"Hit-and-Run" Actions at Dopamine Receptors, Part 1

Mechanism of Action of Atypical Antipsychotics

Stephen M. Stahl, M.D., Ph.D.

Issue: *Hypothetically, if an antipsychotic blocks a dopamine-2 receptor and then rapidly dissociates from it (i.e., "hit-and-run" action), it has atypical antipsychotic properties, namely reduction of psychosis without production of motor side effects.*

All antipsychotics are created equal since they all block dopamine receptors. However, some antipsychotics are more equal than others and become atypical if they leave the dopamine receptor quickly after blocking it.[1] We posed the question, What makes an antipsychotic atypical? in an earlier BRAINSTORMS[2,3] in which the atypical properties were then defined clinically as reduced side effects and pharmacologically as serotonin-2A (5-HT_{2A}) antagonism associated with dopamine-2 (D_2) antagonism. Now, it appears that the length of time these drugs bind to D_2 receptors may be relevant as well.[1] Here we discuss this new hypothesis, and next month we will illustrate it.

BRAINSTORMS is a monthly section of The Journal of Clinical Psychiatry *aimed at providing updates of novel concepts emerging from the neurosciences that have relevance to the practicing psychiatrist.*

From the Neuroscience Education Institute in Carlsbad, Calif., and the Department of Psychiatry at the University of California San Diego.

Reprint requests to: Stephen M. Stahl, M.D., Ph.D., Editor, BRAINSTORMS, Neuroscience Education Institute, 5857 Owens Street, Ste. 102, Carlsbad, CA 92009.

What makes an antipsychotic conventional?

Conventional antipsychotics, also known as classical neuroleptics, all block D_2 receptors throughout the brain.[4] This action theoretically reduces dopamine hyperactivity in mesolimbic dopamine pathways thought to mediate psychosis. It also reduces dopamine activity in nigrostriatal dopamine pathways and causes extrapyramidal side effects and tardive dyskinesia.

Why would 5-HT_{2A} antagonism make an antipsychotic atypical?

Atypical antipsychotics have antipsychotic actions with much reduced or absent extrapyramidal side effects and tardive dyskinesia.[4] Theoretically, this effect could be the result of blockade of 5-HT_{2A} receptors in addition to D_2 receptors.[4,5] The hypothesis for the way 5-HT_{2A} antagonism reduces D_2 binding goes like this: When 5-HT_{2A} receptors are blocked, dopamine is released in the nigrostriatal dopamine pathway but not in the mesolimbic dopamine pathway. This reaction is thought to reverse some of the blockade of D_2 binding by atypical antipsychotics in the nigrostriatal pathway without reversing the blockade of D_2 binding in the mesolimbic dopamine pathway. If there is less D_2 blockade in nigrostriatal pathways, extrapyramidal side effects are reduced; 5-HT_{2A} antagonism in this pathway is sufficient to reverse some of the D_2 blockade there. On the other hand, 5-HT_{2A} antagonism simultaneously in the mesolimbic dopamine pathway is not sufficient to reverse the D_2 blockade there, and thus antipsychotic actions are preserved. The bottom line is that antipsychotics are atypical when their 5-HT_{2A} antagonism superimposed on their D_2 antagonism reduces their D_2 binding enough to reverse motor side effects but not enough to reverse antipsychotic effects.[4–6]

Why would fast dissociation from D_2 receptors make an antipsychotic atypical?

Another idea about why antipsychotics are atypical is that they stay around long enough to cause an antipsychotic action but not long enough to cause side effects.[1] Theoretically, it takes only a quick blockade of the D_2 receptor to cause an antipsychotic ac-

tion, but a longer-lasting action to cause an extrapyramidal side effect. Thus, if the antipsychotic has "hit-and-run" actions, it dissociates from D_2 receptors after antipsychotic actions are established but before motor side effects are induced.

According to this hypothesis, lack of motor side effects comes from low D_2 binding due to fast dissociation, not due to reversal by 5-HT_{2A} antagonism. Support for the hit-and-run hypothesis of atypical antipsychotic action is based in part on evidence from positron emission tomography scans of patients taking antipsychotics, which shows that when D_2 binding in the striatum is high, even in the presence of high 5-HT_{2A} binding in the cortex, motor side effects still occur.[7]

Also, rapid dissociation from the D_2 receptor in vitro is a good predictor of low extrapyramidal side effect potential.[8] Since rapid dissociation occurs more readily when the drug has low potency, low-potency agents (i.e., those requiring higher milligram doses such as clozapine and quetiapine) have faster dissociation from the D_2 receptor than high-potency agents (i.e., those requiring lower milligram doses such as risperidone), with intermediate-potency agents, such as olanzapine, in the middle. This process roughly correlates with the abilities of these drugs to cause motor side effects within the group of atypical antipsychotics and also sets all of them apart from the conventional antipsychotics.

One of the consequences of fast dissociation is that the drug is gone from the receptor until the next dose. This means that natural dopamine can bathe the receptor for a while before the next pulse of drug. Perhaps a bit of real dopamine in the nigrostriatal dopamine system is all that is needed to prevent motor side effects. If natural dopamine is available in the nigrostriatal pathway while there is yet insufficient dopamine in the mesolimbic dopamine system to reactivate psychosis between doses, the drug has atypical antipsychotic clinical properties.

Take-Home Points

- The improved tolerability of atypical antipsychotics is linked to reduced D_2 receptor blockade in parts of the brain where side effects are mediated.
- Reduced D_2 receptor blockade may be linked to antagonism of 5-HT_{2A} receptors.
- Reduced D_2 receptor blockade may also be linked to the ability of a drug to quickly dissociate from the receptor after blocking it.

Summary

Either 5-HT_{2A} antagonism or fast dissociation from D_2 receptors may define an atypical antipsychotic. To have little or no motor symptoms from an antipsychotic, it is clear that D_2 receptor binding in the striatum must be less than that caused by conventional antipsychotics. Pure 5-HT_{2A} antagonism by itself does not result in robust antipsychotic actions. However, 5-HT_{2A} antagonism can reduce D_2 antagonism and thereby reduce motor symptoms without reversing antipsychotic actions. If, however, this 5-HT_{2A} antagonism is overwhelmed by too much D_2 antagonism, it cannot result in such atypical antipsychotic actions.

Another route to reducing D_2 receptor binding appears to be to shorten binding time, also known as rapidly dissociating from the D_2 receptor. Many of the agents with atypical antipsychotic clinical properties hit the D_2 receptor hard enough to cause antipsychotic effects and then run before they cause extrapyramidal side effects.

REFERENCES

1. Kapur S, Seeman P. Does fast dissociation from the dopamine 2 receptor explain the action of atypical antipsychotics? a new hypothesis. Am J Psychiatry 2001;158:360–369
2. Stahl SM. Introduction: what makes an antipsychotic atypical? J Clin Psychiatry 1999;60 (suppl 10):3–4
3. Stahl SM. What makes an antipsychotic atypical? [BRAINSTORMS] J Clin Psychiatry 1998;59: 403–404
4. Stahl SM. Essential Psychopharmacology. 2nd ed. New York, NY: Cambridge University Press; 2000
5. Meltzer HY, Matsubara S, Lee JC. Classification of typical and atypical antipsychotic drugs on the basis of dopamine D_1, D_2 and serotonin 2 pK_i values. J Pharmacol Exp Ther 1989;251: 238–246
6. Meltzer HY. Mechanism of action of atypical antipsychotic drugs. In: Davis KL, Charney D, Nemeroff CL, et al, eds. Neuropsychopharmacology: The Fifth Generation of Progress. New York, NY: Elsevier. In press
7. Kapur S, Zipursky R, Jones C, et al. Relationship between dopamine D_2 occupancy, clinical response, and side effects: a double-blind PET study of first episode schizophrenia. Am J Psychiatry 2000;157:514–520
8. Kapur S, Seeman P. Antipsychotic agents differ in how fast they come off the dopamine D_2 receptors: implications for atypical antipsychotic action. J Psychiatry Neurosci 2000;25:161–166