Do the Causal Paths to Psychosis Converge on D2High?

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Note: *Dr. Mary Seeman writes this Clinical Commentary in response to Dr. Philip Seeman's article entitled "All Psychotic Roads Lead to Increased Dopamine D2High Receptors: A Perspective," which appeared in the January 2008 issue of Clinical Schizophrenia & Related Psychoses.*

Despite the many causes of psychosis, most individuals experiencing a psychotic episode improve with antipsychotic drugs. How is it that patients respond to a similar type of drug treatment whether their illness is associated with a major deletion in chromosome 22, or is a result of birth trauma, or a consequence of the family's genetic predisposition for psychosis, or an end product of the use of street drugs? Why would so many different pathophysiological routes be blocked when blocking dopamine receptors?

A related question is why schizophrenia patients are supersensitive to dopamine-like stimulants (1). Is this related to the relapse seen when switching from a traditional antipsychotic to a medication such as aripiprazole (2, 3)?

These clinical questions are addressed by looking to animal models of psychosis, as limited as these models may be for schizophrenia itself (4). There are many animal models of human psychosis. They include strategically placed brain lesions, long-term dosing with street drugs or steroids, brain anoxia during Caesarian birth, social isolation, and knockout mice of various sorts. The transmission pathways disrupted in these models include acetylcholine, glutamate, dopamine, epinephrine, norepinephrine, adenosine, and trace amines (4). No animal model, of course, does justice to the human condition but the animals do exhibit poor memory, reduced prepulse inhibition, hyperactivity that responds to antipsychotics, impaired latent inhibition, and a pathological reaction to social novelty.

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Almost all the animals in this wide array of models, even when the disrupted pathway has nothing directly to do with dopamine, show supersensitivity to dopamine. This means that the locomotor behavior of the animal over-responds to a low dose of a dopamine-like drug such as apomorphine, amphetamine, metamphetamine or cocaine.

What is remarkable is that all the animals in these models, despite the differences in the neural pathways that are disrupted, reveal a marked increase in the number of dopamine D2 receptors that appear in their high-affinity state, the D2High state (4). D2High receptors increase but the total

number of D2 receptors does not change. Every time there is behavioral dopamine supersensitivity, D2High receptors are elevated. In humans, D2High receptors are not yet measurable, although considerable effort is being made in that direction (5).

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The D2High elevations in the animals are long-lived, usually permanent. This is in contrast to the short-lived and reversible elevations produced by antipsychotics themselves (6). Antipsychotic-induced elevations of D2High receptors, though short-lived, are the probable cause of psychosis resulting from the rapid withdrawal of an antipsychotic or its replacement by a dopamine partial agonist such as aripiprazole (2, 3). Elevations of D2High receptors may be a final common pathway leading to psychosis.

References

1. Lieberman JA, Kane JM, Alvir J. Provocative tests with psychostimulant drugs in schizophrenia. Psychopharmacology (Berl) 1987;91(4):415-433.
2. Ramaswamy S, Vijay D, William M, Sattar SP, Praveen F, Petty F. Aripiprazole possibly worsens psychosis. Int Clin Psychopharmacol 2004;19(1):45-48.
3. Raja M. Improvement or worsening of psychotic symptoms after treatment with low doses of aripiprazole. Int J Neuropsychopharm 2007;10:107-110.
4. Seeman P. All psychotic roads lead to increased dopamine D2High receptors: a perspective. Clinical Schizophrenia & Related Psychoses 2008;1(4):351-355.
5. Willeit M, Ginovart N, Kapur S, Houle S, Hussey D, Seeman P, et al. High-affinity states of human brain dopamine D2/3 receptors imaged by the agonist [11C]-(+)-PHNO. Biol Psychiatry 2006;59(5):389-394.
6. Samaha AN, Seeman P, Stewart J, Rajabi H, Kapur S. "Breakthrough" dopamine supersensitivity during ongoing antipsychotic treatment leads to treatment failure over time. J Neurosci 2007; 27(11):2979–2986.