Cortical Dopamine D2/D3 Receptors Are a Common Site of Action for Antipsychotic Drugs—An Original Patient Data Meta-analysis of the SPECT and PET In Vivo Receptor Imaging Literature

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Subject numbers in neuroreceptor imaging studies of antipsychotic treatment in schizophrenia are generally insufficient to directly test the relationship of regional D2/D3 and 5HT2A receptor binding to clinical efficacy. We selected positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies of antipsychotic dose vs occupancy at both temporal cortex and striatal D2/D3 receptors. We selected corresponding SPECT and PET studies of 5HT2A receptor occupancy. We also selected randomized double-blind clinical trials of antipsychotics, where patients were treated with randomly assigned fixed doses. For each antipsychotic drug, we compared the optimum effective antipsychotic dose with the dose inducing maximal occupancy of D2/D3 receptors in striatum and in temporal cortex as well as at 5HT2A receptors. Both first- and second-generation antipsychotic (FGA, SGA) drugs produced high temporal cortex D2/D3 occupancy. Only FGA produced high striatal D2/D3 receptor occupancy. The clinically effective dose showed correlation with doses inducing maximal dopamine D2/D3 receptor occupancy both in striatum and in temporal cortex, the strongest correlation being with temporal cortex binding. Extrapyramidal side effects (EPSE) were primarily related to striatal D2/D3 receptor occupancy. There was no correlation between 5HT2A occupancy and clinically effective dose. We conclude that cortical dopamine D2/D3 receptor occupancy is involved in antipsychotic efficacy, with striatal D2/D3 occupancy having a likely therapeutic role while also inducing EPSE. We found no evidence for 5HT2A blockade involvement in antipsychotic action, although we cannot exclude this possibility.

Key words: schizophrenia/antipsychotic/efficacy/limbic selectivity/EPSE/SPECT

Introduction

Cortical dopamine D2 receptors have been hypothesized to be a common site of action for both first-generation (typical) antipsychotics (FGAs) and second-generation (atypical) antipsychotics (SGAs).1 The antagonism of 5HT2A receptors has also been hypothesized to play a critical component in SGA therapeutic action.2 Positron emission tomography (PET) and single photon emission computed tomography (SPECT) allow the in vivo imaging of regional antipsychotic medication binding to receptor subtypes to explore the relationship of receptor binding to efficacy and side effects in living schizophrenic patients. These studies are low throughput, high cost, and highly labor intensive. Consequently, sample sizes are usually too small to permit extensive analyses of receptor occupancy vs drug efficacy.

Seeman and Snyder noted a striking correlation between the dose of an antipsychotic to produce D2 receptor occupancy in rodent brain tissue and the clinically effective dose.3,4 We decided to use a similar method, pooling original patient data from multiple centers (total n = 139) and comparing the clinically effective dose for different antipsychotic drugs with the dose required for each drug to induce maximal occupancy at dopamine receptors in striatum and temporal cortex, as well as in 5HT2A receptors. Through this approach, we have been able to explore the role of D2/D3 binding in striatum and temporal cortex plus 5HT2A binding on clinical efficacy.

Methods

Identification and Selection of Regional Dose: Occupancy Studies

Medline and PubMed were searched to identify all PET or SPECT studies examining dopamine and/or serotonin receptor occupancy of FGAs and SGAs, using the keywords “antipsychotic,” “occupancy,” “dopamine,” “serotonin,” and “emission tomography.” We selected
studies in which D2/D3 receptor availability was estimated in the same patient in both striatum and temporal cortex and in which patients were in steady state on an antipsychotic drug (chronic dosing). These criteria were designed to minimize any variation in apparent receptor occupancy due to differences in ligand affinity for receptor subtypes, intersubject variability of receptor expression, and differences in drug dose.

One hundred thirty-nine studies were identified using our Medline search strategy. In total, 15 articles met our inclusion criteria for estimation of regional D2/D3 receptor occupancy with antipsychotic dose,5–19 and 3 articles met our inclusion criteria to analyze the relationship between antipsychotic dose and 5HT2a receptor occupancy.20–22 Of the articles that were excluded, 78 articles reported striatal dopamine receptor occupancy only and 20 were review articles without detailed data. The remaining articles were excluded because they did not involve SPECT or PET radioligands, they were nonhuman studies, or they did not study D2/D3 or 5HT2a receptors.

Consistency of Imaging Studies

The methodology of all the selected imaging studies was broadly comparable, although there were 2 distinct designs of study to measure dopamine D2/D3 receptor occupancy with antipsychotic dose,5–19 and 3 articles met our inclusion criteria to analyze the relationship between antipsychotic dose and 5HT2a receptor occupancy.20–22 Of the articles that were excluded, 78 articles reported striatal dopamine receptor occupancy only and 20 were review articles without detailed data. The remaining articles were excluded because they did not involve SPECT or PET radioligands, they were nonhuman studies, or they did not study D2/D3 or 5HT2a receptors.

Data Extraction—Imaging Studies

For each subject from the dopamine imaging studies, we extracted antipsychotic drug taken, dose of antipsychotic drug, estimated occupancy at striatal dopamine D2/D3 receptors, and estimated occupancy at temporal D2/D3 receptors, contacting the authors where necessary for additional data. From these data, we determined dose vs occupancy on a per-subject basis. We also calculated mean D2/D3 occupancy at striatum and temporal cortex for each drug. In one study,3 we were unable to match antipsychotic doses in a given subject with D2/D3 receptor occupancy data for the same subject, and so we could use data from this study to calculate mean occupancies only.

For the serotonin imaging studies, we extracted estimated mean occupancy of 5HT2a receptors at fixed doses of each antipsychotic drug.

For striatal and temporal cortex D2/D3 receptor occupancy and for 5HT2a occupancy, we calculated the dose at which consistent maximal occupancy occurred (ED95occ). Because FGAs consistently showed significantly higher D2/D3 receptor occupancy in striatum at doses imaged compared with SGAs (which had a mean striatal occupancy of 49%), it is possible that the ED95occ for FGAs (calculated from the doses imaged) may have meant that like was not being compared with like with respect to striatal D2/D3 receptor occupancy. Therefore, we also calculated the dose at which FGAs would be expected to achieve 49% striatal D2/D3 receptor occupancy. We used the slope of the significant linear correlation between FGA dose given to each individual patient, in haloperidol equivalents, and their individual striatal occupancy to estimate the dose necessary to achieve a mean striatal occupancy of 49% for FGAs.

Identification and Selection of Dose:Efficacy and Dose:Side Effect Studies

In order to calculate the dose-response curve for efficacy and extrapyramidal side effects (EPSE), we selected studies in which patients with schizophrenia were randomly assigned to placebo and to fixed doses (or dose ranges—at steady state) of SGAs and efficacy and EPSE assessed by double-blind techniques and included all such trials. The design is necessary for a valid assessment of dose response.

For olanzapine, we included 2 studies that performed dose ranging of acute patients: one assigning patients to placebo and a narrowly defined dose range of 5 ± 2.5, 10 ± 2.5, and 15 ± 2.5 mg/day of olanzapine23 and the other assigning patients to placebo and 1 and 10 mg/day of olanzapine.24 For risperidone, we used 2 large registration trials, one from the United States25 and one from Canada comparing patients to placebo and 2, 4, 8, and 16 mg/day.26 For quetiapine, we used 3 fixed-dose studies: one assigning patients to placebo and 75, 150, 300, 450, and 600 mg/day quetiapine27; the second
assigning patients to placebo, low dose range (< 250 mg/day), and high dose range (>250 mg/day) quetiapine, and the third assigning patients to 400, 600, and 800 mg/day quetiapine. For sertindole, we used 2 studies: one comparing placebo to 8, 12, and 20 mg/day sertindole and 4, 8, and 16 mg/day haloperidol and another comparing sertindole to placebo, 8, 12, and 20 mg/day. For amisulpride, there was only one dose:response study that compared 100, 400, 800, and 1200 mg/day amisulpride, with no placebo group. Adjustment for the placebo effect in this study was made by extrapolating the placebo effect from other studies. For clozapine, there was again only one dose:response study comparing 100, 300, and 600 mg/day. There was no placebo group, but during the washout phase, placebo-treated patients deteriorated, so we used baseline period for an estimate of placebo response.

Using higher doses than necessary can produce an increase in side effects but no greater increase in therapeutic benefit because the dose-response curve is sigmoidal. We calculated the optimal dose from the dose-response curve from the large random assignment double-blind fixed-dose clinical trials. We termed this the ED95 clinically effective dose (ED95eff) because it corresponded to the dose at which the drug is maximally effective for almost all the patients. The methodology of study identification, analysis, and calculating dose-response has been previously described, and more details about such calculations are reported in detail in our previous publication.

### Analyses

**Comparison of Regional Receptor Occupancy in Different Antipsychotic Drugs.** We compared mean D2/D3 receptor occupancy in striatum and temporal cortex or their ratio in FGA vs SGA using unpaired Student’s t test with unequal variances.

**Relationship of Clinical Response to Receptor Occupancy.** We plotted the log of ED95eff (y-axis)
against the log of ED95occ for D2/D3 receptor occupancy in the temporal cortex. Because FGAs did not show comparable striatal D2/D3 receptor occupancies to SGAs at doses imaged (discussed above), we plotted both the dose inducing maximal striatal D2/D3 receptor occupancy by FGAs as well as the estimated FGA dose to achieve the same striatal occupancy as seen with SGAs (49%). We compared the correlations of efficacy vs striatal or temporal cortex with a t-test for the difference between 2 correlations sharing a common variable.34

Because the 5HT2A receptor occupancy studies did not always include doses equivalent to the ED95eff (therapeutic doses), there were 3 dimensions to examine: the dose used to image, the level of 5HT2A occupancy at this dose, and the ED95eff (therapeutic dose). We plotted the range of doses imaged vs 5HT2A occupancy with a line and indicated the ED95eff for each drug using a separate marker.

We examined the relationship between ED95occ and ED95eff for 5HT2A occupancy and for striatal and temporal cortex D2/D3 receptor occupancy using Pearson product-moment correlation.

**Sensitivity Analysis.** Although our estimates of ED95eff were based on the evidence derived from the dose-finding studies of each compound, there remained some uncertainty about the most effective clinical dose for some agents, eg, the 2 dose-response studies of quetiapine yielded slightly different estimates, and opinion differs about the optimal dose of clozapine. In order to address these issues, we performed sensitivity analyses at 28 different doses (approximately 4 on each of the 7 drugs) and correlated these to receptor occupancy.

**Relationship of EPSE to Receptor Occupancy.** We explored the EPSE risk of FGAs by correlating the doses (in haloperidol equivalents) in the individual patients from the imaging studies with striatal and temporal receptor occupancy.

**Comparison of Results Using Different Ligands and Different Modeling Methods.** SPECT and PET studies of occupancy can be divided into those using a single ligand to estimate binding in both striatal and cortical brain regions ([123I]epidepride and [18F]fallypride) and those using different ligands for each brain region ([11C]raclopride for striatum and [11C]FLB-457 for cortical brain regions). Analysis of binding is now usually estimated using the simplified reference tissue model (SRTM). Some earlier studies employed a simpler (ratio) method (see table 1). There has been some concern that different methods of measuring dopamine receptor occupancy may be affected by different imaging methods or different methods of quantification of the radiotracer binding.17,35-38 In order to address these concerns, we included all studies using different methods of analysis in the meta-analysis. We also analyzed the differences in receptor occupancy reported by both single-ligand and dual-ligand methods of imaging separately and then separately analyzed the differences between the SRTM and ratio methods of binding estimation.

To study the difference between the single- and the dual-ligand approach to determine occupancy, we used an analysis of variance (ANOVA) with drug (typical-atypical) and single vs dual ligand as dependent factors and D2/D3 receptor occupancy of striatal or temporal cortex as the dependent variable without the interaction in the final model. A similar ANOVA was done using drug and SRTM vs ratio method and an analysis of covariance (ANCOVA) with single vs dual ligand and SRTM vs ratio methods as covariants, to adjust the typical-atypical differences.

**Results**

**FGA and SGA Drugs and D2/D3 Occupancy**

FGAs (n = 28) produced significantly higher striatal (74 ± SD = 12%) occupancy than SGAs (n = 115, 49 ± 21%; t = 8.8, df = 73.7, P < 4 × 10−13). Both FGAs and SGAs produced 70%–80% D2/D3 occupancy in the temporal cortex, although FGAs had slightly higher cortical occupancy (77 ± 12%) than SGAs (67 ± 19%) (unpaired t test, t = 3.5, df = 62.3, P = .001) (figure 1A).

FGAs showed a significantly greater occupancy of striatal dopamine D2/D3 receptors (S/T ratio = 96%, SD = 24%) than SGAs (S/T ratio = 74%, SD = 35%; t = 3.7, df = 41, P < .001). All SGAs showed greater differentiation between cortical and striatal D2/D3 binding within each subject than FGAs (amisulpride, 36 ± 15%; clozapine, 17 ± 16%; olanzapine, 40 ± 16%; quetiapine, 20 ± 12; risperidone, 26 ± 7%; sertindole, 16 ± 10%, FGAs, 5 ± 17%).

**Correlation of Clinically Effective Dose With Receptor Occupancy**

There was a high correlation of ED95eff with temporal cortex dopamine D2/D3 receptor ED95occ (r = .95, n = 7, P < .001; see figure 1B). A less strong correlation was also found between ED95eff and actual striatal dopamine D2/D3 receptor ED95occ (r = .76, n = 7, P = .046; see figure 1C; significance of difference between r = .95 and r = .76: t = 1.7, df = 4, P = .08). Substituting the FGA ED95occ with the dose required to achieve the same striatal occupancy as SGAs had no significant effect on the correlation (r = .76, n = 7, P = .046). Interestingly, the correlation between the natural log of the antipsychotic doses was highly significant for both striatum and temporal cortex D2/D3 ED95occ vs ED95eff, although temporal cortex still showed a slightly higher correlation (temporal cortex: r = .99, n = 7, P < .0001; striatum: high FGA occupancy, r = .94, n = 7, P < .005; striatum: same FGA occupancy as SGA, r = .86, n = 7, P < .05; significance of difference

792
between $r = .99$ and $r = .86$, $t = 3.1$, $df = 4$, $P = .02$). The correlation between ED95eff and 5HT2A receptor ED95occ was not statistically significant ($r = .29$, $n = 5$, nonsignificant [ns]), partly because amisulpride produced no 5HT2 blockade and also because clozapine led to very high 5HT2A receptor occupancy at subtherapeutic doses (see figure 1D).

**Sensitivity Analysis**

The mean correlation ($r$) between ED95eff and temporal or the actual striatal D2/D3 receptor occupancy using 28 different dose schedules was $r = .98$ for temporal cortex and $r = .69$ for striatum. Thus, the sensitivity analyses were consistent with the primary analysis.

**Antipsychotic Propensity for EPSE and Regional Dopamine Receptor Occupancy**

Doses of FGAs were moderate. Of the 28 subjects, 18 received haloperidol with an average dose of 9 mg/day while most others received high-potency FGAs. Only 3 subjects received doses of haloperidol over 12 mg/day. The FGA dose (in haloperidol equivalents) for each individual was significantly correlated with striatal D2/D3 receptor occupancy ($r = .59$, $df = 22$, $P = .004$; $P = 0.004$),...
but for temporal cortex D$_2$/D$_3$ receptor occupancy, this correlation was not significant ($r = .38$, $df = 22$, $P = ns$).

**Comparison of Results Using SRTM Vs Ratio Modeling**

The mean temporal cortex D$_2$/D$_3$ occupancy estimated was 61% by the ratio method and 78% with SRTM, a difference of 14.6% (95% confidence interval [CI]: to 21, $F = 21.3$, $F = 8.8$: $df = 1$, 127; $P = .004$). However, the ratio and SRTM methods did not produce a significant difference in striatal occupancy. ($F = 1.5$, $df = 1$, 127: ns). Importantly, the SRTM or ratio method did not alter the difference between typical vs atypical occupancy. The interaction of the SRTM/ratio method and typical/atypical drug was essentially zero for both striatal ($F = 0.0$, $df = 1$, 127: ns) and temporal cortex ($F = 0.1$, $df = 1$, 127: ns).

**Comparison of Results Using Single Vs Dual Ligands**

The ANOVA showed a significant difference between the single- and the dual-ligand method used in both brain areas (striatal and temporal). The single-ligand studies reported 18% (95% CI = 10% to 25%) lower striatal D$_2$/D$_3$ receptor binding than the dual-ligand studies ($F = 22; df = 1, 128; P = .000007$). In the temporal cortex, the single-ligand studies found 13% (95% CI = 6% to 21%) higher D$_2$/D$_3$ receptor occupancy than the dual-ligand studies ($F = 13; df = 1, 128; P = .0006$). The interaction of FGA-SGA used with single- vs dual-ligand method was not significant for striatal ($F = 1.5; df = 1, 128; ns$) or temporal cortex ($F = 0.7; df = 1, 128; ns$). After adjustment by ANCOVA with single/dual ligand and SRTM/ratio as covariates, the striatal occupancy was 74% (95% CI = 66% to 82%) for typical antipsychotics and 47% for atypicals (95% CI = 21% to 66%), a difference of 27% (18% to 36%), and statistically significant ($F = 37, df = 1, 127, P = .00000005$).

**Discussion**

This is the first meta-analysis pooling original patient PET and SPECT receptor imaging data to better understand the mode of action of antipsychotic drugs in vivo in patients with schizophrenia. We found that both SGAs and FGAs produce high (70%–80%) D$_2$/D$_3$ occupancy in the temporal cortex but that only the FGAs produce high D$_2$/D$_3$ receptor occupancy in the striatum. The clinically effective dose (ED95eff) showed a highly significant linear correlation with the dose required to induce maximal temporal cortex D$_2$/D$_3$ receptor occupancy. There was a less strong, but still significant, linear correlation with the dose required to induce maximal striatal dopamine D$_2$/D$_3$ receptor occupancy, whether actual doses imaged or estimated FGA dose required to produce the same striatal occupancy as SGAs were used. This suggests that the temporal cortex and striatum are both possible targets for antipsychotic efficacy.

We found that the dose of FGA was linearly related to striatal occupancy and not to temporal cortical occupancy. As propensity to induce EPSE increases with increasing FGA dose, this suggests that EPSE are more closely related to dopamine receptor occupancy in striatum than in temporal cortex.

The absence of a significant correlation between efficacy and 5HT$_2A$ binding, and the fact that atypicals is possible without significant 5HT$_2A$ binding (amisulpride), suggests that 5HT$_2A$ binding is not a central component of either the therapeutic or EPSE components of SGA antipsychotic action, although we cannot completely exclude the possibility that 5HT$_2A$ blockade is important in the functionality of some antipsychotic drugs because high 5HT$_2A$ receptor occupancy at doses used therapeutically is a feature of 4 out of the 5 SGAs investigated in this study.

**Methodological Consideration**

**Assumptions About Drug Mechanisms.** In grouping drugs together (SGA vs FGA), we have made the assumption that these drugs behave similarly to others in the same group. This is not necessarily the case because both FGAs and SGAs have widely varying action at other receptor subtypes besides dopamine D$_2$ receptors. It should be noted that the FGAs imaged were either haloperidol or other high-potency antipsychotic drugs. If lower potency FGAs had been imaged, it is possible that the difference between FGAs and SGAs in terms of striatal and cortical D$_2$ receptor occupancy would not have been so marked.

**Dose: Efficacy and Dose: Occupancy Estimation.** The ideal method of estimating the relationship of clinical efficacy and side effect profile to receptor occupancy is to assess dose-response curves and imaging in the same patient. In order to achieve this, it would be necessary to evaluate large samples of patients who are in an episode of acute psychotic illness at baseline and then again at 3- to 6-week treatment with different antipsychotic drugs. Patients should also be randomly assigned to multiple fixed doses on the log-linear part of the dose-response curve. Three such studies have yielded important results, but they examined striatal D$_2$/D$_3$ receptor occupancy only. $^{39-41}$ We feel that such designs have considerable advantages in that they allow the assessment of dose-response for efficacy and EPSE and measurement of receptor occupancy in the same subject.

Because data employing antipsychotic dosing and simultaneous striatal and extrastriatal D$_2$/D$_3$ receptor imaging in the same patient were not available, we used data from well-designed clinical trials for determination of ED95 for clinical efficacy and EPSE in order to combine with the ED95 receptor occupancy results from the SPECT and PET imaging studies. Patients in the dosing studies were therefore not the same who underwent scanning. It is possible that the doses leading to 95% clinical
had high occupancy at all doses imaged whereas SGAs had a lower D2 receptor occupancy over all doses. This posed some difficulty in plotting 95% D2 receptor occupancy for SGAs, but because occupancy was stable over the dose ranges imaged, we assumed that the imaged occupancy value was the maximum obtainable in the striatum by SGAs and calculated ED95 occupancy on this basis. It is possible that the lower correlation between striatal D2 receptor occupancy and clinically effective dose may have been driven by this difference between SGAs and FGAs. When the dose of typical to produce the same occupancy is plotted, the relationship is clearly nonlinear. This, however, is a projected dose from the individual patient data. We caution the reader to keep this in mind.

Scanning and Modeling Methods. In keeping with previous reports, we found that single-ligand studies tended to report lower striatal occupancy regardless of modeling method used and that dual-ligand studies (employing [11C]FLB-457) reported lower temporal cortex occupancy. One possible reason for this is given by the suggestion that [11C]FLB-457 might not reach equilibrium within the maximum scan time possible with an [11C]-labeled tracer.35 [11C]FLB-457 has also been shown to have significant binding to D2 receptors in the cerebellum, and because this region is used as a reference region in SRTM analysis (assumed to have no significant binding), measures of cortical D2 receptor occupancy might be significantly underestimated using this ligand. On the other hand, the use of a single high-affinity ligand to estimate binding in both striatum and temporal cortex might underestimate striatal occupancy.36

We found a difference between single- and dual-ligand methods, but no interaction between method and drug administered, indicating that the difference in receptor occupancy of typical and atypical drugs occurs with both methods to an approximately equal degree. We also found that method of analysis (ratio vs SRTM) made no significant difference to the results.

It should be noted that interpretation of drug binding studies using PET and SPECT imaging is complex because changes in ligand binding can be affected by the affinity of the ligand, the affinity of the drug, and the level of endogenous dopamine in different brain regions.42 Whether the higher temporal cortex binding by SGAs detected by the single-ligand method is actually a true increase in receptor occupancy by antipsychotic drug or, alternatively, a complex interaction between the affinity state of the D2/D3 receptor, endogenous dopamine, antipsychotic drug affinity, and ligand affinity for the receptor is currently not clear. It is possible that the finding of regional preferential occupancy of antipsychotic drugs is an artifact of the imaging method used. However, the fact remains that PET or SPECT studies employing a single ligand are able to distinguish between high-potency FGAs and SGAs based on the ratio between striatal and temporal occupancy.

Plotting Occupancy Vs Clinical Dose. In striatum, FGAs had high occupancy at all doses imaged whereas SGAs had high occupancy at all doses imaged whereas SGAs.
and ventral striatum might, therefore, be expected to also be involved in antipsychotic efficacy, and so D2/D3 receptor binding in these striatal subregions would be expected to correlate with antipsychotic efficacy. Two pharmacologically distinct SGAs (amisulpride and risperidone) both show selective occupancy of D2/D3 receptors in the head of caudate over the putamen, suggesting that reduced D2/D3 receptor binding in the putamen alone may be the distinguishing feature of atypical antipsychotic drugs.

As very few of the articles included in this meta-analysis examined subregions of the striatum, it is possible that the correlation between antipsychotic efficacy and striatal occupancy may have been driven through dopamine receptor occupancy in caudate or ventral striatum. New developments in SPECT and PET resolution, allowing greater distinction between nigrostriatal, mesolimbic, and mesocortical striatal regions, will help to further elucidate the importance of subregional binding of antipsychotic drugs for efficacy and side effect profile.

Conclusions

This novel meta-analysis of original patient data provides the first human in vivo evidence that the clinically efficacious dose of antipsychotic drugs is related to dopamine D2/D3 receptor occupancy in cortical brain regions. D2/D3 binding in subregions of the striatum is also likely to be therapeutically important. The data suggest that EPSE are primarily related to striatal, and not cortical, D2/D3 occupancy. 5HT2A occupancy does not appear to be a central component of SGA efficacy or EPSE profile.

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