ABSTRACT

According to the dopamine hypothesis of schizophrenia, symptoms of psychosis arise, in part, from dysregulation of central dopaminergic pathways. The activity of dopaminergic neurons is in turn modulated by several neurotransmitters, including, most prominently, serotonin and glutamate. The first generation of antipsychotic drugs (ie, typical antipsychotics) are characterized by potent D₂ dopamine receptor blockade, whereas most second-generation (ie, atypical) antipsychotics are serotonin-dopamine receptor antagonists. By simultaneously blocking both 5-HT₂A serotonin and D₂ dopamine receptors, atypical antipsychotic drugs attenuate the positive symptoms of schizophrenia with few of the extrapyramidal side effects associated with typical antipsychotic drugs. Unfortunately, atypical antipsychotic drugs (eg, clozapine, olanzapine, risperidone, quetiapine, and ziprasidone) can be associated with potentially serious side effects (eg, weight gain, cardiovascular and hematologic abnormalities). Conventional atypical antipsychotic drugs interact with a multiplicity of receptors, in addition to 5-HT₂A serotonin and D₂ dopamine receptors, including various serotonergic, dopaminergic, noradrenergic, muscarinic, and histaminergic receptors. It is likely that the chance interactions of atypical antipsychotic drugs with these and other receptors lead to the associated side effects. The ideal antipsychotic would, therefore, possess a mechanism of action whereby dopaminergic activity is normalized without adverse effects.

Since the 1970s, excessive dopaminergic activity has been the most prominent pharmacologic model for explaining the pathogenesis of schizophrenia, in large part because all effective antipsychotic drugs inhibit dopaminergic neurotransmission. A number of dopaminergic pathways have been implicated in antipsychotic drug actions (Table 1). Thus, positive symptoms of psychosis are believed to arise from excess dopaminergic activity in the mesolimbic pathway, whereas negative and cognitive symptoms are believed to arise from a deficiency in dopaminergic signaling in the mesocortical pathway. First-generation antipsychotic agents suppress positive symptoms through their potent antagonism of D₂ dopamine receptors in the mesolimbic and mesocortical pathways. However, this mechanism of action may further diminish cognition via suppression of dopamine activity in the cortex. Blockade of dopamine activity in the nigrostriatal pathway acutely causes extrapyramidal symptoms (eg, Parkinsonism, acute dystonias) and, chronically, tardive dyskinesia. Suppression of dopaminergic neurotransmis-
sion in the tuberoinfundibular pathway disinhibits prolactin secretion, leading to hyperprolactinemia and subsequent effects on fertility and sexual function. In addition to blockade of D2 dopamine receptors, many atypical antipsychotic drugs have potent antimuscarinic, antialpha1-adrenergic, and/or antihistaminergic actions that produce additional side effects, including cognitive blunting, orthostatic hypotension, and sedation.

An abundance of evidence suggests that a dysfunction of serotonin (5-hydroxytryptamine [5-HT]) neurotransmitter systems also contributes to the pathogenesis of schizophrenia and related psychoses.6-10 5-HT is an indolamine neurotransmitter found in both the central nervous system and in the periphery, where it contributes to a number of physiological functions (eg, cognition, perception, memory, emotion, platelet aggregation, smooth muscle contraction).8 It has long been recognized that blockade of the 5-HT2A serotonin receptor subtype is an important part of atypical antipsychotic drug action,11,12 and recent research is helping us to better understand why.

We now know that 5-HT2A receptors are highly enriched on the pyramidal neurons in the cortex.13,14 These neurons integrate cognitive, emotional, and perceptual input to the brain prior to outputting the information to higher-level neurons to create an individual’s sense of reality. 5-HT2A receptors are highly localized to a particular part of the pyramidal neuron that serves as the physical gate for information transfer in the brain (Figure 1).15,16 Thus, it is now believed that blockade of the 5-HT2A receptor normalizes the firing of pyramidal neurons, thereby stabilizing perception of reality.

This assumption is based on a convergence of evidence relating to the action of a variety of drugs. Thus, hallucinogens, such as lysergic acid diethylamide (LSD) activate 5-HT2A receptors, whereas all approved atypical antipsychotic drugs are potent 5-HT2A receptor antagonists. It is believed that long-term treatment with atypical antipsychotic drugs normalizes the receptor-mediated signaling in cortical pyramidal neurons, thereby improv-
ing positive and negative symptoms of schizophrenia. When activated, 5-HT_1A serotonin receptors, co-localized on pyramidal neurons with 5-HT_2A receptors, also inhibit the firing of pyramidal neurons. Thus, in theory, an ideal drug for normalizing the firing of pyramidal neurons would both activate 5-HT_1A receptors and antagonize 5-HT_2A receptors. Because pyramidal neurons are glutamatergic, activating 5-HT_1A receptors and inhibiting 5-HT_2A receptors may stabilize glutamatergic neurotransmission. Finally, 5-HT_1A partial agonists stabilize the serotonergic system because they are serotonin autoreceptors. Three approved atypical antipsychotic drugs have these opposing actions on 5-HT_1A and 5-HT_2A serotonin receptors: aripiprazole, clozapine, and ziprasidone. Thus, therapy with aripiprazole, clozapine, or ziprasidone is predicted to be associated with a stabilization of the serotonergic and glutamatergic neurotransmission. The pharmacology of these drugs, and atypical drugs in general, is highly complex, however—they interact with numerous other receptors,17 and interactions with other receptors may modulate the actions of antipsychotic drugs on a number of neurotransmitter systems.

**RESOURCE FOR IDENTIFYING MOLECULAR TARGETS**

Determining which pharmacologic actions are essential to achieve therapeutic effects and which generate side effects has become increasingly difficult. The National Institute of Mental Health Psychoactive Drug Screening Program (NIMH-PDSP) has created a unique resource in the public domain that provides information on the abilities of drugs to interact with an expanding number of molecular targets. The NIMH-PDSP database serves as a data warehouse for published and internally derived Kᵢ, or affinity, values for a large number of drugs and drug candidates at an expanding number of G-protein coupled receptors, ion channels, transporters, and enzymes. The flexible user interface provides for customized data mining. Planned enhancements include: (1) a searchable database of agonist/antagonist properties of drugs and drug candidates at various molecular targets; and (2) a chemi-informatics interface, which will allow the user to search the database by homology. The query interface is designed to allow search by any field, or a combination of fields to refine search criteria. Both antipsychotics and drugs of abuse are listed in the database, which provides a listing of the various receptors with which the drug has an affinity (including those identified by the human genome project), the chemical structure of the drugs, and a link to the published material.

Using the NIMH-PDSP database, an analysis of molecular targets for clozapine shows that it is likely to occupy not only the D_2 dopamine and 5-HT_2A receptors, but also a large number of other receptors. The analysis of molecular targets also suggests that even at the highest doses of clozapine clinically achievable, dopamine D_2 receptor occupancy will not exceed 70%, and will typically be less. Studies of in vivo receptor occupancy with positron emission tomography scanning have supported such molecular predictions.18 At the opposite end of the spectrum is aripiprazole, whose structure and in vitro pharmacology is markedly dissimilar from clozapine. Analysis of molecular targets for this drug shows that at the usual clinical dose, it is predicted to occupy more than 90% of dopamine D_2 and D_3 receptors, as well as 5-HT_1A receptors. Clinical studies of aripiprazole show that a dose of 30 mg daily achieved nearly 100% occupancy of striatal D_2 dopamine receptors in normal human volunteers.19 Although classic pharmacologic theory would indicate that complete occupancy of D_2 receptors will result in significant side effects, clinically, aripiprazole has been found to be nearly devoid of extrapyramidal side effects and does not trigger the elevation of serum prolactin that is reported with use of typical antipsychotic drugs.20 This seeming contradiction can be explained by a closer analysis of aripiprazole's pharmacology. Because aripiprazole is a partial agonist, when it binds to the D_2 receptor it partially activates the D_2 dopamine receptor, thus resetting the functional activity of the D_2 receptor to a lower level. In this way, partial agonists are unlike antagonists, which set the functional state of occupied D_2
receptors to zero. Thus, in a situation in which excessive dopamine is released (e.g., the acute psychotic state) and D<sub>2</sub> dopamine receptors are fully activated, a partial agonist will reset the receptor tone to a more normal level. In conditions in which too little dopamine is released (e.g., in the prefrontal cortex of schizophrenic individuals) one would predict that a partial agonist would yield a net activation of D<sub>2</sub> dopamine receptors.

The level of agonist activity seen with partial agonists like aripiprazole is thought to be sufficient to functionally reset the dopaminergic system to achieve the 70% occupancy level seen with clozapine, thereby yielding the same net effect on dopaminergic neurotransmission. A simulation performed by the NIMH-PDSP of aripiprazole's partial agonist activity on dopamine and serotonergic receptor occupancy demonstrates the predicted functional effect (B.L. Roth, manuscript in preparation).

**SIDE EFFECTS AND WEIGHT GAIN**

A detailed knowledge of receptor pharmacology can also be used to predict the side-effect profiles of individual drugs. By identifying the type and number of receptors occupied, we can reliably predict the likelihood of specific side effects. For example, analysis of clozapine with the NIMH-PDSP database demonstrates extensive interactions with a host of receptors that are responsible for many of the drug's side effects. For example, alpha<sub>1</sub>-adrenergic receptor blockade results in hypotension, and muscarinic receptor blockade results in anticholinergic side effects. A similar analysis of haloperidol's receptor interactions predicts few alpha<sub>1</sub>-adrenergic receptor side effects, little interaction with the H<sub>1</sub> receptor (e.g., minimal sedation and weight gain), and little interaction with muscarinic receptors, leading to few anticholinergic side effects. Simulations with aripiprazole also demonstrate little activity with these receptors, predictive of few side effects (Table 2)<sup>17,21,22</sup>; clinical trials indicate that aripiprazole is associated with few adrenergic, histaminergic, or cholinergic side effects.<sup>20</sup>

Weight gain as a side effect of antipsychotic therapy has been noted for more than 30 years and remains a serious side effect of some antipsychotic drugs.<sup>23,24</sup> The mechanism responsible for antipsychotic drug-induced weight gain is somewhat controversial, though clinicians have reported tremendous increases in appetite in schizophrenic patients.

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Side Effect</th>
<th>Ari</th>
<th>Olz</th>
<th>Ris</th>
<th>Zip</th>
<th>Clz</th>
<th>Hal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Hypotension, dizziness</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>H&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Sedation</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>M&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Blurred vision, dry mouth</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

* = no effect; + = minimal side effects; ++ = moderate side effects; +++ = strong side effects.*

All data obtained with cloned human receptors.

Ari = aripiprazole; Olz = olanzapine; Ris = risperidone; Zip = ziprasidone; Clz = clozapine; Hal = haloperidol.

Data from Shapiro et al<sup>21</sup>; Kroeze et al<sup>22</sup>; Roth et al<sup>17</sup>.

Figure 2. Mean Weight Change at 10 Weeks in Patients Taking Antipsychotics at “Standard” Dose

* 4-6 week pooled data from Marder et al.<sup>27</sup>
† Extrapolated from 6-week data.
Adapted with permission from Allison et al. Am J Psychiatry. 1999;156:1686-1696.<sup>25</sup>
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leading to substantial weight gain, with significant implications for metabolic side effects, such as diabetes and hyperlipidemia. To assess correlations between specific antipsychotic drug agents and weight gain, Allison et al conducted a retrospective study that showed a strong association with clozapine and olanzapine use. Figure 2 extrapolates data from Allison’s 1999 analysis and pools it with later data from a multicenter trial assessing weight in patients using aripiprazole. The mechanism responsible for antipsychotic drug-induced weight gain is unknown, although recent studies have suggested an association between weight gain and a silent polymorphism of the 5-HT<sub>2C</sub> receptor. Although many antipsychotic drugs interact with 5-HT<sub>2C</sub> receptors, the propensity of antipsychotic drugs to induce weight gain does not correlate with their actions at 5-HT<sub>2C</sub> receptors, indicating that some other receptor(s) are likely responsible for this serious side effect.

Kroeze et al recently reported results based on a test of the hypothesis that the affinity of an antipsychotic for a certain receptor or subset of receptors will predict whether it induces weight gain, and that this group of receptors would differ from those that predict effectiveness. The investigators obtained weight-gain data for antipsychotic drugs from the meta-analysis published by Allison et al and from the multicenter aripiprazole study and utilized receptor affinity data from the NIMH-PDSP to identify correlations between weight gain and receptor affinities. They found 2 receptors that were responsible for predicting with the highest degree of certainty whether a drug will or will not induce weight gain: the H<sub>1</sub> histamine receptor and the alpha<sub>1</sub>-adrenergic receptor. An individual drug’s ability to interact with these 2 receptors was highly predictive of its ability to induce weight gain. The binding data from Kroeze’s analysis suggests that 2 atypical antipsychotic drugs will not induce substantial weight gain over a 10-week period: ziprasidone and aripiprazole. Clinical trial data also report that aripiprazole and ziprasidone have a relatively low propensity to induce weight gain.

**Conclusion**

Multiple receptors are occupied by antipsychotic drugs, which may activate or inhibit receptor activity. Drugs with dopamine partial/functional agonism may ‘stabilize’ the dopaminergic system with minimal extrapyramidal symptoms. Antagonism of the 5-HT<sub>2A</sub> receptor stabilizes a number of neurotransmitter systems, likely accounting for the salutary effects of atypical antipsychotic medications on cognition and mood. Drugs with 5-HT<sub>1A</sub> receptor agonism further stabilize various neurotransmitter systems (glutamaticergic and serotonergic); this action may account for the mood stabilization seen in patients taking certain atypical antipsychotic drugs. Potential H<sub>1</sub>-receptor antagonism is associated with weight gain and sedation, and drugs with minimal H<sub>1</sub>-receptor antagonism are relatively devoid of these side effects. A detailed knowledge of receptor pharmacology allows reliable prediction of benefits and side effects of antipsychotic drugs.

**REFERENCES**

12. Rasmussen K, Agahianian G. Potency of antipsychotics in reversing the effects of a hallucinogenic drug on locus