Biological Psychiatry: Celebrating 50 Years

Genomic Triplication of the Glycine Decarboxylase Gene and *N*-Methyl-D-Aspartate Receptor Hypofunction: Improvement by Glycine and D-Cycloserine

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Copy number variation refers to the fact that the number of copies of a particular gene in the genotype may vary among individuals. Rare copy number variants (CNVs) have been implicated in neuropsychiatric disorders, such as schizophrenia, bipolar disorder, and autism spectrum disorder. In this issue of *Biological Psychiatry*, Bodkin *et al.* (1) identified several CNVs spanning 9p24.1 in a proband and his mother whose DSM-IV diagnoses were schizoaffective disorder and bipolar disorder with psychotic features, respectively. Interestingly, Bodkin *et al.* (1) identified the mother and son as carriers of a triplication of *GLDC,* the gene encoding glycine decarboxylase. This structural rearrangement appeared to be a de novo event in the mother (2).

Glycine is a well-established inhibitory neurotransmitter at strychnine-sensitive glycine receptors in the central nervous system, especially in the spinal cord and brainstem. Glycine is also an endogenous coagonist at the strychnine-insensitive glycine modulatory site of the *N*-methyl-D-aspartate receptor (NMDAR) in the forebrain (3). Serine hydroxymethyltransferase 1 (SHMT1) is an enzyme that is active in the reversible interconversion between glycine and L-serine (Figure 1). Interestingly, levels of *SHMT1* messenger RNA in the dorsolateral prefrontal cortex of individuals with schizophrenia were reported to be higher than those of control subjects, suggesting a role of *SHMT1* in the pathogenesis of schizophrenia (4). Serine racemase (SRR) converts L-serine to D-serine, which is also an endogenous coagonist at the NMDAR. In 2014, a multistage schizophrenia genome-wide association study showed that several genes involved in glutamatergic neurotransmission (including *SRR*) are associated with schizophrenia (5). Collectively, abnormalities in the glycine–L-serine–D-serine cycle might play a crucial role in excitatory neurotransmission via the NMDAR and may therefore be implicated in psychiatric disorders such as schizophrenia (3).

The degradation of glycine occurs through the glycine cleavage system, which is composed of four mitochondrial protein components: P protein (a pyridoxal phosphate–dependent glycine decarboxylase), H protein (a lipoic acid–containing protein), T protein (a tetrahydrofolate-requiring enzyme), and L protein (a lipoamide dehydrogenase). The P protein encoded by *GLDC* binds to glycine and enables transfer of a methylamine group from glycine to the T protein. *GLDC* mutations are well known to cause nonketotic hyperglycinemia, an inborn error of metabolism characterized by severe neurologic disturbances.

Bodkin *et al.* (1) hypothesized that triplication of *GLDC* would be expected to increase glycine metabolism, resulting in low levels of glycine and D-serine. In their study, they hypothesized that the individuals carrying the *GLDC* triplication would exhibit low levels of the endogenous coagonists, such as glycine and D-serine, resulting in NMDAR hypofunction. They therefore performed a proof-of-principle clinical trial of glycine (a full agonist at the NMDAR) (starting dose 6 g/day, then 3 g/day) and D-cycloserine (50 mg/day) in these 2 patients with NMDAR hypofunction. Low-dose D-cycloserine is a partial agonist at the glycine modulatory site of the NMDAR (3). We previously reported that D-cycloserine significantly increased extracellular levels of D-serine in the hippocampus of wild-type and *SRR* knockout mice after a single oral dose (6), suggesting that SRR is not involved in mechanisms that induce increased D-serine levels in the mouse brain after D-cycloserine treatment. Therefore, in addition to being a partial agonist, D-cycloserine may act as a prodrug for D-serine in the brain (6).

Symptom severity in the 2 patients studied was reduced by administration of glycine or D-cycloserine, although no changes in neurocognition were observed with this treatment. At baseline, plasma levels of glycine were within the normal range and those of L-serine were at the low end of the normal range. Plasma levels of both were markedly increased during glycine treatment, particularly that of L-serine, suggesting that glycine rapidly converts to L-serine via SHMT1. Importantly, D-cycloserine produced a greater benefit than did glycine in these 2 patients. It is possible that D-serine produced in the brain after D-cycloserine treatment, as in our aforementioned murine model, is partially responsible for the therapeutic effects seen with D-cycloserine because D-serine is a more potent coagonist at the NMDAR than glycine.

Both individuals with *GLDC* triplication had elevated plasma levels of kynurenine and kynurenic acid at baseline. Kynurenic acid is an endogenous antagonist at the NMDAR, and therefore elevated levels may have contributed to their NMDAR hypofunction. Interestingly, the kynurenic acid level normalized with administration of glycine or D-cycloserine, suggesting that glycine and D-cycloserine may in part counteract the antagonistic effect of kynurenic acid at the NMDAR in the brain. Notably, D-cycloserine produced substantially greater normalization of kynurenic acid than did glycine. However, the precise mechanisms underlying normalization of kynurenic acid by either glycine or D-cycloserine are currently unknown. Given the various effects observed, it is likely that D-cycloserine is better than glycine when it comes to treating the manifestations of *GLDC* triplication in these two carriers of that genotype.

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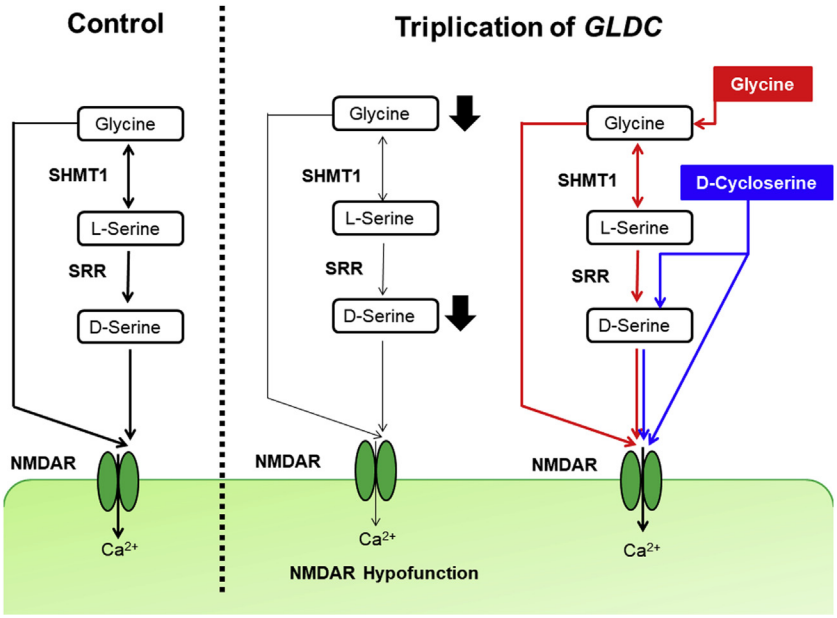

Figure 1. Proposed mechanism of *N*-methyl-D-aspartate receptor (NMDAR) hypofunction in individuals carrying *GLDC* triplication and improvement by NMDAR agonists. Individuals carrying triplication of *GLDC* have lower levels of glycine and D-serine, resulting in NMDAR hypofunction. Glycine and D-cycloserine bind to the glycine modulatory site of the NMDAR. Glycine is metabolized to L-serine by serine hydroxymethyltransferase 1 (SHMT1), and L-serine is then metabolized to D-serine by serine racemase (SRR) while D-cycloserine is metabolized directly to D-serine. Subsequently, D-serine binds to the glycine modulatory site of the NMDAR. These NMDAR agonists can then stimulate the receptor, resulting in improvement of psychotic symptoms in patients carrying *GLDC* triplication.

We also reported that blood levels of D-serine were lower and levels of L-serine were higher in patients with schizophrenia compared with those in healthy control subjects (7). In addition, we reported a decreased ratio of D-serine to total serine and an increased ratio of glutamine to glutamate in the cerebrospinal fluid of drug-naïve patients with a first episode of schizophrenia (8,9). Collectively, the evidence suggests that abnormalities in the D-serine–L-serine cycle as well as the glutamine–glutamate–gamma-aminobutyric acid cycle play a role in the early stage of schizophrenia (3,10). Therefore, it would be of interest to determine cerebrospinal fluid levels of NMDAR-related amino acids, such as glutamate, glutamine, D-serine, L-serine, glycine, and gamma-aminobutyric acid, at baseline and after D-cycloserine treatment.

In conclusion, NMDAR modulators (e.g., D-cycloserine, D-serine, glycine, sarcosine, and sodium benzoate) appear to be potential therapeutic agents for patients carrying gene mutations, including CNVs, which cause NMDAR hypofunction.

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Article Information

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