Biological Psychiatry: Celebrating 50 Years

Can D_2 Receptor–Based Therapies Fix Presynaptic Dopamine?

Jodi J. Weinstein

The pursuit of better treatment for schizophrenia has motivated a large body of work in biological psychiatry. One of the most well-established findings is the presence of excess dopaminergic (DAergic) function in the striatum (1), which has led to ongoing discussion in the field of whether psychosis may be fundamentally a pre- or postsynaptic DA dysfunction (2). Current antipsychotic treatments block dopamine D_2 receptors (D_2), but it is possible that the therapeutic mechanism of D_2 blockers is to reduce presynaptic DA. This is particularly important since D_2 blockers, when administered long-term, seem to induce D_2 hypersensitivity, necessitating further D_2 blockade for effective treatment of chronic psychotic disorders. However, if the primary abnormality in psychosis is excess presynaptic DA, then drugs that directly reduce DA could prove to be effective. Testing this is complicated by the pathophysiology of the illness itself, which may make therapeutic intervention a moving target. Molecular imaging of first-episode psychosis may help us address these important questions and has the potential to identify specific neurochemical targets for novel treatments of psychosis before it develops into a chronic illness.

Excess presynaptic DAergic function in schizophrenia has been observed using various imaging approaches, one of which is thought to reflect DA synthesis capacity (DSC) (1). Several previous studies have observed excess striatal DSC in patients with schizophrenia, and the associative and limbic striatal subregions appear to have the greatest excess in DSC in antipsychotic-responsive patients with schizophrenia (1). More recently, excess DSC has been identified in patients with psychosis regardless of a diagnosis of bipolar disorder or schizophrenia (3). In a report from McGowan *et al.* (4) of excess DSC in a group of patients with schizophrenia compared with healthy control subjects, the patients were all taking antipsychotic medications and were all minimally symptomatic, suggesting that DSC may not be affected by antipsychotic medications; however, the patients' pretreatment illness severity could not be accounted for in the cross-sectional study design, so it is difficult to rule out the possibility that excess DSC may have been reduced by the antipsychotic medications.

This issue of *Biological Psychiatry* includes the first longitudinal study examining DSC before and after the treatment of first-episode psychosis. In Jauhar *et al.* (5), 17 patients having their first psychotic episode underwent [^{18}F]dihydroxyphenyl-L-alanine ([^{18}F]DOPA) radioligand positron emission tomography imaging before and after several weeks of treatment with a second-generation antipsychotic medication.

The authors hypothesized that DSC—a proxy measure of presynaptic DAergic function—would be initially elevated and decrease with effective antipsychotic treatment, as might be expected given multiple observations of the correlation of the severity of psychosis in patients with schizophrenia with excess DSC (1), suggesting that this measure might reflect a state component of psychosis. Thus, if psychosis decreases, DSC might decrease as well. Indeed, the only previous longitudinal study of DSC with antipsychotic treatment by Grunder *et al.* (6) showed that striatal DSC in patients with schizophrenia decreased by 25% after effective treatment. Furthermore, excess DSC has been observed in treatment-responsive but not in treatment-resistant patients with schizophrenia, suggesting that a treatment-responsive subtype of the illness is associated with abnormalities of DSC that correct with antipsychotic medications.

Preclinical studies make the story more interesting. In wild-type rodents, when administered long-term, antipsychotic medications—all D_2 blockers—silence the firing of several midbrain DA neurons via the prolonged antipsychotic binding to D_2-like autoreceptors. This result is dependent on striatal input [see Grace *et al.* (7)], implicating a mechanism whereby antipsychotic medications reduce presynaptic DAergic function, and, in turn, DSC. In contrast with expectation, however, Jauhar *et al.* (5) report that DSC remains high in patients with first-episode psychosis, even in the presence of a significant therapeutic response to antipsychotic medication: after 5 weeks of antipsychotic treatment, no changes were observed in striatal DSC (indexed as [^{18}F]DOPA influx rate constant [K_i^{cer}]), and there were no observable treatment-related changes in K_i^{cer} in the thalamus or midbrain.

Replicating previous findings, Jauhar *et al.* (5) did see a significant positive relationship between the baseline imaging measure K_i^{cer} in associative striatum and positive symptom severity change with treatment. However—and contrary to what one might expect if excess DSC was a state measure of psychosis—the decrease in positive symptom severity in individual subjects was not correlated with changes in K_i^{cer}. This result conflicts with the findings of Grunder *et al.* (6), whose study sample, it must be said, was significantly less symptomatic, included patients with schizophrenia but none with psychosis secondary to bipolar disorder, and were all treated with first-generation antipsychotic medications with high D_2 occupancy. Moreover, and perhaps most importantly, Grunder *et al.* (6) largely studied chronic patients; this is likely a germane difference given that sensitization models of schizophrenia and its treatment (8) suggest that the DAergic system is affected by chronic psychosis and by exposure to D_2 blockade, such that individuals in their first episode of psychosis may respond differently to antipsychotic medications.

SEE CORRESPONDING ARTICLE ON PAGE 79

https://doi.org/10.1016/j.biopsych.2018.10.017
ISSN: 0006-3223

If we interpret Jauhar *et al.*'s findings (5) as a suggestion that DSC is not affected by long-term D_2 blockade or a reduction in psychotic symptoms, we might infer that excess presynaptic DAergic function is part of the illness and that the therapeutic mechanism of antipsychotic medication is to reduce postsynaptic transmission by blocking D_2. This provides the rationale for continuing antipsychotic medications, even after symptoms resolve, to maintain a D_2 blockade and prevent relapse. However, we still do not know that long-term treatment does not further alter the DAergic system. For example, if long-term antipsychotic treatment results in D_2 hypersensitization, it is possible that DSC may increase concordantly and thereby indicate an increased risk for symptom relapse. It will be important to follow the course of illness for these individuals and repeat DSC measurements longitudinally to determine whether DSC tracks with other aspects of the course of illness or its treatment.

Also, given that there are multiple biochemical contributions to the DSC imaging measure, we do not know whether antipsychotic-induced decreases in phasic DA release may be offset by increases in tonic DA activity, and so we cannot rule out the possibility that the various contributions to the DSC imaging measure are not rebalanced in some way while still maintaining a net zero change of overall DSC.

Since no reduction in excess presynaptic DAergic function was observed, this study cannot tell us whether lowering presynaptic DA may reduce psychosis. It is still possible that by lowering presynaptic DAergic function (e.g., DA synthesis or release), psychotic symptoms may be treatable without blocking D_2 postsynaptically. To determine whether psychotic disorder may be fundamentally a pre- or postsynaptic DA dysfunction we need experimental paradigms that can distinguish between pre- and postsynaptic DAergic (dys)functions in patients. Proof of concept studies, such as DA depletion versus D_2 blocking strategies, will be crucial. If modulating presynaptic DA can reduce severity or progression of psychotic illness, it would be exciting to find out whether pharmaceuticals that modulate presynaptic DA, such as trace amino acid receptor 1a (9) or kappa-opioid receptor (10)—both of which are in the pipeline for use in humans—can be effective treatments.

Acknowledgments and Disclosures

Early Career Investigator Commentaries are solicited in partnership with the Education Committee of the Society of Biological Psychiatry. As part of the educational mission of the Society, all authors of such commentaries are mentored by a senior investigator. This work was mentored by Anissa Abi-Dargham, M.D.

This work was supported by National Institute of Mental Health Grant No. K23 MH115291.

I thank Anissa Abi-Dargham for her mentorship, time, and wisdom while facilitating this commentary.

The author reports no biomedical financial interests or potential conflicts of interest.

Article Information

From the Department of Psychiatry, Stony Brook Medicine, State University of New York, Stony Brook, New York.

Address correspondence to Jodi J. Weinstein, M.D., Department of Psychiatry, Stony Brook Medicine, 101 Nicolls Rd, Health Science Center T10-020, State University of New York, Stony Brook, NY 11794; E-mail: jodi.weinstein@stonybrookmedicine.edu.

Received Oct 19, 2018; revised and accepted Oct 25, 2018.

References

1. Howes OD, Kambeitz J, Kim E, Stahl D, Slifstein M, Abi-Dargham A, *et al.* (2012): The nature of dopamine dysfunction in schizophrenia and what this means for treatment. Arch Gen Psychiatry 69:776–786.
2. Weinstein JJ, Chohan MO, Slifstein M, Kegeles LS, Moore H, Abi-Dargham A (2017): Pathway-specific dopamine abnormalities in schizophrenia. Biol Psychiatry 81:31–42.
3. Jauhar S, Nour MM, Veronese M, Rogdaki M, Bonoldi I, Azis M, *et al.* (2017): A test of the transdiagnostic dopamine hypothesis of psychosis using positron emission tomographic imaging in bipolar affective disorder and schizophrenia. JAMA Psychiatry 74:1206–1213.
4. McGowan S, Lawrence AD, Sales T, Quested D, Grasby P (2004): Presynaptic dopaminergic dysfunction in schizophrenia: A positron emission tomographic [18F]fluorodopa study. Arch Gen Psychiatry 61:134–142.
5. Jauhar S, Veronese M, Nour MM, Rogdaki M, Hathway P, Natesan S, *et al.* (2019): The effects of antipsychotic treatment on presynaptic dopamine synthesis capacity in first-episode psychosis: A positron emission tomography study. Biol Psychiatry 85:79–87.
6. Grunder G, Vernaleken I, Muller MJ, Davids E, Heydari N, Buchholz HG, *et al.* (2003): Subchronic haloperidol downregulates dopamine synthesis capacity in the brain of schizophrenic patients in vivo. Neuropsychopharmacology 28:787–794.
7. Grace AA, Bunney BS, Moore H, Todd CL (1997): Dopamine-cell depolarization block as a model for the therapeutic actions of antipsychotic drugs. Trends Neurosci 20:31–37.
8. Miyamoto S, Duncan GE, Marx CE, Lieberman JA (2005): Treatments for schizophrenia: A critical review of pharmacology and mechanisms of action of antipsychotic drugs. Mol Psychiatry 10:79–104.
9. Lindemann L, Meyer CA, Jeanneau K, Bradaia A, Ozmen L, Bluethmann H, *et al.* (2008): Trace amine-associated receptor 1 modulates dopaminergic activity. J Pharmacol Exp Ther 324:948–956.
10. Tejeda HA, Bonci A (2018): Dynorphin/kappa-opioid receptor control of dopamine dynamics: Implications for negative affective states and psychiatric disorders [published online ahead of print Sep 19]. Brain Res.