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Chronic Administration of NMDA Glycine Partial Agonists Induces Tolerance in the Porsolt Swim Test

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LOPES, T., P. NEUBAUER AND K. M. K. BOJE. *Chronic administration of NMDA glycine partial agonists induces tolerance in the Porsolt swim test.* PHARMACOL BIOCHEM BEHAV **58**(4) 1059–1064, 1997.—The Porsolt swim test (PST) was used to assess behavioral effects following acute or chronic treatment with two *N*-methyl-D-aspartate (NMDA) glycine partial agonists, 1-aminocyclopropanecarboxylic acid (ACPC), and D-cycloserine (DCS). Consistent with previous findings in mice, single intravenous doses of ACPC in rats produced a significant, dose-dependent reduction in immobility in the PST compared to saline. Single dose DCS also elicited significant dose-dependent reductions in PST immobility times. Single-dose ACPC or DCS (200 mg/kg) reduced immobility ($p < 0.05$) by 26 or 30%, respectively, compared to saline. However, multiple dosing with either ACPC or DCS (6 daily doses, 200 mg/kg) produced an apparent behavioral adaptation, as the immobility data were indistinguishable from chronic saline administration. Moreover, pretreatment with a 5-day course of ACPC or DCS promoted the development of a behavioral cross-tolerance following a sixth dose of DCS or ACPC, respectively. The development of a behavioral tolerance in the PST following chronic therapy of these drugs appears to be a general feature of glycine partial agonists. In toto, these findings support the hypothesis that chronic administration of NMDA glycine partial agonists produces a behavioral tolerance putatively through an adaptation of the NMDA receptor complex.

1-Aminocyclopropanecarboxylic acid D-cycloserine Glycine Desensitization Porsolt Swim test Rat N-Methyl-D-aspartate receptor

THE excitatory neurotransmitter glutamate plays critical roles in physiological and pathophysiological processes. Over excitation of glutamate receptors is a key element in the development of acute or chronic neurological diseases. Many central nervous system disorders, for example, epilepsy, depression, anxiety, and neurodegeneration subsequent to ischemia or trauma (6,7,8,32,50,52–55), are linked to inappropriate activation of the *N*-methyl-D-aspartate (NMDA) receptor complex, a glutamate receptor subtype.

The NMDA receptor complex is a highly regulated ligand-gated ion channel. Under depolarizing conditions, binding of the required coagonists, glutamate and glycine, relieves the magnesium blockade of the ion channel to permit sodium and calcium influx (20,24). Ample evidence obtained from electrophysiologic and radioligand binding studies demonstrate a functional allosteric coupling between the glutamate and glycine sites (2,11,16,18,21,31,34,46,47). The affinity of glutamate for its receptor site can be positively or negatively modulated by a variety of glycinergic ligands, and conversely, glycine affinity can be reciprocally modulated by glutaminergic ligands (3,7, 11,15,19,47).

Pharmacologic ligands for the glutamate, glycine or ion channel sites can effectively modulate channel activity. Because glycine is essential for the in vivo activation of the NMDA receptor, compounds with partial agonistic activity at the glycine site may function as NMDA receptor antagonists (51). The cyclic glycine analogues, D-cycloserine (DCS) and 1-aminocyclopropanecarboxylic acid (ACPC), are high affinity, partial agonist ligands for the strychnine-insensitive glycine site of the NMDA receptor complex (12,14,15,22,30,35,57,58).

D-Cycloserine is broad spectrum antibiotic presently approved as an adjunctive agent in the treatment of susceptible gram positive or negative bacteria and Mycobacterium tuberculosis. The antidepressant activities of DCS were first de-

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scribed in the late 1950s after Crane serendipitously observed that depressed tuberculosis patients showed an improvement in mood (9). Subsequent clinical reports described the anxiolytic, antidepressant, and adverse CNS effects of DCS in tuberculosis patients (10,23,26). In recent years, low-dose DCS has attracted interest in its potential to enhance NMDA-mediated learning and memory tasks (25). Higher doses of DCS have anticonvulsant activity against electrically or chemically induced seizures in rodents (1,40,41,48,61). However, DCS was ineffective in preventing glutamate-mediated neurotoxicity in cerebellar granule cell cultures (3).

A single dose of ACPC has been shown to have pharmacological effects similar to that of competitive and noncompetitive NMDA antagonists (54,60). ACPC's effects include neuroprotective, anticonvulsant, anxiolytic, and antidepressant activities in in vitro and in vivo systems (3,50,51,53–56,59,60). Depending on the experimental system, the pharmacological activity of chronically dosed ACPC is either maintained (53), persists for a remarkable time during the washout phase of the drug (51,56), or is lost following chronic treatment (3,13, 51). Notably, ACPC's anxiolytic effects were maintained in the elevated plus-maze during chronic dosing (53), and positive neuroprotective benefits of chronic ACPC persisted even after a 1-day drug washout interval in animal models of neurodegeneration (27,56). However, chronic ACPC dosing produced a loss of behavioral activity in the Porsolt swim test (51), and sustained exposure of ACPC was ineffective in protecting cultured cerebellar granule cells against glutamate toxicity (3,13).

The present study sought to further examine the effects of ACPC and DCS after acute and chronic dosing using an in vivo behavioral paradigm, the Porsolt swim test (PST). Given the early reports of DCS antidepressant activity, it was hypothesized that an acute dose DCS would be active in PST. In analogy to the results previously reported for chronic ACPC dosing, the PST behavioral effects of DCS were also examined after chronic dosing. In addition, experiments were conducted to test the hypothesis that a behavioral crosstolerance would be manifest following chronic administration of ACPC or DCS.

METHOD

The animal studies were approved by the University of Buffalo Institutional Animal Care and Use Committee and performed according to the guidelines set forth by the National Institutes of Health guide for the care and use of laboratory animals (NIH Publications No. 85-23, revised 1985).

Male Sprague–Dawley rats (200–250 g) were acclimated to the University of Buffalo Laboratory Animal Facilities for a minimum of 1 week. Thereafter, right jugular vein catheters for drug administration were surgically implanted under ether anesthesia. Following an overnight recovery period with free access to food and water, the animals were processed in the Porsolt forced swim test (45). In brief, rats were subjected to a 15-min conditioning swim 1 day before the 5-min test swim. All behavioral testing was performed between 1230–1600 h. The test was conducted using a Plexiglas cylinder (diameter, 20 cm; height, 40 cm) filled to a height of 20 cm with 25°C water. On the study day, the 5-min test swim was recorded on video for behavioral immobility scoring by an investigator who was blinded to the drug treatments. Immobility was scored as described by Paul et al. (37), and was defined as the cumulative time intervals where animals did not engage in escape-orientated movements, such as extended sniffing, circling, diving, climbing, and jumping.

To test the behavioral effects of acute drug administration, groups of rats underwent surgery on day 1, the conditioning swim on day 2, and drug effect assessment in the test swim on day 3. Rats were randomly assigned to receive an intravenous dose of saline (sal) or 200 mg/kg of either ACPC (Research Organics, Cleveland, OH; 200 mg/kg) or DCS (Sigma, St. Louis, MO) 15 min or 60 min prior to the 5-min swim test. A

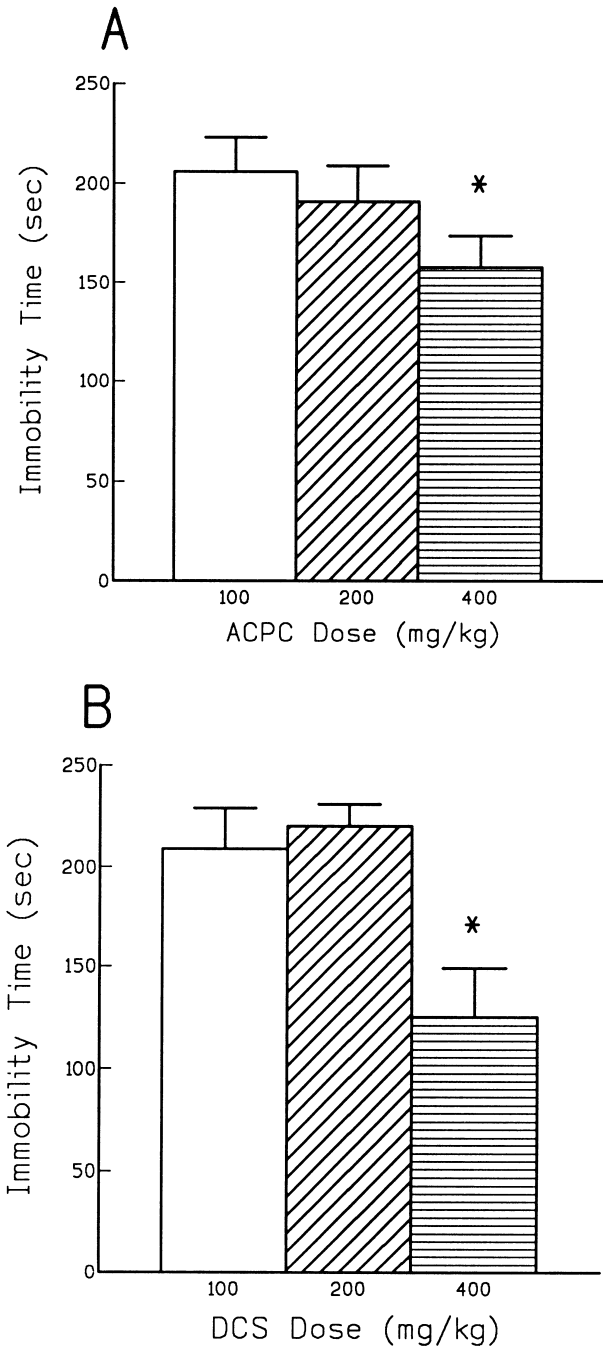

FIG. 1. Dose–response relationships for ACPC and DCS. Rats were tested 15 min after intravenous drug administration. Values represent mean ± SEM (n = 5–6). *Significantly different from saline treated group (210 ± 12, n = 6), $p < 0.05$.

positive control group treated with imipramine (Sigma, St. Louis, MO), was processed concurrently with the drug test groups. Imipramine (20 mg/kg) was dosed intraperitoneally immediately after the conditioning swim and 1 h prior to the 5-min test swim.

To test the effects of chronic drug treatment, rats were treated with five daily doses of saline or drug (200 mg/kg ACPC or DCS), followed by a sixth dose (200 mg/kg ACPC or DCS) dosed 1 h prior to behavioral testing in the PST. A positive control group was treated with four daily doses of saline followed by 2 days of one-a-day dosing with imipramine (20 mg/kg). Specifically, rats were surgically cannulated on day 1, and dosed daily (between 1200–1300 h) with saline or drug on days 2–5. The conditioning swim occurred prior to the fifth drug dose (saline, ACPC, DCS, or imipramine) on day 6. On the study day (day 7), rats received their final (6th) dose 1 h before the test swim.

Data Analysis

Data are expressed as mean ± SEM (n). Statistical significance was assessed by Student's unpaired t-test with appropriate use of Bonferroni's correction for multiple comparisons.

RESULTS

Imipramine is a classical tricyclic antidepressant with demonstrated activity in the PST (38,43,51). Using this drug as a positive treatment control, imipramine produced a significant ($p < 0.05$) reduction in immobility time (169 ± 22 s; $n = 7$) compared to an acute dose of saline (227 ± 12 s; $n = 8$).

The dose–response relationship for ACPC or DCS was determined 15 min after intravenous administration (Fig. 1). At a dose of 400 mg/kg, both compounds produced a significant decrease in immobility compared to saline. Although a 200 mg/kg dose of either drug did not elicit a statistically significant effect 15 min after dosing, these doses were effective 1 h after dosing, producing statistically significant reductions in immobility time compared to saline (saline: 210 ± 12 s, $n = 6$; *ACPC 153 ± 6 s, $n = 6$; *DCS 142 ± 10 s, $n = 6$; *$p < 0.01$ compared to saline).

Figure 2 presents data following chronic dosing of rats with ACPC or DCS. In contrast to a challenge dose of ACPC (200 mg/kg) following a 5-day treatment regimen with saline, a reduction in immobility time was not maintained following chronic ACPC treatment (200 mg/kg, once a day for 6 consecutive days) (Fig. 2A). Similar results were observed for DCS, in that the behavioral effects of chronically dosed DCS rats were also indistinguishable from rats treated with only chronic saline (Fig. 2B). A positive control group treated with imipramine demonstrated a significant reduction ($p < 0.02$) in immobility time (150 ± 19 s, $n = 5$) compared to chronic saline dosing (214 ± 8 s, $n = 5$).

Figure 3 presents data in support of the hypothesis that dosing of one agent would elicit a behavioral tolerance to the other drug. Chronic treatment with DCS followed by ACPC challenge (DCS/ACPC) or vice versa (chronic ACPC/DCS challenge) produced an insignificant reduction of 3 and 7% in immobility time, compared to the chronic saline/saline challenge group.

DISCUSSION

The Porsolt swim test is generally regarded as a preclinical behavioral drug screen used for the detection of antidepressant drug activity. This behavioral paradigm was originally

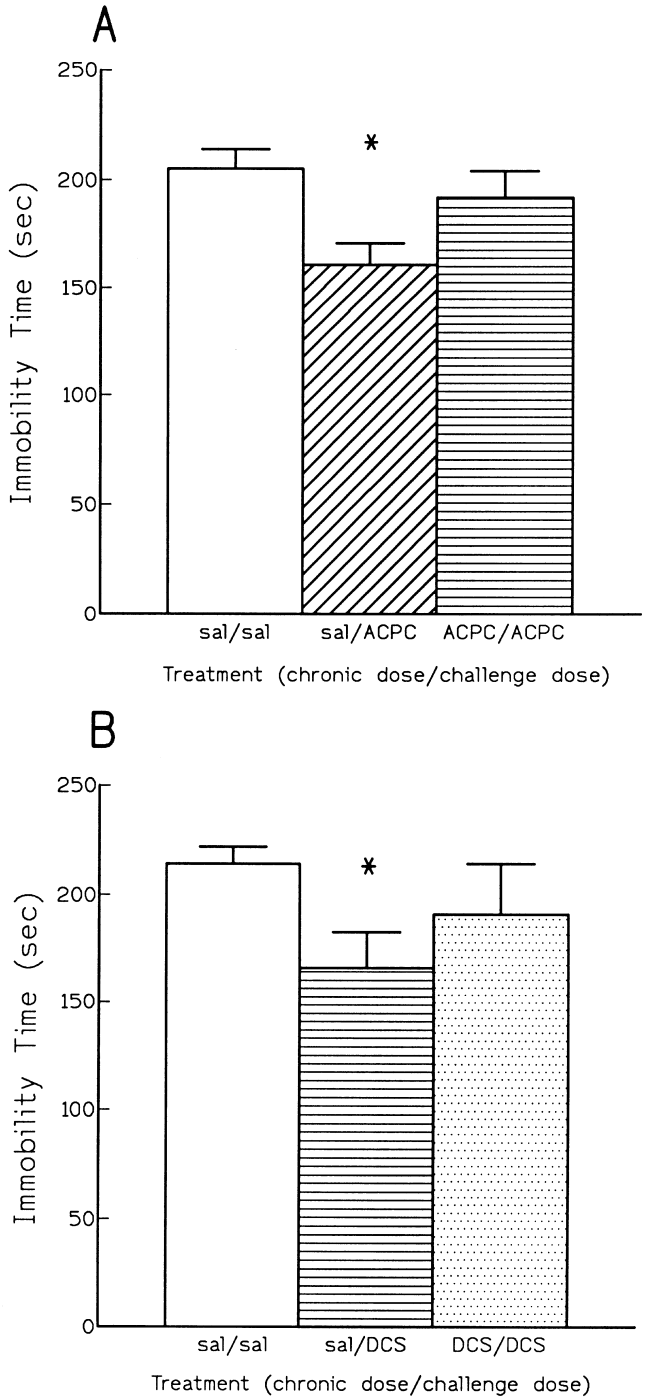

FIG. 2. Drug effects on immobility time of rats following 5 days of chronic treatment with saline, ACPC, or DCS followed by challenge with saline or drug on the sixth day. Rats were tested 1 h after drug administration. All drug doses were 200 mg/kg. Values represent mean ± SEM (n = 5–6). Treatment groups: sal/sal = chronic dosing with saline prior to challenge with saline; sal/ACPC = chronic dosing with saline followed by challenge with ACPC; sal/DCS = chronic dosing with saline followed by challenge with DCS; ACPC/ACPC = chronic dosing with ACPC followed by challenge with ACPC; DCS/DCS = chronic dosing with DCS followed by challenge with DCS. *Significantly different from sal/sal group, $p < 0.05$.

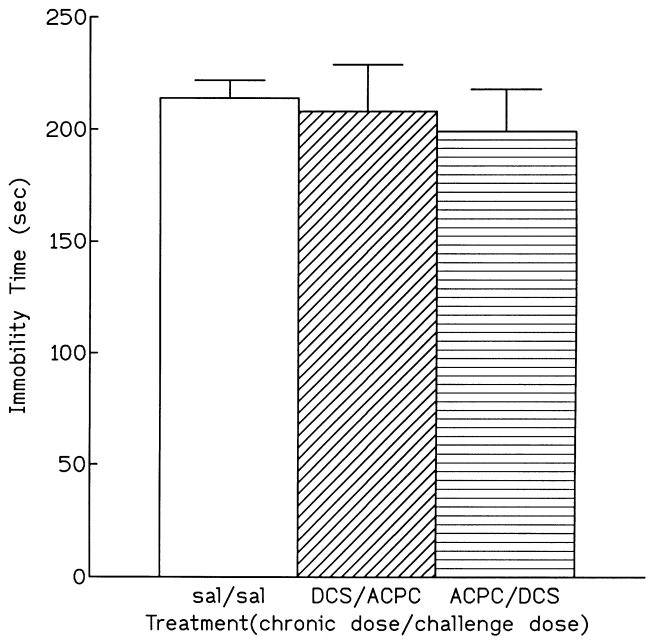

FIG. 3. Drug effects following 5 days of chronic treatment of rats with saline, ACPC, or DCS followed by drug challenge on the sixth day. Rats were tested 1 h following challenge dose. All doses were 200 mg/kg. Values represent mean ± SEM (n = 5). *Significantly different from sal/sal group, $p < 0.05$.

developed using imipramine, a prototypical tricyclic antidepressant. The premise of the test is that clinically effective antidepressants reduce the time of immobility, or the "behavioral despair" that animals typically display after unsuccessful attempts to flee from an inescapable pool of water (28,42–45). To obtain meaningful data, the experimental conditions of the PST test must be rigorously controlled. For example, the need for a conditioning swim prior to the test swim, the water temperature, and water depth can influence rodent performance (4,19,38,44). Additionally, documented behavioral performance differences occur among rodent strains (38,43) or species (43).

The PST behavioral paradigm was originally developed using subacute dosing of imipramine (two to three doses over a 30-h period), and as such, is a reliable predictor of clinical antidepressant activity for the tricyclics and most older monoamine oxidase inhibitors. However, the PST did not consistently predict the clinical activity of some serotonin reuptake inhibitors and atypical antidepressants (39). Another limitation of the PST is that the behavioral results do not always correlate with observed neurochemical changes (38,39).

The meaningfulness of the PST antidepressant predictive ability following chronic drug therapy is presently unclear. Because many clinically effective antidepressants were tested in the PST following one to three doses within a 24–48 h period, information is lacking on the correlation between clinical efficacy and PST predictive ability following chronic drug dosing. Limited data on chronic imipramine dosing in mice (15 mg/kg daily for 8 days) showed PST activity comparable to acute dosing (16 mg/kg single dose) (51). Another neurochemical assay, i.e., glycine inhibition of 5,7-dichlorokynurenic acid binding to NMDA strychnine-insensitive glycine sites, may be a better predictor of antidepressant activity than the PST or β-adrenoceptor down regulation (39).

Given these caveats, the PST can still be used as a behavioral paradigm to assess whether drug activity is present after an acute dose and maintained or lost during following chronic dosing. In the present study, a single dose of either ACPC or DCS (200 mg/kg) reduced PST immobility time comparable to that observed with the imipramine dosing regimen. While the doses of ACPC are within the previously published ranges (5,27,36,50,51,53–56), the doses of DCS used in this study are considerably higher than the dosing range (5–30 mg/kg, IP) used in other cognitive and anxiolytic studies (25,48). At the highest DCS dose used in this study, DCS will act not only at the glycine site of the NMDA receptor, but may also have confounding effects on other enzymes, for example, transaminases (25,29). Another potential concern is a possible drug-induced hypermotility, which may underlie the reduction in immobility time. Trullas et al. (55) ruled out a hypermotility effect when they observed a temporal dissociation between PST immobility times and open-field ambulatory times over a 6-h period following a single high ACPC dose (400 mg/kg) in mice. We conducted preliminary studies of the motor activity effects of acute and chronic ACPC dosing in our rat preparation, which involved manually recording the number of square crossings per minute in a 30″ × 30″ × 20″ activity area. No significant hyperlocomotion effects at 15 and 60 min after dosing with IV saline or ACPC (200 mg/kg) were observed after acute dosing [data are mean ± SEM (n)]: 15-min saline treatment—5.3 ± 1.8 (5) vs. 15-min ACPC treatment—7.7 ± 2.5 (6); 60-min saline treatment—6.7 ± 3.6 (5) vs. 60-min ACPC treatment 9.5 ± 6.2 (6). Similarly, nonsignificant motor effects were observed after chronic saline or ACPC (200 mg/kg) dosing. Moreover, the nonsignificant effects in motor activity at 60 min after acute ACPC dosing contrast to the statistically significant reduction in PST immobility. These data argue against hypermotility as an explanation for the effects of ACPC in the PST.

The experimental finding of single dose DCS activity in the PST is consistent with early reports of DSC antidepressant activity in tuberculosis patients (9,10,23,26). While human data on the antidepressant activity of ACPC is presently unavailable, clinical reports (9,10,23,26) and acute preclinical PST data (this study) of DCS activity provides indirect support for the hypothesis that glycine site partial agonists may be potentially useful clinical antidepressants (51,54,55).

In contrast to the acute dosing regimen, a significant loss of PST behavioral activity was observed following chronic dosing of ACPC or DCS (200 mg/kg every day for 6 days). The present experimental findings with single and multiple dose ACPC administration to rats confirm published reports demonstrating single and multiple dose activity in mice (51,54,55). The loss of PST behavioral activity with prolonged DCS treatment is also consistent with Wla et al.'s observation that DCS anticonvulsant activity in mice was diminished following eight daily doses of DCS (60) and is consistent with Quartermain et al.'s observation that the memory-enhancing effects of DCS in mice were lost with chronic DCS treatment (49).

In the present study, the development of behavioral cross-tolerance was also observed when one agent was dosed daily for 5 days followed by a single dose of the other agent on the sixth day. These in vivo results are consistent with the in vitro homologous desensitization induced by DCS or ACPC at the glycine site of the NMDA receptor complex in cultured cerebellar granule cells (3,13). These results suggest that both drugs may produce their tolerance effects through a similar mechanism, putatively through the glycine site of the NMDA receptor complex.

The Porsolt swim test measures a whole animal effect that does not provide direct evidence on the mechanisms of drug-mediated behavioral changes. The loss of pharmacological effect in the PST with chronic ACPC or DSC dosing could be explained by alterations in drug pharmacokinetics or pharmacodynamics. Increased drug metabolism (by autoinduction) is an unlikely pharmacokinetic mechanism, because previous studies of ACPC kinetics in mice or rats show that the pharmacokinetics are linear with chronic dosing and dose escalation (5,17,33). It is also unlikely that the accumulation of an antagonistic metabolite is an operative mechanism, as ACPC metabolism studies failed to uncover evidence of significant biotransformation (5,17).

On the other hand, literature data strongly implicate pharmacodynamic mechanisms involved in the observed behavioral tolerance with multiple ACPC or DCS dosing. Physiologic functioning of the NMDA receptor complex involves complicated and reciprocal allosteric interactions between the glutamate and glycine receptor sites (7,11,15,21,34,46,47). Paul and Skolnick (36,39) hypothesized that functional tolerance to the effects of chronic ACPC administration is intimately related to an uncoupling of the allosteric interaction(s) between glycine and glutamate receptor sites of the NMDA receptor (51,56). In support of this hypothesis, radioligand binding studies clearly demonstrated significant changes in the allosteric regulation between the required coagonists, glutamate and glycine, after chronic treatment of ACPC and other antidepressant agents (36,39).

Electrophysiologic studies may provide another avenue to better appreciate the allosteric coupling of the glycine and glutamate sites following acute and chronic drug exposure. Using cultured rat cortical neurons, Priestly and Kemp kinetically characterized an allosteric coupling mechanism whereby acute application of glycinergic partial agonists accelerated glutamate dissociation at a rate inversely proportional to the partial agonist's intrinsic activity (21,47). Although similar kinetic analyses after chronic application of glycinergic agonists are presently lacking, such studies may further advance the hypothesis proposed by Paul and Skolnick (36,39).

In conclusion, the results of the present article indicate that single doses of NMDA glycine partial agonists, ACPC or DCS possess positive behavioral effects in the Porsolt swim test. The development of a behavioral tolerance in the PST following chronic therapy of these drugs appears to be a general feature of glycine partial agonists. Current evidence points to mechanisms likely to involve deregulation of the allosteric coupling between glutamate and glycine. Given the regional heterogeneity of central NMDA receptors, understanding of the allosteric regulation of these receptors will undoubtedly provide insights into the therapeutic utility of drugs targeting this critical receptor complex.

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