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Early Intervention for Psychosis with *N*-Methyl-D-Aspartate Receptor Modulators

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TO THE EDITOR

Accumulating evidence suggests that patients with schizophrenia exhibit nonpsychotic, nonspecific prodromal symptoms for several years before the onset of frank psychosis. A meta-analysis demonstrated that cognitive impairment is a common feature of the prodromal state of psychosis.[1] Accordingly, interest in the potential benefit of early intervention in psychosis is increasing.[2-5]

We read the recent article by Kantrowitz *et al*.,[6] concerning the efficacy of D-serine (an endogenous co-agonist at the *N*-methyl-D-aspartate receptor; NMDAR) on negative symptoms in individuals at clinical high risk of schizophrenia, with great interest. In a double-blind, placebo-controlled trial, these authors compared D-serine (n=20, 60 mg/kg) and placebo (n=24) for 16 weeks. The primary endpoint was scores on the negative subscale of the Scale of Prodromal Symptoms (SOPS). D-Serine induced a significant (35.7%) improvement in negative symptoms compared to placebo, although the number of conversions (one in the D-serine group and two in the placebo group) was too small for statistical analysis, in part due to the short duration of treatment. Nevertheless, these pilot data suggest that D-serine is an effective treatment of prodromal schizophrenia symptoms, despite the small sample size.[6]

Previously, we reported that serum D-serine levels in patients with schizophrenia were lower compared to control subjects, whereas serum L-serine levels were higher in patients than in controls.[7,8] Furthermore, we reported a reduced ratio of D-serine to total serine (DL-serine) in the cerebrospinal fluid of first-episode and drug naïve schizophrenia patients, indicating decreased NMDAR neurotransmission in the brain in early phase patients.[9] Combined, these findings suggest that disturbed NMDAR neurotransmission, due to decreased D-serine levels, plays a causative role in the pathogenesis of schizophrenia.[2] In the brain, D-serine is synthesized from L-serine by serine racemase (SRR). A recent genome-wide association study confirmed the association between *SRR* and schizophrenia.[10] Furthermore, we reported that D-serine supplementation at between 5 and 10 weeks could prevent schizophrenia-like behavioral abnormalities in adult mice (11 weeks old) after neonatal disruption of SRR, suggesting that early intervention with D-serine prevents the onset of psychosis in adults.[11] Finally, glycine, another NMDAR co-agonist, was associated with a 10-15% reduction in negative SOPS symptoms in high-risk subjects.[12]

In conclusion, given the role of NMDAR hypofunction in prodromal symptoms (e.g., cognitive impairment) and early stage schizophrenia,[2] NMDAR modulators, including D-serine, glycine, D-alanine, and sarcosine, may be effective early intervention for psychosis because they all occur naturally in humans.

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