

# Novel Therapeutics for Schizophrenia: Targeting Glycine Modulation of NMDA Glutamate Receptors

By Stephen M. Stahl, MD, PhD

## NEW TREND IN PSYCHOPHARMACOLOGY

Currently, a major hypothesis for the pathophysiology of schizophrenia<sup>1-10</sup> proposes that numerous risk factors converge on the N-methyl-D-aspartate (NMDA) receptor for the neurotransmitter glutamate, resulting in neurodevelopmental abnormalities at glutamate synapses and hypofunction of NMDA receptors. This hypothesis was presented in a previous "Trends in Psychopharmacology" column.<sup>9</sup> Novel treatments are now in development that can theoretically boost the function of NMDA receptors by enhancing actions at the glycine co-transmitter site of this receptor complex.<sup>10-20</sup> Early studies<sup>15-20</sup> already indicate that this may lead to improvement in negative and cognitive symptoms of schizophrenia, especially when added as augmenting agents to atypical antipsychotics.

## NEW TREATMENT STRATEGIES FOR SCHIZOPHRENIA

The NMDA receptor hypofunction hypothesis for schizophrenia<sup>1-5</sup> arises from observations that the NMDA receptor antagonist phencyclidine can produce a psychotic condition similar to the positive, negative, and cognitive symptoms of schizophrenia. These observations, coupled with genetic studies in schizophrenia that also implicate dysfunctional NMDA receptors,<sup>6</sup> have led to a new strategy for the treatment of schizophrenia, namely targeting mechanisms that enhance deficient NMDA receptor functioning.<sup>3,10-20</sup>

Pharmacologic approaches that involve direct enhancement of glutamate risk excitotoxicity from excessive glutamate action.<sup>3-5,10</sup> Thus, a potentially safer way to enhance glutamate is to exploit the fact that NMDA glutamate receptors also require glycine actions at a co-transmitter site.<sup>3,10-20</sup> NMDA receptors are an interesting type of "coincidence detector" that can open to allow calcium into the neuron to trigger postsynaptic actions from glutamate neurotransmission only when three things occur at the same time: glutamate occupies its binding site on the NMDA receptor, glycine or D-serine binds to its site on the NMDA receptor, and depolarization occurs.<sup>3,7,8,10</sup>

In order to understand the actions of new drugs directed at the glycine co-transmitter site on NMDA receptors, it is useful to review the synthesis of endogenous agonists for this site, including glycine and D-serine.

## SYNTHESIS OF GLUTAMATE CO-TRANSMITTER GLYCINE

Glycine is not known to be synthesized by glutamate neurons, so glutamate neurons must acquire the glycine they need for their NMDA receptors from glycine neurons or from glial cells (Figure 1).<sup>3,7,8,10</sup> Glycine neurons release glycine. However, they contribute only a small amount of glycine to glutamate synapses, since glycine is unable to diffuse far from neighboring glycine neurons because the glycine they release is taken back up into those neurons by

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a type of glycine reuptake pump known as the type-2 glycine transporter (Figure 1).

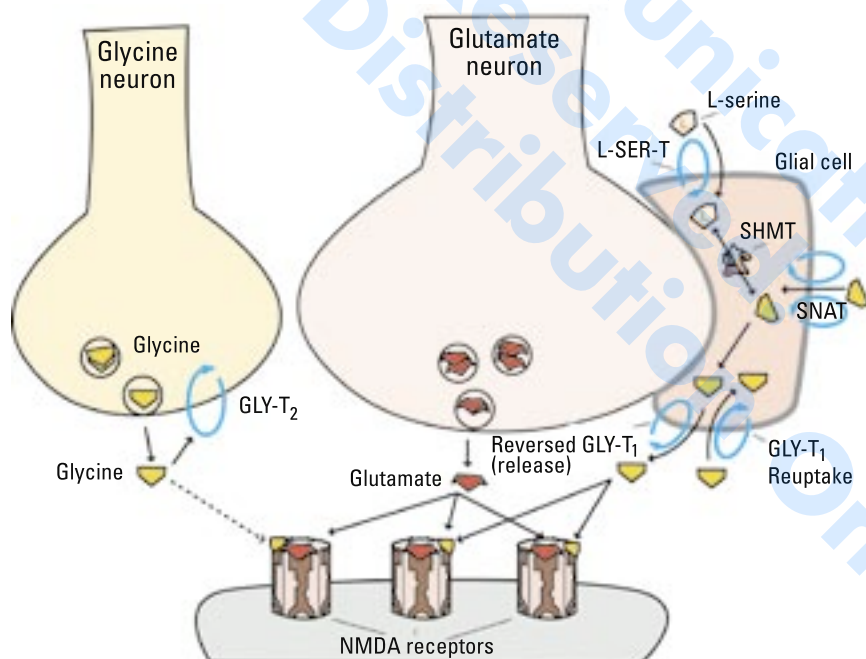
Thus, neighboring glial cells are thought to be the source of most of the glycine available for glutamate synapses. Glycine itself can be taken up into glial cells either by a type-1 glycine transporter (GLY-T<sub>1</sub>) or by a glial specific neutral amino acid transporter (Figure 1).<sup>10,13-17</sup> Glycine is released into glutamate synapses from glial cells by riding on a reversed GLY-T<sub>1</sub> transporter (Figure 1).<sup>10</sup> Once outside, glycine can re-enter the glial cell by riding on an inwardly directed GLY-T<sub>1</sub>, which functions as a reuptake pump and is the main mechanism responsible for terminating the action of synaptic glycine (Figure 1).<sup>10</sup>

Glycine can also be synthesized from the amino acid L-serine, which is transported into the glial cell by an L-serine transporter, and then converted from L-serine into glycine by the glial enzyme serine hydroxy methyl transferase (Figure 1).<sup>10</sup> This enzyme functions in both directions, either converting L-serine into glycine or glycine into L-serine.<sup>10</sup>

## SYNTHESIS OF GLUTAMATE CO-TRANSMITTER D-SERINE

D-serine is unusual in that it is a D-amino acid, whereas the 20 known essential amino acids are all L-amino acids, including D-serine's mirror image amino acid L-serine.<sup>3,7,8,10</sup> It just so happens that D-serine has a high affinity for the glycine site on NMDA receptors, and that glial cells are equipped with an enzyme that can convert regular L-serine into the neurotransmitting amino acid D-serine by means of an enzyme that can go back and forth between D- and L-serine (D-serine racemase) (Figure 2). Thus, D-serine can be derived from glycine or from L-serine, both of which can be transported into glial cells by their own transporters, and then glycine converted to L-serine by serine hydroxy methyl transferase, and finally L-serine converted into D-serine by the enzyme D-serine racemase (Figure 2). D-serine's actions are not only terminated by synaptic reuptake via the inwardly acting glial serine transporter but also by an enzyme D-amino acid oxidase that converts D-serine into hydroxy-pyruvate (Figure 2).

**FIGURE 1.**  
NMDA receptor co-transmitter glycine is produced<sup>3</sup>



NMDA=*N*-methyl-D-aspartate; L-SER-T=L-serine transporter; SHMT=serine hydroxy methyl transferase; GLY-T<sub>1</sub>=type-1 glycine transporter; SNAT=specific neutral amino acid transporter; GLY-T<sub>2</sub>=type-2 glycine transporter.

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## TARGETING GLYCINE MODULATION OF NMDA RECEPTORS

### Glycine Agonists

Agonists at the glycine site of NMDA receptors include the naturally occurring amino acids glycine and D-serine (Figure 3).<sup>3,5,7,8,10,15-19</sup> An analogue of D-serine, called D-cycloserine is also active at the glycine co-agonist site of NMDA receptors. All of these agents have been tested in schizophrenia with evidence that they can reduce negative and/or cognitive symptoms.<sup>5,7,8,10-19</sup> Further testing of these naturally occurring agents is in progress and synthetic agonists with greater potency are in discovery.

### GLY-T<sub>1</sub> Inhibitors

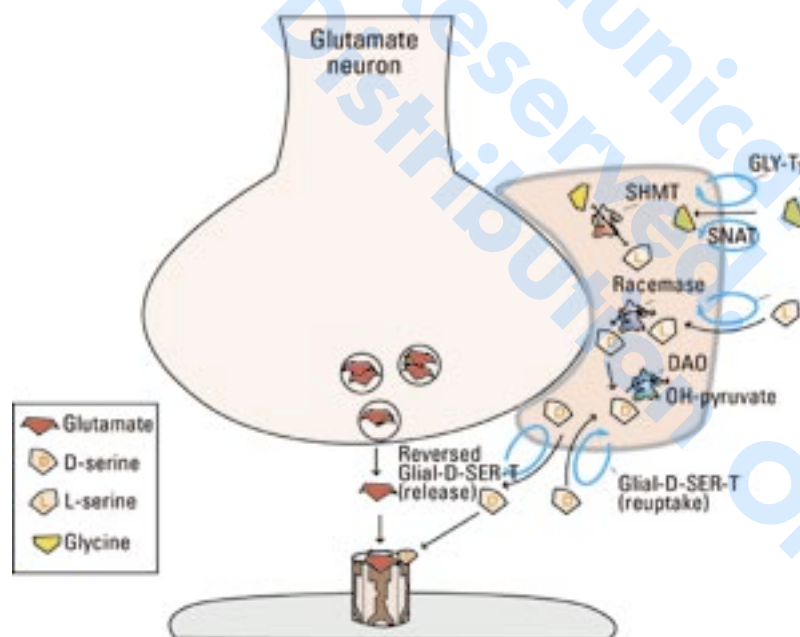
The GLY-T<sub>1</sub> reuptake pump is the major route of inactivation of synaptic glycine (Figure 1), so it is logical to explore the ability of GLY-T<sub>1</sub> inhibitors to enhance synaptic actions of glycine, and thus, of NMDA receptors (Figure 4).<sup>3,5,7,8,10-17,19,20</sup> Several GLY-T<sub>1</sub> inhibitors are now in testing, including the

natural agent *N*-methyl-glycine, also known as sarcosine, as well as drugs in preclinical testing, such as SSR 504734, SSR 241586, JNJ17305600, and Org 25935. GLY-T<sub>1</sub> inhibitors are analogous to drugs that inhibit reuptake of other neurotransmitters, such as the serotonin selective reuptake inhibitors and their actions at the serotonin transporter. When GLY-T<sub>1</sub> pumps are blocked by a GLY-T<sub>1</sub> inhibitor, this increases the synaptic availability of glycine, and thus enhances NMDA neurotransmission (Figure 4). Sarcosine has been shown to improve negative, cognitive, and depressive symptoms, including symptoms such as alogia and blunted affect in schizophrenia.<sup>19,20</sup> The hope is that GLY-T<sub>1</sub> inhibitors with greater potency, such as those in preclinical testing mentioned above, will be even more effective.

## CONCLUSION

An outgrowth of the NMDA receptor hypofunction hypothesis of schizophrenia is the novel therapeutic strategy of enhancing the glycine mod-

**FIGURE 2.**  
NMDA receptor co-transmitter D-serine is produced<sup>3</sup>

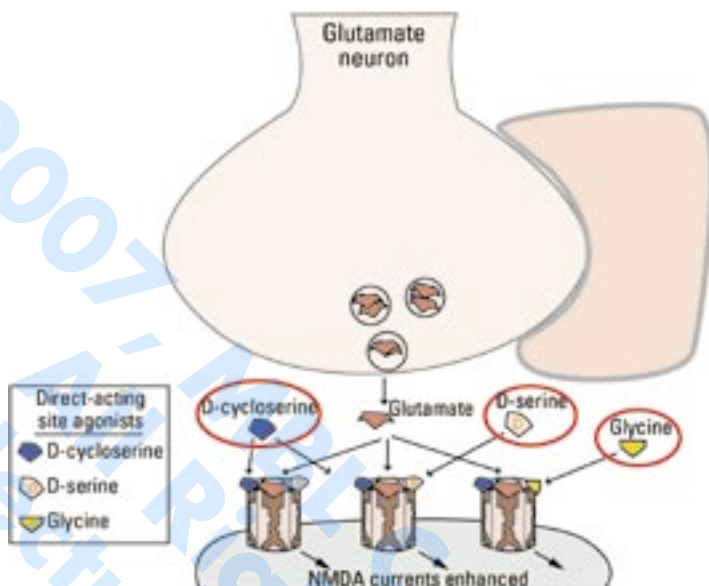


NMDA=*N*-methyl-D-aspartate; GLY-T<sub>1</sub>=type-1 glycine transporter; SNAT=specific neutral amino acid transporter; SHMT=serine hydroxy methyl transferase; L-SER-T=L-serine transporter; DAO=D-amino acid oxidase; OH=hydroxy; D-SER-T=D-serine transporter.

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**FIGURE 3.**  
**Novel glutamatergic treatments for schizophrenia: direct-acting glycine site agonists<sup>3</sup>**

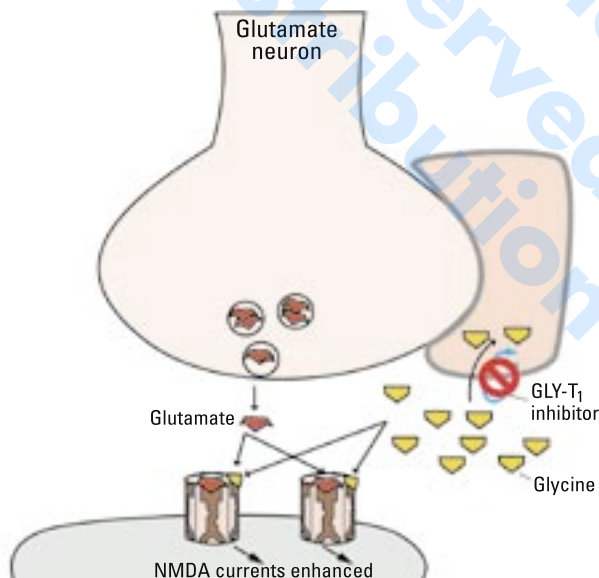


NMDA=*N*-methyl-D-aspartate.

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**FIGURE 4.**  
**Novel glutamatergic treatments for schizophrenia: glycine transporter on glial cells inhibited (GLY-T<sub>1</sub> inhibitor)<sup>3</sup>**



GLY-T<sub>1</sub>=type-1 glycine transporter; NMDA=*N*-methyl-D-aspartate.

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ulatory component of neurotransmission at these receptors. Already, early testing with direct-acting agonists at the glycine modulatory site, such as D-serine and D-cycloserine, as well as indirect enhancers of synaptic glycine that act by blocking the glycine reuptake transporter or GLY-T<sub>1</sub>, such as sarcosine, is yielding encouraging results. **CNS**

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