

D-Cycloserine: An Evolving Role in Learning and Neuroplasticity in Schizophrenia

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As a partial agonist at the glycine site of the NMDA receptor, D-cycloserine (DCS) has been viewed as lacking potency to fully test the NMDA receptor hypofunction theory of schizophrenia. However, findings of full agonist activity at a subset of NMDA receptors that may have particular relevance to schizophrenia, plus a growing body of evidence demonstrating enhancement of learning and neuroplasticity in animal models, suggest novel therapeutic strategies with DCS in schizophrenia. Preliminary studies with once-weekly administration have supported this potential new role for DCS in schizophrenia by demonstrating benefit for negative symptoms, memory consolidation, and facilitation of cognitive behavioral therapy for delusions.

Key words: NMDA/negative symptoms/memory consolidation/cognitive behavioral/therapy/D-cycloserine

Introduction

Roughly 20 years ago, we considered D-cycloserine (DCS) the best available agent to test the emerging NMDA receptor hypofunction model for schizophrenia, given DCS's penetrance across the blood–brain barrier, selectivity for the strychnine-insensitive glycine site of the NMDA receptor, extensive safety record and because it was already approved by the Food and Drug Administration for daily dosing. Unlike glycine, D-alanine, and D-serine, which act as full agonists at the glycine site, DCS was believed at that time to be a classic partial agonist,¹ which might ensure greater protection against neurotoxicity but also could potentially limit therapeutic efficacy. The historical context of studies with DCS and other glycine site agonists is provided by Joe Coyle in this issue. Our understanding of DCS activity at NMDA receptors has changed significantly since that time, leading to novel therapeutic strategies that recently have shown promise in early trials.

Early Trials with DCS in Schizophrenia

We started by conducting a dose-finding study consisting of consecutive 2-week single-blind escalating-dose trials

of placebo, DCS 5, 15, 50, and 250 mg added to first-generation antipsychotics; videotapes of clinical assessments were scored in random order by a blinded rater.² An inverted *U*-shaped dose-response curve was found for negative symptoms, with only the 50 mg/d dose associated with improvement. In a subsequent 8 week fixed dose, placebo-controlled trial of DCS 50 mg/d in 51 schizophrenia patients meeting criteria for the deficit syndrome and treated with first-generation antipsychotics, negative symptoms again improved compared with placebo (effect size 0.8), in the absence of change in other symptom domains or in cognitive performance.³ Notably, one subject, who developed a high serum DCS concentration experienced worsening of psychotic symptoms consistent with earlier open trials that employed DCS doses of 250 mg/d and higher.^{4,5} In a subgroup of subjects studied by Deborah Yurgelun-Todd with functional magnetic resonance imaging at baseline and week 8, DCS significantly increased activity in temporal cortex during performance of a verbal fluency task, which correlated with improvement in negative symptoms.⁶

Evidence from animal models^{7,8} and ketamine challenge in humans⁹ suggested that the newly introduced second-generation antipsychotics might differ from first-generation antipsychotics in reversing behavioral effects of NMDA antagonists, best demonstrated with clozapine. For this reason, we repeated the single-blind DCS dose-finding protocol in schizophrenia patients treated with clozapine and found a worsening of negative symptoms with the 50 mg/d dose.¹⁰ This finding was replicated in a placebo-controlled cross-over trial.¹¹ When Eden Evins in our group repeated this exercise with risperidone-treated subjects, DCS 50 mg/d produced a modest but significant improvement in negative symptoms, intermediate in magnitude between the improvement of negative symptoms observed in subjects treated with first-generation antipsychotics and the worsening observed in clozapine-treated subjects. Because Corbett and colleagues⁸ had reported that both clozapine and olanzapine reversed phencyclidine-induced social

withdrawal in rats, we decided to study the relationship between glutamatergic effects of olanzapine and response of negative symptoms in collaboration with Perry Renshaw. We switched schizophrenia patients from first-generation antipsychotics to olanzapine and, using proton magnetic resonance spectroscopy, found that olanzapine-associated elevation of glutamate/glutamine concentrations in cingulate cortex predicted improvement in negative symptoms.¹² In summary, at the end of this early series of studies, the evidence suggested that DCS selectively improved negative symptoms following an inverted-*U* dose-response curve with the possibility of worsening of psychotic symptoms at higher doses and that improvement of negative symptoms was more robust when added to first-generation agents compared with second generation. Our findings also suggested that clozapine and olanzapine might exert efficacy for negative symptoms via glutamatergic mechanisms; in the case of clozapine, this effect could be reversed by DCS.

Although these early findings with DCS seemed compelling, results from subsequent studies were inconsistent. In 2 small placebo-controlled cross-over studies, Heresco-Levy and colleagues^{13,14} found improvement of negative symptoms with DCS 50 mg/d but reported that efficacy appeared to be similar whether DCS was added to clozapine, other atypicals, or first-generation antipsychotics. Van Berckel and colleagues¹⁵ reported selective improvement in negative symptoms in a single-blind trial of escalating doses of DCS in medication-free schizophrenia subjects; improvement of negative symptoms was lost when the DCS dose was raised to 250 mg/d. However, when van Berckel and colleagues¹⁶ subsequently added DCS 100 mg/d to first-generation agents in a fixed-dose, placebo-controlled trial they found significant worsening of psychotic symptoms. We failed to find improvement in negative symptoms in a 6-month placebo-controlled add-on trial of DCS 50 mg/d, although this trial was confounded by a high dropout rate.¹⁷ Finally, in a 4-week trial of DCS 50 mg/d in 20 schizophrenia patients treated with first-generation antipsychotics, Duncan and colleagues¹⁸ detected no improvement in negative symptoms or cognition.

The CONSIST Trial

The most comprehensive test of DCS add-on treatment, the Cognitive and Negative Symptoms in Schizophrenia Trial (CONSIST), also failed to demonstrate symptomatic or cognitive benefit with either DCS 50 mg/d or glycine in a three-arm placebo-controlled add-on trial involving 157 schizophrenia inpatients and outpatients treated with any antipsychotic except clozapine.¹⁹ The previously observed differential response to DCS in patients treated with first- versus second-generation antipsychotics could not be assessed due to an inadequate

number of subjects treated with first-generation agents; fewer than 10 subjects in each arm were treated with first-generation antipsychotics. However, despite this small sample, glycine was significantly more effective than placebo for negative symptoms in subjects treated with first-generation agents ($P = 0.005$), whereas DCS was nonsignificantly more effective. Results of CONSIST were complicated by significant differences in response of negative symptoms between sites. For example, DCS was more effective than placebo for negative symptoms at a site that had the highest mean baseline SANS score (49.4) and the smallest placebo response (a 3% reduction in the SANS total). Baseline SANS scores at the other sites ranged from 33.9 to 39.9 and placebo responses at the other 3 sites ranged from approximately 10%–41%. Regardless of the constraints imposed by variability in response between sites, CONSIST did establish that the addition of DCS to second-generation antipsychotics does not produce a sufficiently large or consistent therapeutic effect to be replicated in a large representative clinical trial.

DCS Pharmacology and Animal Behavioral Studies

In sharp contrast to the mixed results from trials with DCS in schizophrenia, a large literature has established consistent robust effects in animal models of learning and consolidation of fear extinction memory that led to trials in which DCS successfully facilitated cognitive behavioral exposure therapy in anxiety disorders.²⁰ These findings, along with recent insights into unique pharmacologic properties of DCS, point to new therapeutic strategies for DCS in schizophrenia.

DCS activity at NMDA receptors is more complex than previously appreciated. DCS binds to the glycine recognition site of the NR1 subunit of the NMDA receptor, but the resulting degree of depolarization is determined by NR2 receptor subunits, to which glutamate binds.²¹ At NMDA receptors composed of NR1 plus NR2A or NR2B subunits, DCS was found to produce approximately 50% depolarization in the presence of NMDA compared with the endogenous agonist, glycine.²² In contrast, at NMDA receptors that contain NR2C subunits, DCS produces approximately 200% activity compared with glycine.²² Hence, depending on ambient concentrations of glycine and D-serine, DCS may act as an agonist or antagonist at NMDA receptors containing NR2A or NR2B subunits, whereas at NMDA receptors containing NR2C subunits, DCS is a potent agonist regardless of glycine concentration.

In several animal models and in trials in schizophrenia, DCS has demonstrated different, and in some cases opposing, effects at low dose vs high dose, a dose-response pattern which is not typical of classic partial agonists. In an early study, Watson and colleagues¹ demonstrated with oocytes expressing NMDA receptors that DCS

acted like an uncomplicated partial agonist over a wide range of concentrations, producing 40%–50% activity compared with glycine. In contrast, Emmett and colleagues²³ found an inverted *U*-shaped dose-response relationship when they studied mouse cerebellar tissue. Importantly, cerebellum has a relatively high density of NR2C subunits. Hence, at low DCS concentrations, agonist activity may reflect binding to NR2C subunit-containing receptors, whereas at higher DCS concentrations antagonist effects may become prominent with increased binding to receptors containing NR2A and NR2B subunits. This possible explanation was supported recently by evidence from Dravid and colleagues,²¹ who demonstrated that DCS produced approximately 200% activity compared with glycine at NR2C-containing NMDA receptors at concentrations approximately one order of magnitude lower than those required to produce maximal activity at receptors containing NR2A and NR2B subunits. At high concentrations, DCS produced 90% activity at NR2A-containing receptors and 65% activity at NR2B-containing receptors. This activity profile would be expected to produce a bimodal dose response, with a second peak of partial agonist activity occurring at higher concentrations reflecting maximal agonist activity mediated by NMDA receptors containing NR2A and NR2B subunits.

Clinical Relevance of Unique DCS Pharmacology

The potent enhancement of activity by DCS at NMDA receptors containing NR2C subunits may have important clinical implications. NR2C-containing receptors are primarily found on cerebellar granule cells but also are found on interneurons in prefrontal cortex and hippocampus, oligodendrocytes, the medial dorsal nuclei of the thalamus, and in spiny stellate neurons of layer 4 which are the primary somatosensory target in cortex for thalamocortical input.²⁴ In a postmortem study of prefrontal cortex, NR2C subunit expression was found to be the only NMDA receptor subunit selectively reduced in individuals with schizophrenia compared with healthy subjects and psychiatric controls.²⁵ NMDA receptors containing the NR2C subunit differ from other NMDA receptor subtypes in exhibiting a reduced sensitivity to Mg block and also have a higher affinity for glutamate. As a result, unlike other NMDA receptors, NR2C-containing receptors do not serve as delayed “coincidence detectors” requiring postsynaptic partial depolarization but instead can be activated by low concentrations of ambient glutamate.²⁶ Finally, NR2C knockout mice display impairment on tests of fear conditioning, working memory, and consolidation of extinction memory but show no difference compared with wild types in recognition or reference memory, spontaneous locomotor activity, basal anxiety, pain sensitivity, or forced swim-induced immobility.²⁷

In animal models, DCS administered as a single dose reversed cognitive impairment produced by hippocampal lesions, anticholinergic agents, and early social deprivation. In healthy animals, DCS enhanced extinction of conditioned fear,²⁸ performance on maze tasks,²⁸ and visual recognition memory.²⁹ In fear extinction models and in facilitation of cognitive behavioral therapy (CBT) for phobic patients, DCS does not affect performance during training; instead, it selectively improves memory consolidation for new learning typically assessed 24 h after training.³⁰ Importantly, DCS enhancement of memory consolidation appears to be limited to novel learning.³¹ In addition, tachyphylaxis rapidly develops with repeated dosing of DCS. A single dose of DCS administered within 30 min of extinction training increases 24 h retention of fear extinction approximately 3-fold, whereas this effect was completely attenuated by 5 doses of DCS administered over 10 days preceding the extinction training.³² Tachyphylaxis for cognitive effects of DCS may reflect endocytosis of NMDA receptors mediated by glycine site activation.³³

Once-Weekly Dosing of DCS in Schizophrenia

To test the effects of DCS on memory consolidation in schizophrenia and to avoid possible tachyphylaxis of cognitive effects associated with daily dosing, we conducted a placebo-controlled add-on trial of DCS 50 mg administered once-weekly for 8 weeks in 38 stable schizophrenia patients.³⁴ Compared with placebo, once-weekly DCS was associated with significant improvement of negative symptoms measured by the SANS total score at week 8, 7 days after the last dose of DCS. The persistence of negative symptom improvement with once-weekly dosing is suggestive of neuroplastic changes—unlike memory effects, it is not clear whether tachyphylaxis occurs for effects on negative symptoms. Memory consolidation was evaluated by the Logical Memory Test from the Revised Wechsler Memory Scale. Subjects, after hearing a brief story, are asked to recall details and themes of the story. To assess memory consolidation, recall of the themes of story A was tested after a 7-day delay at baseline. Story B was presented to subjects 1 h after the first dose of DCS, and subjects were asked to recall themes from story B 7 days later. Delayed recall of themes from the Logical Memory Test was selected because previous work in healthy subjects demonstrated that memory consolidation enhances recall of the “gist” of newly learned material³⁵ and because this form of learning may be applicable to CBT. Consistent with animal models, DCS had no effect on immediate recall but significantly enhanced 7-day delayed thematic recall. The cognitive effects of DCS were limited to memory consolidation, as no improvement was detected in any domain on a standard cognitive battery performed at baseline and week 8. Because standard cognitive batteries, including the

MATRICES, are designed to eliminate “learning effects,” memory consolidation is not routinely tested in drug trials even though impairment of learning may substantially contribute to functional disability.

Members of our group have shown that 24 h consolidation of procedural memory³⁶ and fear extinction memory³⁷ are impaired in individuals with schizophrenia. Dara Manoach found that impairment of memory consolidation on a procedural memory task was associated with abnormalities of sleep architecture (primarily a decrease in sleep spindle density),³⁸ consistent with abnormal thalamic oscillatory activity, which may be driven by NMDA receptors containing NR2C subunits.²⁶ Diminished density of sleep spindles has been linked to positive symptoms.³⁹ The impairment of 24-h delayed fear extinction recall demonstrated in schizophrenia subjects by Daphne Holt has also been observed in NR2C knockout mice²⁷ and can be produced by injection of an NMDA receptor blocker into medial ventral prefrontal cortex.⁴⁰ Herbener and colleagues⁴¹ demonstrated that schizophrenia subjects were able to recall patterns associated with reward immediately after training at a level comparable to healthy controls but were significantly impaired when tested after a 24-h delay. This finding links the impairment of memory consolidation to a deficit in reward anticipation—a finding consistent with impaired anticipatory pleasure underlying anhedonia in schizophrenia.⁴²

We recently questioned whether impaired memory consolidation might contribute to the persistence of delusions in schizophrenia, hypothesizing that delusions represent a failure to extinguish or “unlearn” a false belief despite exposure to evidence that contradicts the belief. Twenty schizophrenia patients treated with any antipsychotic except clozapine and with residual delusions were administered a single dose of DCS 50 mg or placebo 1 h before a CBT exercise developed by Jennifer Gottlieb in which they were trained to formulate alternative explanations for a series of neutral social scenarios (eg, a taxi driver is staring at you) culminating in a scenario related to their own delusion.⁴³ CBT exercises were performed twice, 1 week apart, accompanied by DCS or placebo in random order. Delusional severity was rated at baseline and 7 days after each CBT session. Delusional severity, including items rating distress and conviction, was reduced after the 2 CBT sessions in subjects who received DCS first compared with subjects who received placebo first. This finding is consistent with animal studies demonstrating that DCS facilitates learning of novel training but has no effect if extinction has previously been performed.³¹ The effect size of 0.8 for response of delusions following a 2-session CBT treatment was quite remarkable, given that a recent meta-analysis found an effect size of 0.22 for the response of positive symptoms in methodologically rigorous CBT trials that typically involved 16 or more sessions,⁴⁴ although our finding requires replication in a parallel-group design.

Neuroprotection and Neuroplasticity

DCS additionally may have neuroprotective and neuroplastic properties. In 2 studies, mice treated with a single, low-dose (10 mg/kg) of DCS 24 or 72 h after closed head injury exhibited significantly more rapid and complete recovery of motor and memory function compared with untreated controls.^{45,46} Examination of the hippocampal CA1 region revealed significant improvement of long-term potentiation and elevation of brain-derived neurotrophic factor following DCS treatment. DCS also enhances neuroplasticity in other models that have been shown to be abnormal in schizophrenia. For example, medicated and unmedicated schizophrenia subjects exhibited large reductions in neuroplasticity measured by repeated transcranial magnetic stimulation (rTMS) evoked movement of the thumb before and after training.⁴⁷ Similar reductions in this measure of neuroplasticity were produced in healthy subjects by administration of dexamethorphan,⁴⁸ a weak NMDA antagonist that binds with highest affinity to NR2C-containing receptors.⁴⁹ A single dose of DCS 100 mg significantly enhanced neuroplasticity measured by rTMS in healthy subjects.⁵⁰

Conclusions

In summary, early add-on studies with low-dose DCS added to first-generation antipsychotics produced improvement of negative symptoms in the absence of cognitive enhancement or effects on other symptom domains. Improvement of negative symptoms correlated with increased temporal lobe perfusion. However, these findings were not supported by the multicenter CONSIST trial, possibly due, in part, to reduced DCS efficacy when combined with second-generation antipsychotics. Recent evidence indicates that DCS acts as an agonist with twice the activity of glycine at NMDA receptors containing the NR2C subunit. At low doses, DCS may act as a relatively selective agonist, whereas antagonism at other NMDA receptor subtypes may become prominent at higher doses. NR2C subunits are involved in fear conditioning and memory consolidation and were found to be reduced in PFC of individuals with schizophrenia. Animal models have demonstrated robust enhancement of consolidation of novel learning with a single dose of DCS and tachyphylaxis with repeated doses; preliminary work also suggests enhancement of neuroplastic recovery following brain injury. Consistent with these characteristics of DCS, we recently found persistent improvement of negative symptoms with once-weekly dosing, improvement of memory consolidation, and, when DCS was combined with CBT, a marked reduction in delusional severity. The full extent of potential therapeutic benefits which may result from neuroplastic effects of intermittent dosing with DCS in schizophrenia remain to be explored, but early findings are promising.

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