Dopamine System Stabilizers, Aripiprazole, and the Next Generation of Antipsychotics, Part 2

Illustrating Their Mechanism of Action

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

Issue: *The ideal mix of dopamine-2 (D_2) receptor stimulation and D_2 receptor blockade may stabilize the dopamine system and reduce psychosis without creating extrapyramidal motor side effects. Dopamine system stabilizers (DSSs) strike this balance, resulting in a novel antipsychotic that does not produce motor side effects. Aripiprazole is the prototype DSS.*

A new class of antipsychotics, called dopamine system stabilizers (DSSs) (Figures 1 and 2A), is in research and development and could become the next generation of treatment for schizophrenia and psychotic illnesses.[1–9] On the one hand, DSSs reduce dopaminergic neurotransmission when dopamine is excessive in the limbic system (Figure 2B); on the other hand, these agents maintain or enhance dopaminergic neurotransmission so that it is in the normal range in motor areas of the brain (the nigrostriatal system) (Figure 2C). DSSs thus reduce the hyperactivity of dopamine neurons that mediate psychosis and at the same time restore dopamine activity in the cortical regions that mediate negative and cognitive symptoms as well as the brain areas that regulate motor movements and prolactin.

These new therapeutic agents are sometimes called "Goldilocks" antipsychotics[1] because they find a desirable position between too much and too little dopamine receptor stimulation, much like Goldilocks found a soup that was neither too hot or too cold (Figure 2D). If the result is "just right," antipsychotic actions are accompanied by a decrease in negative and cognitive symptoms without the production of motor side effects or prolactin elevation.

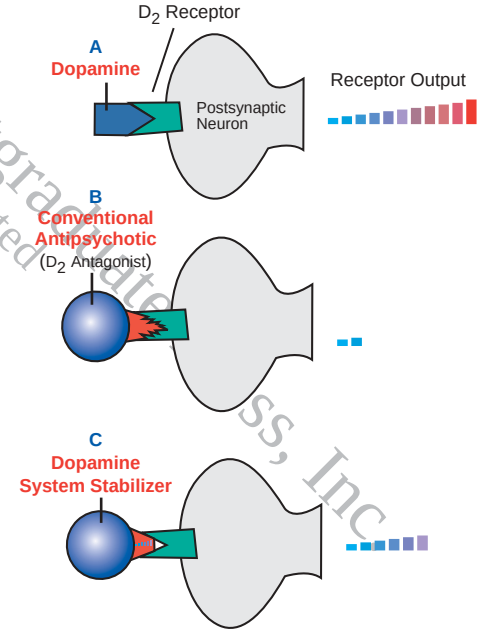


Figure 1. Effects of Dopamine and Antipsychotics on Receptor Output

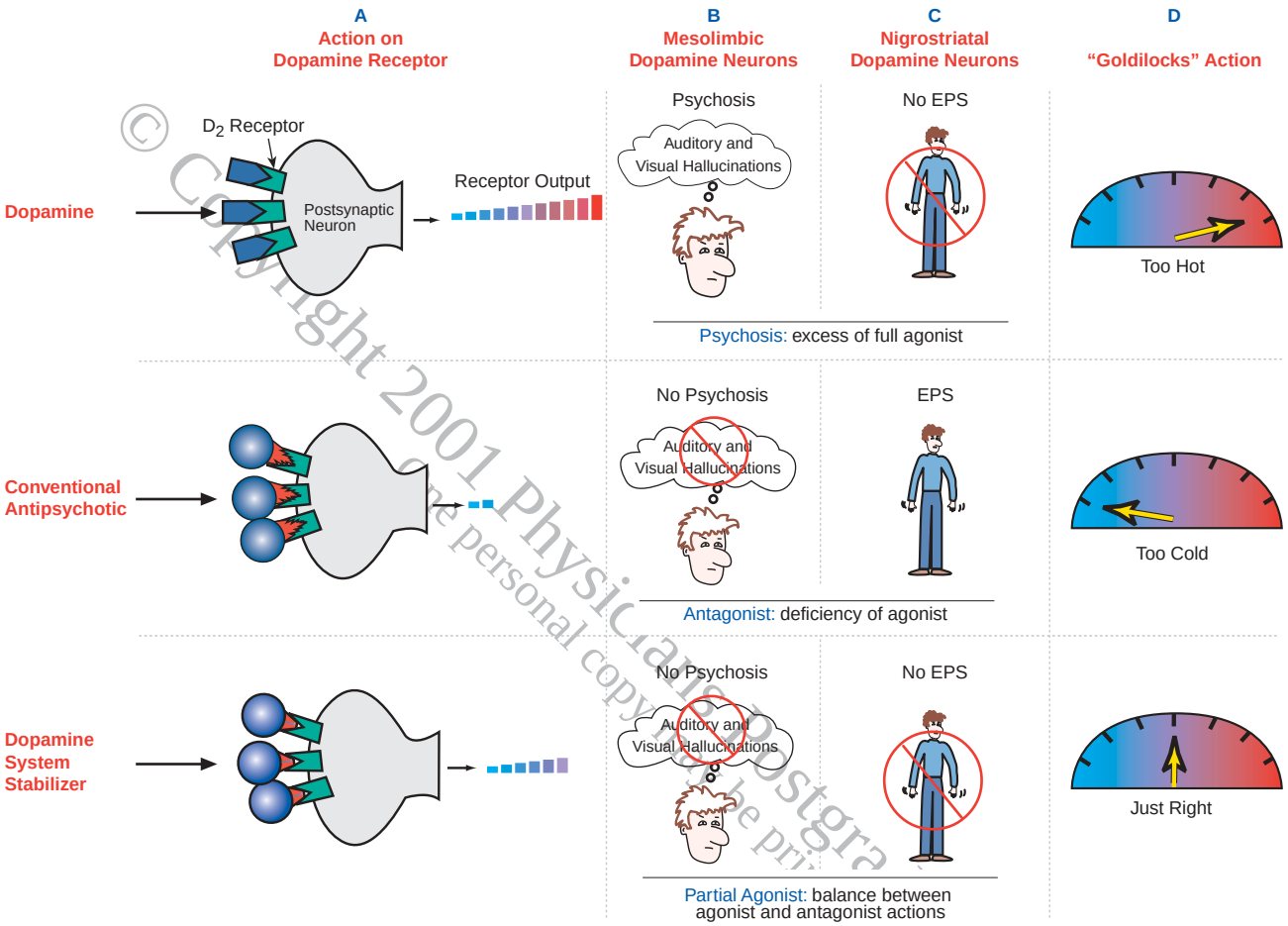
Dopamine itself is a full agonist and causes full receptor output (A). Conventional antipsychotics are full antagonists and allow little if any receptor output (B). Dopamine system stabilizers partially activate dopamine receptor output and cause a stabilizing balance between stimulation and blockade of dopamine receptors (C).

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.

Figure 2. Action on Dopamine Receptors by Dopamine and Antipsychotic Agents



Dopamine and antipsychotic agents bind to D_2 receptors and affect dopamine output (A). Excessive dopamine output from mesolimbic dopamine neurons causes psychosis (B). Both conventional antipsychotics and dopamine system stabilizers (DSSs) reduce this output. Although the reduction in dopamine output is not as robust for the DSSs as for the conventional antipsychotics, it is reduced sufficiently and stabilized enough to produce a comparable degree of antipsychotic action. Dopaminergic tone in nigrostriatal neurons must be maintained for optimal motor functioning (C). Conventional antipsychotics reduce this tone so much that extrapyramidal motor side effects (EPS) are produced. On the other hand, DSSs allow continuing dopaminergic tone in these neurons so that motor side effects are not produced. The resultant shift from too much or too little dopamine to better regulated dopamine release—a "just-right" amount—is the "Goldilocks" action produced by DSSs (D).

REFERENCES

1. Stahl SM. J Clin Psychiatry 2001;62:841–842
2. Carlsson A, Waters N, Carlson ML. Biol Psychiatry 1999;46:1388–1395
3. Toru M, Miura S, Kudo Y. Neuropsychopharmacology 1994;10:122S
4. Lawler CP, Prioleau C, Lewis MM, et al. Neuropsychopharmacology 1999;20:612–27
5. Burris KD, Molski TF, Ryan E, et al. Aripiprazole is a high affinity partial agonist at human D_2 dopamine receptors. Presented at the 22nd annual meeting of the Congress of the College of International Neuropsychopharmacology; July 9–13, 2000; Brussels, Belgium
6. Ekesbo A, Andren PE, Gunne LM, et al. NeuroReport 1997;8:2567–2570
7. Andree TH, Stack G, Rosenzweig-Lipson S, et al. WAY-135452: a potent novel D_2/D_3 partial agonist for the treatment of schizophrenia. Presented at the 38th annual meeting of the American College of Neuropsychopharmacology; Dec 12–16, 1999; Acapulco, Mexico
8. Van Vliet BJ, Ronken E, Tulp M, et al. DU-127090: a highly potent, atypical dopamine receptor ligand—high potency but low efficacy at dopamine D_2 receptors in vitro. Presented at the 13th annual meeting of the European College of Neuropsychopharmacology; Sept 9–13, 2000; Munich, Germany
9. Lahti AC, Weiler MA, Corey PK, et al. Biol Psychiatry 1998;43:2–11