = 183, r = 0.97, P < .001).

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established high interrater reliability in the use of these clinical instruments. The rater was blind to occupancy (the main variable of interest) but was not blind to dose. The scales were administered at baseline before the initiation of quetiapine, again at the time of the PET examination (days 21-28), and finally at the end of the clinical phase of the study at week 12.

PET SCANNING PROCEDURES

The PET scans to estimate D2 occupancy were obtained after the injection of 10 mCi of high-specific activity [11C]-raclopride (300-1600 Ci/mmol) through the use of a bolus plus infusion protocol and head-dedicated PET camera (GEMS 2048-15B; General Electric Medical Systems, Milwaukee, Wis). The methods employed here are identical to those described in previous studies of risperidone, olanzapine, and clozapine and have been explained in detail before.6,23 An estimate of the D2 binding potential of [11C]-raclopride (D2BP) was obtained from a ratio of the striatal to the cerebellar activity minus 1, in the 35- to 73-minute period after injection. In our laboratory, this method yields a within-subject scan-rescan SD of 6% and is operationalized to yield a high interrater and intrarater reliability of greater than 0.95 (as measured using intraclass correlation coefficient [ICC]).

To calculate D2 receptor occupancy, one requires a pretreatment estimate of available D2 receptors. In 2 of the 3 neuroleptic-naive patients in this study, we were able to obtain their baseline D2BP, and this was used in the calculation of their D2 occupancy. However, for most of our patients we used an age-corrected baseline derived from a separate sample of 12 antipsychotic-naive patients with schizophrenia and 13 age-matched normal controls.6,23

The 5-HT2a scans were obtained using a bolus injection of 5 mCi of high specific activity [18F]-setoperone (360-6210 Ci/mmol) after the method developed and standardized by Blin et al.23,24 The 5-HT2 occupancy was determined in the prefrontal cortex using regions of interest drawn on the [18F]-setoperone scan using a standardized method. An index of the 5-HT2 receptors was obtained from the prefrontal cortex to cerebellar activity ratio over the 65- to 90-minute period. The details of this method have been described before,25 in which we show that the method yields an average within-subject scan-rescan SD of 7% and an acceptably high interrater reliability (ICC, r>0.95). Occupancy was calculated using an age-corrected 5-HT2a BP obtained from 11 neuroleptic-free patients with schizophrenia and 26 age-matched normal controls reported recently.26

At the time of the PET scans, blood was drawn for a quetiapine level and prolactin level analysis. The levels of quetiapine were determined by Keystone Analytical Laboratories (North Wales, Penn) in heparinized plasma using a liquid chromatography/mass spectroscopy/mass spectroscopy method. Prolactin levels were determined using a 2-site chemoluminometric immunoassay with a minimum detectable limit of 0.3 ng/mL and a coefficient of variance of 3.6% to 4.5% (ACS; Ciba-Corning Diagnostics, Corning, NY).

STATISTICAL ANALYSES

Statistical analyses were implemented using SPSS v.8.0 (SPSS Inc, Chicago, Ill). The change in clinical indices was assessed using a repeated-measures analysis of variance (ANOVA). Change was considered significant only if the omnibus test (Pillai trace) showed the probability of type 1 error of α<.05, and the within-subject change was significant with an α<.05. The relationship between dose, plasma levels, and occupancy was assessed using a simple general linear model (correlation and linear regression), with significance set at α<.05. The D2 and 5-HT2a occupancy were compared using a 2-sided paired t test, with α<.05.

Twelve hours after the last dose, quetiapine had a weak effect on D2 occupancy (Figure 1). Two subjects (Table 1) exhibited negative occupancies (ie, the D2BP on quetiapine was higher than that expected from naïve patients at that age) of −24% and −29%, a finding that probably reflects baseline variance and/or receptor up-regulation from previous treatments. Even if these subjects are removed, the finding is unchanged: the average D2 occupancy was −2%±2% from 150 mg/d; 5%±7% from 300 mg/d; 14%±11% from 450 mg/d; and 19%±1% from 600 mg/d.

Because of the implications of receptor up-regulation and variance caused by lack of an individual baseline, the results in the 3 neuroleptic-naive subjects are particularly important. These 3 subjects received (by random assignment) 150, 300, and 450 mg/d, respectively. For the patients who received 150 and 300 mg/d (Table 1), we had individual [11C]-raclopride baseline data. The change in their D2 binding potential as measured before and after the drug was administered was 3%, which is well within the scan-rescan error (6%-8%) of our method.6 The subject taking 450 mg/d showed an occupancy of 27%, which reflects certain, if low, occupancy of D2 receptors at this dose. Thus, it would seem that even in patients with individual baseline and no D2 up-regulation, the quetiapine D2 occupancy at 12 hours after dose is still low.

Figure 1. The relationship between serotonin type 2a (5-HT2a) receptor occupancy and quetiapine plasma levels in 11 patients. The curve is fit to the equation 5-HT2 occupancy = 100 × plasma level/plasma level + 29 ng/mL, where the 29 ng/mL is the level for 50% occupancy, and the 95% confidence interval for this constant is 14 to 44 ng/mL. A reliable equation could not be obtained to characterize the relationship between type 2 dopamine occupancy and quetiapine plasma levels.

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On observing low D2 occupancies at 12 hours, we were interested in investigating the time course of D2 occupancy. This was studied in 2 additional patients who were receiving quetiapine outside of the controlled study. One of these subjects was receiving 400 mg in a single dose at night. His D2 occupancy, 3 hours after a single 400 mg dose, was 58% (plasma levels, 770 ng/mL), but this rapidly declined to a D2 occupancy of 20% in the next 400 mg dose, was 58% (plasma levels, 770 ng/mL), but this rapidly declined to a D2 occupancy of 20% in the next 4 hours. This transiently high D2 occupancy was associated with a transiently high prolactin level of 19 µg/L (upper limit of normal for men is 17.7 µg/L), which decreased to 4.4 µg/L. A second patient was given long-term quetiapine treatment with a single dose of 450 mg at bedtime. His D2 occupancy reached 64% at 2 hours, but declined to 0% in 24 hours; an excursion that was associated with an abnormally high prolactin level of 27.9 µg/L at 2 hours, which declined to 1.8 µg/L by 24 hours (Figure 2).

Quetiapine’s 5-HT2a occupancy was measured after the scan to measure its D2 occupancy. Quetiapine had a greater effect 5-HT2a than D2 occupancy for each subject (paired t-test: t1,9=7.6; P < .001). Fourteen to 15 hours after the last dose, 5-HT2a occupancy increased as a function of dose (F1,8=20.2; r=0.83, P = .001): 20%±2% at 150 mg/d; 57%±12% at 300 mg/d; 68%±13% at 450 mg/d; and 78%±15% at 600 mg/d.

CLINICAL MEASURES AND OUTCOME

Treatment with quetiapine was associated with significant improvement on clinical scales (CGI as well as PANSS total scores), significant effects on positive symptoms, and a trend towards a significant effect on general symptoms. The improvements obtained at the 3- to 4-week mark were sustained at the end of the study. The details are presented in Table 2. Patients had low levels of EPS at entry into the study, which remained unchanged throughout the duration of the study. Five of 12 patients showed akathisia at baseline; of these, 4 improved by the time of the PET scan and all were improved by the end of study, although this trend did not achieve significance. With regards to prolactin levels, all but 1 patient showed a decrease (Table 1); the 3 patients whose levels were elevated in the abnormal range at baseline normalized by the time of the PET examination.

The major finding of this study is that quetiapine induces an antipsychotic effect with only transiently high D2 occupancy. This finding questions the assumption that continuously high D2 occupancy is required for response. However, the study has several limitations—clinical as well as technical—and these findings should be considered preliminary and will need to be replicated.

The main limitation of this study is the lack of control for any nonpharmacological factors that may influence treatment. It is possible that the improvement we observed in this sample may result from nonspecific therapeutic factors, such as hospitalization, sedative effects of the drug, or a placebo effect. While the nature and magnitude of the clinical improvement noted here is consistent with previous large-scale, placebo-controlled studies,16,17 an appropriate nonpharmacological control would be essential to accurately determine the true contribution of pharmacological antipsychotic effect. Furthermore, we could not quantify the peak occupancy in each patient. While there can be little doubt that patients do have a transient peak of D2 occupancy based on our data and other recent PET findings,30 the exact magnitude of that peak in each patient was not determined. A more optimal design should measure both peak and trough within each patient and thus build a stronger case for the connection between the transient D2 occupancy and response. Finally, [11C]-raclopride provides only striatal D2 occupancy. This raises the question of whether extrastriatal D2 occupancy of quetiapine is higher or more sustained than striatal D2 occupancy. While this is possible, it is unlikely. One study31 did find a higher limbic

Table 1. Quetiapine Dose and Plasma Levels, Receptor Occupancy, and Prolactin Levels in 12 Patients*

<table>
<thead>
<tr>
<th>Patient No./Age, y/Sex</th>
<th>Quetiapine Dose, mg/d</th>
<th>Previous Treatment (mg/d)</th>
<th>11C-Raclopride Scan</th>
<th>[18F]-Setoperone Scan</th>
<th>D2 Occupancy, %</th>
<th>5-HT2a Occupancy, %</th>
<th>Baseline PRL ng/mL</th>
<th>PET PRL ng/mL†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/30/M 300 Loxapine (20)</td>
<td>114.2</td>
<td>32.2</td>
<td>19</td>
<td>63</td>
<td>10.40</td>
<td>1.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/28/M 300 Haloperidol (1.5)</td>
<td>135.1</td>
<td>97.3</td>
<td>8</td>
<td>79</td>
<td>24.30t</td>
<td>6.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/40/M 450 Risperidone (8)</td>
<td>29.3</td>
<td>17.2</td>
<td>19</td>
<td>23.00t</td>
<td>9.95</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/22/M 150 Risperidone (4)</td>
<td>297.1</td>
<td>226.1</td>
<td>7</td>
<td>53</td>
<td>25.4</td>
<td>2.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/28/M 450 Risperidone (3)</td>
<td>25.2</td>
<td>14.4</td>
<td>−29</td>
<td>22</td>
<td>2.50</td>
<td>7.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6/25F 150 Olanzapine (15)</td>
<td>161.1</td>
<td>125.2</td>
<td>−24</td>
<td>94</td>
<td>20.00t</td>
<td>6.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7/38F 600 Olanzapine (20)</td>
<td>328.7</td>
<td>218.1</td>
<td>20</td>
<td>78</td>
<td>6.1</td>
<td>7.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8/31/M 600 Olanzapine (20)</td>
<td>84.8</td>
<td>53.0</td>
<td>27</td>
<td>74</td>
<td>7.0</td>
<td>5.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9/24/M 450 None</td>
<td>21.4</td>
<td>12.7</td>
<td>3</td>
<td>46</td>
<td>12.0</td>
<td>7.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10/32/M 300 None</td>
<td>32.9</td>
<td>18.3</td>
<td>2</td>
<td>39</td>
<td>17.2</td>
<td>10.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11/21/F 300 Haloperidol (1.5)</td>
<td>77.2</td>
<td>47.0</td>
<td>11</td>
<td>71</td>
<td>2.7</td>
<td>1.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* D2 indicates type 2 dopamine receptor; 5-HT2, serotonin type 2 receptor; PRL, prolactin levels; PET, positron emission tomography; M, male; and F, female.
† The PET PRL levels are the average of the PRL levels at the time of the [11C]-raclopride and [18F]-setoperone scans, except patient 11, who only had an [11C]-raclopride scan.
‡ Indicates patients with abnormal levels of baseline prolactin.
occupancy with atypical antipsychotics; however, quetiapine was not tested in that study. The study that examined quetiapine found no evidence for preferential blockade of mesolimbic D2 receptors for any antipsychotic.3,32

A recent study comparing striatal with extrastriatal D2 occupancy of clozapine found no significant regional differences in D2 occupancy,33 although a published letter on this issue does make such a claim.34 Since the issue

Figure 2. Transient type 2 dopamine (D2) occupancy with quetiapine, showing a transverse section through added [11C]-raclopride positron emission tomography (PET) scans in patients who were scanned twice after their last dose of quetiapine. Top, The patient received a dose of 400 mg. Bottom, The patient received a dose of 450 mg of quetiapine.

Table 2. Summary of Clinical Data*

<table>
<thead>
<tr>
<th>Scale</th>
<th>Ratings at Baseline, Mean ± SD</th>
<th>PET Ratings (Weeks 3-4), Mean ± SD</th>
<th>Final Ratings (Weeks 10-12), Mean ± SD</th>
<th>Repeated-Measures ANOVA Test of Significance for Within-Subjects Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGI Severity of Illness</td>
<td>4.2 ± 0.7</td>
<td>2.9 ± 1.2</td>
<td>2.9 ± 1.7</td>
<td>F2,22 = 8.8; P = .001</td>
</tr>
<tr>
<td>Improvement</td>
<td>2.7 ± 0.9</td>
<td>3.3 ± 1.9</td>
<td></td>
<td>F2,22 = 5.5; P = .012</td>
</tr>
<tr>
<td>PANSS Total</td>
<td>62.8 ± 17.1</td>
<td>53.5 ± 20.9</td>
<td>52.9 ± 24.4</td>
<td>F2,22 = 6.5; P = .007</td>
</tr>
<tr>
<td>Positive</td>
<td>16.8 ± 5.4</td>
<td>13.2 ± 6.9</td>
<td>13.1 ± 7.4</td>
<td>F2,22 = 10.2; P = .001</td>
</tr>
<tr>
<td>Negative</td>
<td>16.3 ± 8.2</td>
<td>14.9 ± 8.8</td>
<td>15.2 ± 10.5</td>
<td>F2,22 = 0.7; P = .47</td>
</tr>
<tr>
<td>Simpson Angus Scale</td>
<td>0.3 ± 0.7</td>
<td>0.3 ± 0.6</td>
<td>0.3 ± 0.6</td>
<td>F2,22 = 1.0; P = .39</td>
</tr>
<tr>
<td>Barnes Akathisia Scale (global)</td>
<td>1.3 ± 2</td>
<td>0.7 ± 1.3</td>
<td>0.2 ± 0.4</td>
<td>F2,22 = 2.0; P = .15</td>
</tr>
<tr>
<td>Prolactin levels, ng/mL</td>
<td>13.0 ± 6.6</td>
<td>7.4 ± 3.2</td>
<td>7.6 ± 4.5</td>
<td>F2,22 = 7.1; P = .005</td>
</tr>
</tbody>
</table>

* PET indicates positron emission tomography; ANOVA, analysis of variance; CGI, Clinical Global Impression Scale; and PANSS, Positive and Negative Syndrome Scale.
† All the within-subject effects that are reported as significant here were also significant when tested without sphericity, by applying the Greenhouse-Geisser correction.
of extrastriatal occupancy is not fully resolved, future studies may want to explore if quetiapine leads to higher or more sustained extrastriatal D₂ occupancy.

In large-scale, placebo-controlled clinical studies, it has been shown that the level of quetiapine does not produce EPS or sustained prolactin level elevation.⁶,¹⁷ Since previous studies have shown that prolactin level elevation and EPS are encountered only with high levels of D₂ occupancy,³⁸ the present findings can easily explain why quetiapine would not induce these adverse effects. Since 300 to 600 mg/d of quetiapine does not reach the thresholds of D₂ occupancy that usually lead to these adverse effects, one could speculate that even higher doses of quetiapine, 750 to 1000 mg/d, would be unlikely to provoke either EPS or sustained prolactin level elevation.

As compared with other atypical antipsychotics (risperidone, olanzapine and clozapine), quetiapine shows much lower D₂ and 5-HT₂₅ blockade when one compares data 12 hours after the last dose.⁶ While the low levels of D₂ occupancy can easily explain the lack of EPS and prolactin level elevation, the really interesting question brought up by this study is how quetiapine manages to induce antipsychotic response despite having rather low D₂ occupancy at 12 hours. Either quetiapine’s D₂ occupancy is not relevant and the antipsychotic effects are mediated by other receptors (a non-D₂ hypothesis), or, as we suggest, it is quetiapine’s transient D₂ occupancy that mediates its antipsychotic action (the transient D₂ hypothesis).

Our study demonstrates that 300 to 600 mg/d of quetiapine occupies 57% to 78% 5-HT₂₅ receptors. Since it has an even greater affinity for the histamine, receptors,²⁻³²⁵ it is reasonable to assume that these receptors were also highly occupied. Can these high levels 5-HT₂₅ occupancy account for an antipsychotic effect by itself? We think it is unlikely for several reasons. First, the investigational drug MDL 100907, one of the most specific 5-HT₂a antagonists and had no effects on negative symptoms.³⁶ Second, a high D₂ occupancy,⁵,⁸ the present findings can easily explain why quetiapine’s transient D₂ occupancy may be sufficient to induce antipsychotic response despite having rather low D₂ occupancy at 12 hours. Either quetiapine’s D₂ occupancy is not relevant and the antipsychotic effects are mediated by other receptors (a non-D₂ hypothesis), or, as we suggest, it is quetiapine’s transient D₂ occupancy that mediates its antipsychotic action (the transient D₂ hypothesis).

Quetiapine, a new atypical antipsychotic, shows a modest peak of D₂ occupancy with a rapid decline. It is suggested that transient D₂ occupancy may be sufficient to induce antipsychotic response; its low D₂ occupancy may explain quetiapine’s freedom from EPS and sustained prolactin level elevation. However, as the study has clinical and technical limitations, these results should be viewed as preliminary and in need of replication. Future studies should implement a more controlled clinical design and should manipulate the level of transient D₂ occupancy directly.

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REFERENCES

2. Seeman P, Tallierio T. Antipsychotic drugs which elicit little or no parkinsonism bind more loosely than dopamine to brain D2 receptors, yet occupy high levels of these receptors. Mol Psychiatry. 1998;3:123-134.