"Hit-and-Run" Actions at Dopamine Receptors, Part 2

Illustrating Fast Dissociation From Dopamine Receptors That Typifies Atypical Antipsychotics

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Issue: *A new hypothesis to explain why atypical antipsychotics have antipsychotic properties without inducing motor side effects is that these drugs rapidly dissociate from dopamine-2 receptors ("hit-and-run" action).*

In last month's BRAINSTORMS,[1] we discussed a new hypothesis on the mechanism of action of atypical antipsychotics, namely the "hit-and-run" hypothesis.[2] Here we illustrate this concept.

REFERENCES

1. Stahl SM. "Hit and run" actions at dopamine receptors, pt 1: possible mechanism of action of atypical antipsychotics. J Clin Psychiatry 2001;62:670–671
2. 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

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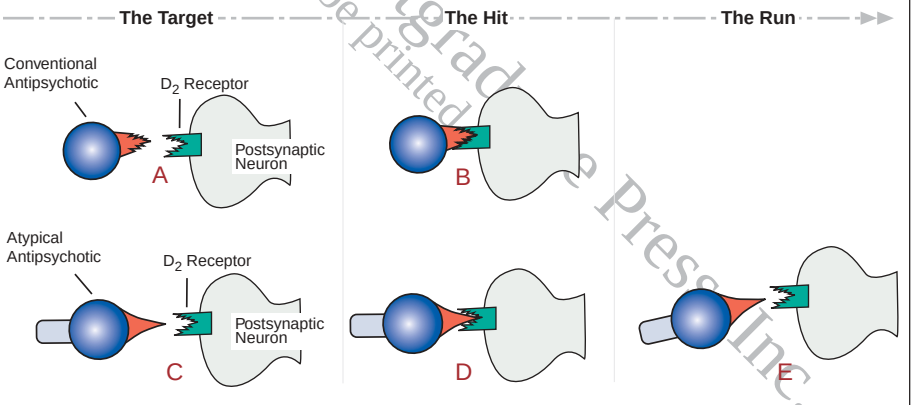
Figure 1. Conventional vs. Atypical Antipsychotic Mechanisms

Conventional: Because of the biochemical properties of conventional antipsychotics, their binding to postsynaptic dopamine D_2 receptors is tight and long lasting, as shown by the teeth on the binding site of the conventional antipsychotic (A). The D_2 receptor on the right has grooves where the teeth of the drug can bind tightly, locking the drug into the receptor binding site (B) to block it in a long-lasting manner.



Atypical: The biochemical nature of binding for atypical antipsychotics to postsynaptic D_2 receptors is loose, as shown by its smooth binding site, which does not fit well into the grooves of the receptor (C). *The Hit:* Note that the drug fits loosely into the D_2 receptor without getting locked into its grooves (D), unlike conventional antipsychotics. *The Run:* Because an atypical antipsychotic fits loosely into the D_2 receptor, it slips off easily after binding only briefly, then runs away (E). This process is also called rapid dissociation.

Shown below are the curves of D_2 receptor blockade as well as the concomitant clinical effects after 2 doses of either a conventional (Figure 2) or an atypical antipsychotic (Figure 3).

Figure 2. Hypothetical Action of a Conventional Antipsychotic Over Time

Prior to dosing a schizophrenic patient with a conventional antipsychotic (A), there is no D_2 receptor blockade, and the schizophrenic patient has positive symptoms of psychosis such as delusions and auditory and visual hallucinations. Also, in the absence of drug, there will be no extrapyramidal motor side effects (EPS) (shown by a slash through the patient with parkinsonism). After a dose of a conventional antipsychotic (B), D_2 receptors are blocked so tightly that they both cause antipsychotic actions and induce EPS. After another dose of a conventional antipsychotic (C), the D_2 receptors stay persistently blocked, so that antipsychotic actions are always associated with EPS.

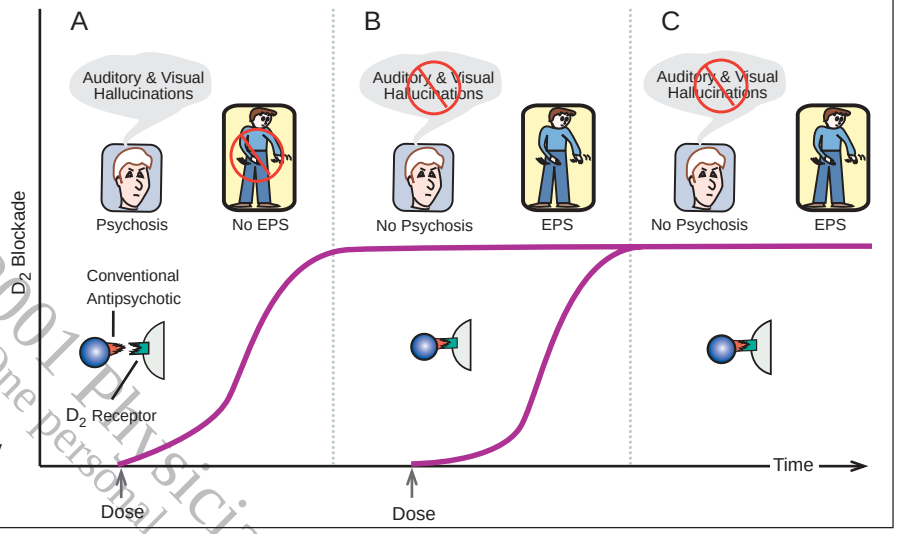


Figure 3. Hypothetical Action of an Atypical Antipsychotic Over Time

Prior to dosing a schizophrenic patient with an atypical antipsychotic (A), there is no D_2 receptor blockade, and the schizophrenic patient has positive symptoms of psychosis, just as with a conventional agent as shown above. Also, in the absence of drug, there will be no extrapyramidal motor side effects (EPS). After a dose of an atypical antipsychotic (B), D_2 receptors are blocked initially, but become unblocked when the drug slides off the receptor. Theoretically, antipsychotic actions require only initial blockade of D_2 receptors, whereas EPS require persistent blockade of D_2 receptors. Since the nature of atypical antipsychotic binding is to rapidly dissociate from D_2 receptors after binding to them, these drugs can have antipsychotic actions without inducing EPS by hitting the D_2 receptor hard enough to cause antipsychotic effects and then running before they cause EPS. Since this happens dose after dose (C), antipsychotic actions are persistent and long lasting, but EPS do not develop over time.