Serotonin-Dopamine Interactions and Atypical Antipsychotic Drugs

Atypical antipsychotic drugs have a definite antipsychotic effect in schizophrenic patients without producing significant extrapyramidal symptoms (EPS).

by HERBERT Y. MELTZER, MD

Atypical antipsychotic drugs have a definite antipsychotic effect in schizophrenic patients without producing significant extrapyramidal symptoms (EPS). Sulpiride, a selective D₂ dopamine (DA) receptor blocker, and clozapine, a drug with a very complex neurochemical profile, were the first antipsychotic drugs suggested to be atypical with regard to EPS severity. Despite the low EPS profile of both drugs, there are clear neurochemical and clinical reasons to consider these two agents as members of different classes, as I have discussed elsewhere. Clozapine is the prototype of the most important group of putative atypical antipsychotic drugs because its advantages over neuroleptic drugs go beyond low EPS and include: 1) the ability to diminish positive, negative, and disorganization symptoms in treatment-resistant schizophrenia; 2) little or no causation of tardive dyskinesia; 3) improvement in some cognitive functions; and 4) no serum prolactin elevations in humans.

Many putative atypical antipsychotic drugs share in common with clozapine the ability to produce a relatively strong blockade of serotonin (5-HT₂) and weak blockade of D₂ DA receptors. Some of the more prominent compounds of this type currently under study are listed in Table 1. Olanzapine has similar characteristics in vivo, as will be discussed sub-

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consequently, but in vitro it has been reported to have relatively similar affinities for D₂ and 5-HT₂ receptor binding sites. This article will review the evidence for considering the relative amounts of 5-HT₂-D₂ receptor blockade important in achieving a clozapine-like profile, as well as other aspects of 5-HT-DA interaction, e.g., the influence of 5-HT₃ receptor stimulation on DA release, which may contribute to the clinical advantages of clozapine and the drugs listed in Table 1. These issues have been discussed in some detail elsewhere.¹ ³ ⁴ In this article, citation of the original literature is sometimes precluded. Some key studies are cited. Interested readers should consult other reviews for primary citations.¹ ³ ⁴

**D₂ RECEPTOR ANTAGONISM AND OTHER DA MECHANISMS**

Clozapine has a relatively low affinity for the D₂ DA receptor compared with other antipsychotic drugs (approximately 250 nM), but this affinity has been reported to correlate extremely well with its average clinical dose. However, Fardé et al.⁵ reported that clozapine occupies only 40% to 60% of striatal D₂ receptors at clinical doses, compared with 70% to 90% occupancy by typical antipsychotic drugs.

The low in-vivo occupancy of striatal D₂ receptors by clozapine has been offered as an explanation of why it produces fewer EPS. Regardless of whether this conclusion is correct, it cannot explain why clozapine is a superior antipsychotic. Moreover, we have found that the dose needed to occupy 50% of D₂ receptors in the rat olfactory tubercle, a limbic system component, by acute administration of clozapine is significantly less than the dose needed for comparable occupancy of striatal D₂ receptor (pED₅₀: 4.8 and 4.3, respectively), which suggests it could be hazardous to conclude that the occupancy of limbic D₂ receptors by clozapine is less than that of typical neuroleptic drugs on the basis of striatal data alone.⁶

There is evidence that these atypical antipsychotic drugs, as a class, have weaker D₂ receptor blocking properties than typical antipsychotic drugs in vitro and in vivo. The mean D₂ affinities (expressed as pKᵢ or negative log of the Kᵢ) of 20 typical and 17 putative atypical antipsychotic drugs were reported to be significantly different (pKᵢ D₂ for typical 8.89 ± 0.66 and atypical 7.02 ± 1.04 SD, p = 0.001).⁶ There was, however, significant overlap between the two groups of drugs with regard to pKi D₂ values. Therefore, low absolute affinity for the D₂ receptor, by itself, does not define an atypical antipsychotic.

The ED₅₀ (dose that produces 50% blockade) of atypical antipsychotic drugs to block striatal and olfactory tubercle D₂ receptors has also been reported to be significantly greater than that of typical

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*More potent at 5-HT₂ receptors in vivo.²*
antipsychotic drugs. The potential clinical significance of 5-HT$_2$ relative to D$_2$ receptor blockade is supported by a recent study of the relative effects of risperidone (strong 5-HT$_2$, weak D$_2$ affinities), ocapride (strong 5-HT$_2$ and D$_2$ affinities) and haloperidol (strong D$_2$, weak 5-HT$_2$ affinities) on amphetamine-stimulated locomotor activity in the rat. The 5-HT$_2$ blocking effects of risperidone and ocapride were suggested to modulate the effect of D$_2$ blockade by increasing DA turnover.

Clozapine has also been suggested to produce its unique clinical profile via more potent blockade of D$_1$, D$_3$, or D$_4$ receptors. Of the three effects, blockade of the D$_4$ receptor seems more promising as a site of clozapine’s action, because of the relatively high affinity of clozapine for the D$_4$ compared with the D$_1$, D$_2$ and D$_3$ receptors, and because the D$_4$ receptor is enriched in some areas of the limbic system compared with the striatum.

CLOZAPINE, SEROTONIN, AND THE 5-HT$_2$-D$_2$ INTERACTION

There have been suggestions since 1974 that the ability of clozapine to block 5-HT receptors may be relevant to its low EPS. This hypothesis was based on two observations: first, that diminishing striatal serotoninergic activity blocks catalepsy, the rodent equivalent of EPS, and second, that clozapine is an effective 5-HT antagonist in vitro and in vivo. The existence of such functional interactions between the serotoninergic and dopaminergic systems is well established.

For example, there is extensive evidence for an influence of 5-HT on neuroleptic-induced catalepsy. Haloperidol- or chlorpromazine-induced catalepsy can be diminished by electrolytic lesions of the dorsal raphe, which includes the cell bodies of the ascending 5-HT neurons, or by blocking 5-HT synthesis with t-chlorophenylalanine (PCPA). The cataleptic effects of haloperidol and pimozide are promoted by the 5-HT antagonists methysergide and cyproheptadine.

Drugs specific for 5-HT$_{1B,1C}$ and D$_2$ receptors have recently been found to modulate DA turnover in the striatum and limbic forebrain. These data, plus other evidence reviewed elsewhere, suggest that decreasing serotonergic neurotransmission reverses or prevents catalepsy induced by D$_2$ receptor blockade. Data consistent with this conclusion have been obtained in monkeys. It has been shown that 5-HT can inhibit the firing of nigral (A9) DA neurons that project to the striatum. 5-HT can also inhibit DA synthesis and release in striatal synaptosomes. However, as in most examples of neurotransmitter interactions, the situation is more complicated and there is evidence that 5-HT can also stimulate DA synthesis and release under some circumstances. In humans, the 5-HT$_2$ antagonist ritanserin has been reported to diminish EPS caused by neuroleptic drugs while fluoxetine, a 5-HT uptake inhibitor, has been reported to produce EPS, apparently because of its ability to increase 5-HT neurotransmission.

There is also evidence for a serotonergic influence on the limbic system. Briefly, a 5-HT$_2$-dependent mechanism can depolarize neurons located in the nucleus accumbens and can inhibit DA synthesis and release in the nucleus accumbens. Serotonin can block the hyperactivity caused by bilateral injections of DA into the accumbens. Electrolytic lesion of the medial raphe nuclei increases accumbens DA turnover. Furthermore, Ügedo et al have reported ritanserin, a 5-HT$_2$-
Drugs specific for 5-HT\textsubscript{1B,1C} and 2 receptors have recently been found to modulate DA turnover in the striatum and limbic forebrain.

HT\textsubscript{1C} antagonist, can increase the burst firing and firing rate of DA neurons with cell bodies in the ventral tegmentum (as well as the zona compacta of the substantia nigra).

The ability of clozapine to increase DA release in the accumbens but not the caudate has been shown to be enhanced in rats in which the serotonergic system has been chemically lesioned. Conversely, decreasing the firing of dorsal raphe serotonergic neurons by infusing the 5-HT\textsubscript{1A} agonist 8-OH-DPAT into the raphe produced significant decreases in extracellular DA as well as 5-HT in the nucleus accumbens. These results suggest that 5-HT may have a tonic inhibitory effect, mediated by 5-HT\textsubscript{2} or 5-HT\textsubscript{1C} receptors, on midbrain DA cell activity.

Clozapine also has a high affinity for 5-HT\textsubscript{1C} binding sites as do some other atypical antipsychotic drugs, e.g., flupertapine, but others, e.g., meliperone, do not. Chronic administration of clozapine can downregulate 5-HT\textsubscript{1C} sites, just as it does 5-HT\textsubscript{2} sites. The functional significance of these effects must be studied further. Those atypical antipsychotic drugs that are potent 5-HT\textsubscript{2} or 5-HT\textsubscript{1C} antagonists, or both, might be expected to produce greater increases in midbrain DA cell activity compared with typical neuroleptic drugs, which are weaker in-vivo 5-HT\textsubscript{2}/5-HT\textsubscript{1C} blockers at clinically effective doses.

**IN-VITRO AND IN-VIVO STUDIES OF ATYPICAL ANTI PSYCHOTICS AS 5-HT\textsubscript{2}, D\textsubscript{2}, AND D\textsubscript{1} ANTAGONISTS**

The ability of 5-HT to modulate dopaminergic function in the striatum and nucleus accumbens can occur via 5-HT\textsubscript{2}-dependent mechanisms, although there is evidence that 5-HT\textsubscript{1A} and 5-HT\textsubscript{2} dependent mechanisms may also effect dopaminergic neurotransmission. There is considerable evidence that clozapine and other related atypical antipsychotic drugs can antagonize 5-HT\textsubscript{2} receptors, but the pK\textsubscript{a} values for cortical 5-HT\textsubscript{2} receptors of 20 typical and 17 atypical antipsychotic drugs were not significantly different (8.34 ± 0.73 vs. 8.36 ± 1.03 SD, respectively). The atypical antipsychotic drugs have a greater affinity for the 5-HT\textsubscript{1A} than the D\textsubscript{2} receptor by 1.30 log units, whereas the typical drugs have a greater affinity for the D\textsubscript{2} than the 5-HT\textsubscript{2} site by 0.26 log units. Thus, there is a 1.56 log unit (35.3 fold) difference between the two classes of drugs, on average, suggesting that in vivo there should be marked differences in occupancy of 5-HT\textsubscript{2} and D\textsubscript{2} receptors between the two groups.

We have confirmed this in patients treated with clozapine or typical antipsychotic drugs using positron emission tomography (PET) to view binding sites for \textsuperscript{11}C-N-methylspiperone. Careful clinical testing of all these compounds is essential to determine the significance of relatively potent 5-HT\textsubscript{2}/weak D\textsubscript{2} blocking properties for EPS, antipsychotic effects, etc. Failure to observe superior antipsychotic activity, fewer EPS, or minimal prolactin stimulation with compounds with high in-vivo blockade of the 5-HT\textsubscript{2} receptor and weak (>40<60\%) blockade of D\textsubscript{2} receptors would lead to rejection of this hypothesis in its simplest form.

There is some evidence that D\textsubscript{1} receptor blockade may also be important to the action of clozapine. Clozapine occupies a higher proportion of D\textsubscript{1} receptors in humans than typical neuroleptic drugs. However, D\textsubscript{1}-5-HT\textsubscript{2} relative potency did not distinguish typical and atypical antipsychotic drugs as a group. There is, as yet, no clinical evidence that D\textsubscript{1} antagonists are clinically effective or
TABLE 2
ED$_{50}$ Values of Typical and Atypical Antipsychotic Drugs for Cortical 5-HT$_2$ and Striatal and Olfactory Tubercle D$_2$ Binding Sites

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Cortical</th>
<th>Striatal</th>
<th>O.T.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>1.5</td>
<td>0.13</td>
<td>0.17</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>0.52</td>
<td>0.19</td>
<td>0.22</td>
</tr>
<tr>
<td>Clozapine</td>
<td>0.73</td>
<td>16.9</td>
<td>5.5</td>
</tr>
<tr>
<td>Fluperlapine</td>
<td>0.58</td>
<td>28.8</td>
<td>13.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ratios</th>
<th>Cortical/Striatal</th>
<th>Cortical/O.T.*</th>
<th>Striatal/O.T.*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>11.5</td>
<td>8.8</td>
<td>0.76</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>2.7</td>
<td>2.4</td>
<td>0.86</td>
</tr>
<tr>
<td>Clozapine</td>
<td>0.043</td>
<td>0.13</td>
<td>3.1</td>
</tr>
<tr>
<td>Fluperlapine</td>
<td>0.020</td>
<td>0.042</td>
<td>2.1</td>
</tr>
</tbody>
</table>

*Olfactory tubercle
See reference 3 for methodology.

produce fewer EPS than D$_2$ blockers in schizophrenia or that neuroleptic drugs, such as flupenthixol, which are potent D$_1$ and D$_2$ antagonists, have any clinical advantages.

There have been several preclinical attempts to study the effect of the combination of D$_2$ and 5-HT$_2$ receptor antagonists. Lappalainen et al reported that chronic haloperidol administration decreased DA metabolism in the caudate while chronic administration of ritanserin decreased 5-HT and 5-HIAA levels in the dorsal raphe nucleus. Chronic clozapine administration produced neither effect. Coadministration of ritanserin and haloperidol did not modify the effect of haloperidol. However, the doses of haloperidol used, 0.5 mg/kg, may have produced too strong (e.g., >60% to 70%) D$_2$ receptor blockade.

Recently, Brougham et al reported results more consistent with the importance of 5-HT$_2$ antagonism to the action of clozapine. They studied the interaction of amfonelic acid (AFA), a nonamphetamine stimulant that can facilitate impulse-induced release of DA in the striatum, with haloperidol or clozapine administration in the presence or absence of ritanserin. AFA inhibited the ability of clozapine to increase the levels of the DA metabolites dihydroxyphenylacetate (DOPAC) or homovanillic acid (HVA), whereas it potentiated the ability of haloperidol to increase the levels of both.

Ritanserin blocked the effect of AFA on the haloperidol-induced increases in DOPAC or HVA but had no effect on clozapine plus AFA. It was concluded that 5-HT$_2$ receptor blockade does modulate nigrostriatal dopaminergic neurotransmission and that this is a relevant component of clozapine’s action.

In vivo binding studies may provide further information about differences between typical and atypical compounds with regard to occupancy of 5-HT$_2$ and D$_2$ sites. We have used [$^3$H]-N-methylspiperone (N MSP) to label cortical 5-HT$_2$, striatal, and olfactory tubercle D$_2$ binding sites. The two typical drugs, haloperidol and fluphenazine, were 11.5 and 2.7 times more potent at occupying striatal D$_2$ than cortical 5-HT$_2$ binding sites for [H]-NMSP, respectively (Table 2). Similar differences were found for the cortical/olfactory tubercle ratios. Both drugs were slightly more potent in the striatum than the olfactory tubercle. The two atypical drugs, clozapine and fluperlapine, were 23.2 and 49.7 times more potent at occupying cortical 5-HT$_2$ than striatal D$_2$ [H]-NMSP sites, respectively. The corresponding ratios between cortex and olfactory tubercle were 7.5 and 23.8, respectively.

The differences in the cortical/striatal and cortical/olfactory tubercle ratios for both drugs reflects the greater capacity for both clozapine and fluperlapine to occupy limbic compared with striatal [H]-NMSP sites. The striatal/olfactory
There is some evidence that $D_1$ receptor blockade may also be important to the action of clozapine.

5-HT$_3$ MECHANISMS

Clozapine also has a potent effect to block 5-HT$_3$ receptors in vitro and in vivo.$^3$ 5-HT$_3$ receptor stimulation can enhance DA release.$^{22}$ Clozapine may decrease DA release by 5-HT$_3$ receptor blockade, although there is evidence that clozapine maintains DA release in the accumbens or striatum more so than typical neuroleptic drugs.$^{18}$ If 5-HT$_3$ antagonism is relevant to the antipsychotic action of clozapine, it may be via its effect on firing of cortical 5-HT neurons. The 5-HT$_3$ receptor antagonist MDL 73,147EF has been reported to inactivate both A9 and A10 DA neurons, suggesting that 5-HT$_3$ antagonism might not produce the well-known selectivity of clozapine for the A9 neurons.$^{23}$

CLINICAL STUDIES

Clinical data are consistent with the results of the clozapine in-vivo binding studies reported here. The plasma cortisol response to the 5-HT precursor, L-5-hydroxytryptophan (5-HTP), was significantly blocked in clozapine-treated schizophrenic patients.$^4$ This effect of 5-HTP is likely to be mediated, in part, by stimulation of 5-HT$_2$/5-HT$_{1C}$ receptors since it is blocked by ritanserin. Clozapine also blocks the MK-212-induced increase in plasma cortisol (Figure) and the plasma growth hormone response to apomorphine (data not presented). Olanzapine is another putative 5-HT$_2$/D$_2$ atypical antipsychotic. It is more potent in blocking 5-HT$_2$ than D$_2$ mediated endocrine response in the rat.$^{24}$ The inhibition of the MK-212 response is consistent with 5-HT$_2$/5-HT$_{1C}$ blockade, and the apomorphine effect is consistent with D$_2$ blockade.

It is not yet known whether strong 5-HT$_2$ relative to D$_2$ properties account for one or more of the advantages of clozapine previously discussed. Clinical study of other such compounds or supplementation of clozapine with drugs that alter the 5-HT$_2$/D$_2$ balance in vivo could put the hypothesis to a more definitive test. It will be critical to test the hypothesis in such a way that the balance of 5-HT$_2$ and D$_2$ blockade in vivo is in accord with that of clozapine. If doses of atypical antipsy-

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AMPEROZIDE

Amperoxide is a novel agent suggested to have atypical antipsychotic properties in preliminary clinical trials. It has no D$_2$ blocking properties in vivo but has a potent effect on inhibiting stimulated DA release and on blocking 5-HT$_2$ receptors in vivo.$^{21}$

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chotic drugs that occupy 80% to 90% of D₂ as well as 5-HT₂ sites are used, the advantages of these types of drugs should be lost.

It is beyond the scope of this article to consider the intriguing evidence that 5-HT-DA interactions may underlie some of the neurodevelopmental aspects of schizophrenia. However, some recent literature pointing toward abnormalities in the 5-HT system following lesions of the DA system at birth and the effect of isolation in infancy on 5-HT-DA mechanism and behavior in adults suggest this may be clinically relevant and could provide the substrate for 5-HT₂/D₂ drugs to act.25-27

In conclusion, 5-HT₂, in relation to D₂ receptor antagonism, appears to be of value for heuristic purposes to further study the mechanism of action of clozapine and to identify other candidate atypical antipsychotic drugs. The effects of clozapine on 5-HT₂ and D₂ receptors may influence its ability to maintain and even increase DA release in the limbic system and frontal cortex, respectively.28 It is, however, premature to assign any or all of clozapine’s special features to this relationship. D₁, D₃, 5-HT₁c and 5-HT₃ receptor antagonism may also be important to the action of clozapine. However, the role of 5-HT in schizophrenia and perhaps even other conditions in which clozapine is effective, e.g., L-dopa psychosis and refractory manic-depressive illness, deserves special attention.

REFERENCES
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