Beyond the dopamine hypothesis of schizophrenia to three neural networks of psychosis: dopamine, serotonin, and glutamate

Stephen M. Stahl

Issue: Psychosis is now widely hypothesized to involve neural networks beyond the classical dopaminergic mesolimbic pathway, including serotonin and glutamate systems as well.

Take-Home Points

- The dopamine hypothesis of psychosis has become classic and one of the most enduring ideas in psychopharmacology, especially as it relates to schizophrenia.
- However, schizophrenia is not the only psychosis and dopamine is not the only neurotransmitter linked to psychosis.
- Increasing evidence implicates both serotonin and glutamate networks as well as dopamine networks in the pathophysiology and treatment of some forms of psychosis, especially those related to Parkinson’s disease, dementias, and psychotomimetic drugs.

Overview of 3 Hypotheses of Psychosis

In addition to the classical dopamine theory of psychosis (Table 1 and Figure 1), there is also the glutamate theory of psychosis (specifically the N-methyl-d-aspartate or NMDA hypofunction theory), which proposes that NMDA receptor hypofunction in the prefrontal cortex can result in psychosis (Table 1 and Figure 2), and also the serotonin theory, which postis that cortical serotonin/5-hydroxytryptamine 5-HT2A hyperfunction can also result in psychosis (Table 1 and Figure 3). Each of these theories and neuronal networks will be reviewed here briefly.
Although there are now at least 3 major theories, 3 major neurotransmitters, and 3 major neuronal networks hypothesized to underlie one or another psychosis, it is also important to keep in mind that all 3 theories involve interconnected pathways, and it is likely that in many different forms of psychosis, more than 1 of these pathways is involved (see Figures 2–4).

If one stops to think about it, clinicians have known about these 3 neurotransmitters and how they are linked to different causes of psychosis for a long time based on pharmacological models (Table 2).4,9 That is, clinicians have long observed the psychotomimetic effects of psychostimulants, dissociative anesthetics, and psychedelics.4,9 Psychostimulants such as cocaine and amphetamine release dopamine and cause D2 receptor stimulation that results mostly in auditory hallucinations and paranoid delusions (Table 2).1,2,4 Dissociative anesthetics such as phencyclidine (PCP) and ketamine are NMDA antagonists that result in visual hallucinations and paranoid delusions as well as a dissociative state (Table 2).5 Hallucinogens/psychedelic drugs such as lysergic acid diethylamide (LSD) and psilocybin are mostly 5-HT2A agonists that result in visual hallucinations and mystical delusions, sometimes with retained insight (Table 2).6–9

Supporting these pharmacologic observations of specific psychotic symptoms in users of different drugs are observations that symptoms of psychosis caused by neurological and psychiatric disorders are also not identical to each other. This suggests that different causes of psychosis involve different degrees of input from the 3 psychosis-linked pathways. For example, the auditory hallucinations and paranoid delusions of theoretically hyperactive dopamine neurons in schizophrenia are not identical to some of the symptoms of Parkinson’s disease psychosis and psychosis associated with dementia. These latter psychoses are associated with mainly visual hallucinations and persecutory or jealous delusions, often with retained insight, at least early in the course of the disease.3,10,11 Also, these latter forms of psychosis can be treated with the 5HT2A antagonist pimavanserin, which lacks D2 dopamine antagonist properties.3 Such observations suggest a more robust involvement of the serotonin 2A receptor and the serotonin network in the psychosis associated with Parkinson’s disease and with dementia.

The Classical Dopamine Hypothesis of Psychosis and Hyperactivity at Dopamine D2 Receptors in Dopamine Neural Networks

The classical and well-worn theory of psychosis of course is that dopamine hyperactivity in the mesolimbic dopamine pathway at dopamine D2 receptors is the cause of the positive symptoms of schizophrenia, with all antipsychotics acting to block D2 receptors there.1,2 Hyperactivity of dopamine in the ventral striatum from neuronal projections coming from the ventral tegmental area (Figure 1) is theoretically to blame for delusions, often paranoid, and hallucinations, often auditory, especially in schizophrenia and manic psychosis. The “price of doing business” in blocking D2 receptors in this mesolimbic dopamine pathway is to simultaneously block the D2 receptors in the nigrostriatal pathway from the substantia nigra to the dorsal striatum, causing movement disorders such as akathisia, drug induced parkinsonism, and long-term tardive dyskinesia1,12 (see also Figure 1).
An exciting and relatively more recent development in the theories of psychosis is the notion that dopamine hyperactivity is actually a downstream consequence of glutamate dysregulation in the prefrontal cortex\(^2\). Specifically, the NMDA hypoactivity theory of psychosis suggests that hypofunctional NMDA receptors on GABA interneurons in the prefrontal cortex—perhaps due to abnormal neurodevelopment—lead to overactive downstream dopamine networks via the mesolimbic pathway. Overactivation of this pathway may result in excess dopamine in the ventral striatum via the mesolimbic pathway.
by excessively stimulating the mesolimbic dopamine pathway in the ventral tegmental area (VTA) is actually the cause of auditory hallucinations and paranoid delusions.

The paradigm-breaking observation for these psychotic illnesses was that 5HT2A antagonism without D2 antagonism has proven effective in treatment of psychotic symptoms due to Parkinson’s disease with preliminary evidence for efficacy in psychosis of dementia as well.3 This naturally leads to the question of whether serotonin is hyperactive at 5HT2A receptors in these disorders (Figures 3 and 4),12,13 just like what happens when psychedelic hallucinogens cause psychosis (Table 2).6–9 If so, one might also ask, “How does serotonin became hyperactive at 5HT2A receptors and thus how is 5HTA antagonism without D2 antagonism therapeutic?” The answer seems to be that excess serotonin activation of 5HT2A receptors in Parkinson’s disease psychosis or the dementia of psychosis can be due to excess release of serotonin activating 5HT2A receptors, to an increase in the expression of 5-HT2A receptors, or both.3,12,13 Regardless of the mechanism of activation, the result is the same: downstream release of glutamate (Figures 3 and 4). As it turns out, some of these glutamate neurons project to the VTA and activate it (Figure 3). This process can then further activate the mesolimbic dopamine pathway as part of a chain reaction leading to psychosis causing

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**Figure 4.** Excess glutamate signaling in the cerebral cortex, particularly the visual cortex, is thought to be associated with visual hallucinations. Upregulated 5-HT2A receptors on glutamate neurons, excessive serotonin release, or a psychedelic hallucinogenic 5HT1A agonist could all increase signaling to visual cortex and cause visual hallucinations.
typical auditory hallucinations and paranoid delusions (Figure 3). Glutamate hyperactivity driving neurons in the visual cortex may even more commonly cause visual hallucinations (Figure 4).

Summary and Conclusions

In summary, there are 3 interconnected pathways theoretically linked to hallucinations and delusions: dopamine hyperactivity at D2 dopamine receptors in the mesolimbic pathway, which extends from the VTA to the ventral striatum; NMDA receptor hypoactivity at GABAergic interneurons in the prefrontal cortex; and serotonin hyperactivity at 5-HT2A receptors on glutamate neurons in the cerebral cortex. All 3 neuronal networks and neurotransmitters are linked together, and both 5HT2A and NMDA receptor actions can result in hyperactivity of the downstream mesolimbic dopamine pathway.

References: