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# Antidepressant-like effects of 1-aminocyclopropanecarboxylic acid and D-cycloserine in an animal model of depression

Mariusz Papp *, Elzbieta Moryl

*Institute of Pharmacology, Polish Academy of Sciences, 12 Smetna Street, 31-343 Krakow, Poland*

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**Abstract**

Antidepressant activity of partial agonists at strychnine-insensitive glycine receptors, 1-aminocyclopropanecarboxylic acid (ACPC) and D-cycloserine, was studied in a chronic mild stress model of depression. In this model, a substantial decrease in consumption of a palatable sucrose solution is observed over time in rats subjected to a variety of mild stressors. This decrement can be reversed by chronic administration of antidepressant drugs. Chronic (5 weeks) treatment with ACPC gradually reversed chronic mild stress-induced reductions in sucrose consumption, and the magnitude of this effect was comparable to that observed following similar administration of imipramine (10 mg/kg). The time-course for reversal of chronic mild stress-induced deficits in sucrose consumption by ACPC was dose-dependent. Thus, the first statistically significant effect of the low dose of ACPC (100 mg/kg) was observed after four weeks of treatment (comparable to the 3–5 weeks required for imipramine), while only two weeks of treatment was required in the group receiving a higher dose (200 mg/kg) of ACPC. Like imipramine, reversal of chronic mild stress-induced deficits in sucrose consumption by ACPC persisted for at least one week following cessation of treatment. The effects of chronic D-cycloserine were variable, and apparently not dose-related in the chronic mild stress model. D-cycloserine (10 mg/kg) increased sucrose intake in stressed animals, but the magnitude of this effect was smaller than in either imipramine or ACPC treated animals. Lower (2.5 mg/kg) and higher (40, 100 mg/kg) doses of D-cycloserine were ineffective. These results suggest that ACPC may have antidepressant properties comparable to conventional drugs, but with a faster onset of action.

*Keywords:* ACPC (1-aminocyclopropanecarboxylic acid); D-cycloserine; Imipramine; Stress; Chronic; Anhedonia; Antidepressant action

## 1. Introduction

Most clinically effective antidepressant drugs have readily demonstrable effects on the disposition or metabolism of biogenic amines such as norepinephrine and serotonin (see Caldecott-Hazard et al., 1991). However, over the past five years, converging lines of evidence indicate that functional NMDA antagonists (compounds that block or impair activity at the NMDA subtype of glutamate receptor) possess antidepressant-like actions (Klimek and Papp, 1994; Layer et al., 1995; Maj et al., 1994; Papp and Moryl, 1994; Paul et al., 1992; Trullas and Skolnick, 1990; Trullas et al., 1991). For example, uncompetitive (e.g., dizocilpine, memantine: Maj et al., 1992a; Moryl et al., 1993; Trullas and Skolnick, 1990) and competitive (AP-7; CGP 37849 CGP 39551: Trullas and Skolnick, 1990; Maj et al., 1992b) NMDA receptor antagonists, polyamine site antagonists (e.g., eliprodil: Layer et al., 1995), and a glycine receptor partial agonist (1-aminocyclopropanecarboxylic acid; ACPC: Trullas and Skolnick, 1990; Trullas et al., 1991) mimic clinically effective agents in preclinical tests (e.g., forced swim and tail suspension) predictive of antidepressant action. Moreover, chronic treatment with dizocilpine, ACPC, and eliprodil downregulate $\beta$-adrenoceptors in rodent cortex (Klimek and Papp, 1994; Paul et al., 1992; Layer et al., 1995), an action shared by many, but not all antidepressant drugs. Despite these findings, the psychotomimetic-like symptoms produced by uncompetitive and competitive NMDA receptor antagonists (Grotta et al., 1995; Sveinbjornsdottir et al., 1993) would be likely to limit the use of such compounds to all but life threatening situations. In contrast, Phase I clinical trials indicate that functional NMDA receptor antagonists such as eliprodil and ACPC are devoid of psychotomimetic-like

* Corresponding author. Tel.: (48-12) 374-022; Fax: (48-12) 374-500; e-mail: nfpapp@cyf-kr.edu.pl


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actions, (Cherkofsky, 1995; Patat et al., 1994), and a Phase II trial of ACPC in depression has been designed (M. Maccecchini, Symphony Pharmaceuticals).

Despite the efficacy of functional NMDA receptor antagonists in preclinical tests predictive of antidepressant action, there is a need to examine such compounds in models that more realistically simulate depression (reviewed in Willner, 1991). Thus, the former procedures require only one or two administrations of a drug, and there is evidence indicating that the efficacy of some types of functional NMDA receptor antagonists (e.g., ACPC) in the forced swim test is reduced following chronic administration (Skolnick et al., 1992). Moreover, these preclinical tests are performed on 'normal' animals, and clinical experience with antidepressants indicates these drugs are devoid of mood-elevating effects in normal subjects (Pillard and Fisher, 1978). Thus, despite the predictive validity of the forced swim and tail suspension tests (Borsini and Meli, 1988; Porsolt et al., 1978), it is unclear whether the preclinical efficacy of functional NMDA receptor antagonists is directly relevant to the clinical action of antidepressant drugs. Therefore, it appears justified to conduct studies into the action of potential antidepressants using preclinical procedures which may more closely simulate aspects of depression (Willner, 1991). One such procedure is a chronic mild stress (chronic mild stress) paradigm, in which animals subjected to a variety of mild stressors for a prolonged period of time show a substantial diminution in the response to rewarding stimuli. This deficit is usually monitored by a decrease in the consumption of a palatable, weak (1%) sucrose solution (see Willner et al., 1992), but is also manifested in other tests such as place preference conditioning (Papp et al., 1991, 1992, 1993; Muscat et al., 1992) or intracranial self-stimulation (Moreau et al., 1992). Since a subsensitivity to reward appears to reflect anhedonia (i.e., an inability to experience pleasure), a core symptom of major depressive disorders (American Psychiatric Association, 1987), chronic mild stress may serve as a suitable research tool in studies into the mechanisms of action of antidepressant drugs.

In previous studies, it was demonstrated that the chronic mild stress-induced subsensitivity to reward can be effectively reversed by chronic treatment with antidepressant drugs, including tricyclics, 'atypical' agents, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, but not with drugs devoid of antidepressant properties (for review see Papp et al., 1996; Willner et al., 1992). In the present study, we examined the effects of two glycine receptor partial agonists (ACPC and D-cycloserine; D-cycloserine) in the chronic mild stress model of depression. These compounds exhibit functional NMDA receptor antagonist properties (Anthony and Nevins, 1993; Long and Skolnick, 1994; Skolnick et al., 1989; Trullas et al., 1989) and are both readily available after either parenteral or oral administration (Anthony and Nevins, 1993; Cherkofsky, 1995; Trullas et al., 1991). We report here that the chronic mild stress-induced deficit in sucrose intake was gradually reversed by chronic ACPC treatment with the magnitude comparable to that observed following similar administration of imipramine. The time-course of this effect was dose-dependent, and at the higher dose used, ACPC restored normal behaviour in stressed animals more rapidly than imipramine. Chronic administration of D-cycloserine produced weak and inconsistent effects in the chronic mild stress model.

## 2. Materials and methods

The experiments were carried out in accordance with the Polish governmental regulations concerning experimentations on animals (decree of the Ministry of Higher Education No. 71, art. 492 of December 28, 1959), and the appropriate permission was received.

### 2.1. Animals

Male Wistar rats were maintained in a colony room for two months prior to initiating these experiments. Except as described below (see stress procedure), the animals were singly housed in plastic cages ($40 \times 25 \times 15$ cm) with food and water freely available. Animals were maintained on a 12 h light/dark cycle at a temperature of $22 \pm 2$°C. At the start of the experiments, animal weights ranged between 300–350 g.

### 2.2. Stress procedure

All animals were first trained to consume a sucrose solution. The training consisted of seven 1 h baseline tests, in which 1% sucrose solution was presented in the home cage following 14 h of food and water deprivation. Sucrose intake was calculated as the weight difference in bottles containing the sucrose solution before and after the test. Subsequently, sucrose consumption was monitored at weekly intervals (under similar conditions) throughout the course of the experiment. Animals were divided into two matched groups based on sucrose intakes in the final baseline test. One group of animals was subjected to a chronic mild stress procedure for a period of 9 weeks. Each week of the stress regime consisted of: Two periods of food or water deprivation, two periods of 45° cage tilt, two periods of intermittent illumination (light on and off every 2 h), two periods of soiled cage (200 ml water in sawdust bedding), two periods of paired housing, two periods of low intensity stroboscopic illumination (150 flashes/min), and two periods of no stress. All the stressors were of a 12–14 h duration and were applied randomly and continuously, day and night. Non-stressed control animals were housed in a separate room and had no contact with the stressed animals. Control groups had food and water freely available in their home cage, except for a

14 h period of food and water deprivation, preceding each sucrose test.

### 2.3. Drug administration

The study consisted of 2 consecutive experiments. In each experiment, both stressed and control animals were further divided into matched subgroups on the basis of sucrose intake scores following 3 weeks of stress. Subsequently, separate groups of control and stressed animals ($n = 8$ rats/group) received daily injections of vehicle, imipramine (10 mg/kg, i.p.) or ACPC (100 and 200 mg/kg, i.p.) in experiment 1, or vehicle, imipramine (10 mg/kg, i.p.) or D-cycloserine (2.5, 10, 40 and 100 mg/kg i.p.) in experiment 2. In both experiments, the drugs were administered at 12.00 a.m., and weekly sucrose tests were carried out 22 h following the last drug injection. After five weeks, the treatments were terminated and after one week of withdrawal a final sucrose test was carried out. Stress was continued throughout the period of treatment and withdrawal.

### 2.4. Drugs

The following agents were used: Imipramine (Polfa), ACPC (Symphony Pharmaceuticals, Malvern, PA, USA) and D-cycloserine (Sigma, St. Louis, MO, USA). All agents were dissolved in distilled water which was used for vehicle injections.

### 2.5. Statistics

The results were analyzed by a multiple analysis of variance, followed by the Fisher's least significant difference (LSD) test for post hoc comparisons of means.

## 3. Results

In both experiments, chronic mild stress produced a decrease in the consumption of a 1% sucrose solution. Prior to initiating drug treatment, sucrose intakes in controls and stressed animals were significantly different (experiment 1: $P < 0.01$, experiment 2: $P < 0.001$, see Figs. 1 and 2). In all animals receiving vehicle, this difference was maintained for the remainder of the treatment period resulting in a highly significant Group effect in both experiments (experiment 1: $F(1,84) = 63.06$; $P < 0.001$, experiment 2: $F(1,84) = 61.31$; $P < 0.001$).

In control animals, chronic administration of imipramine produced a slight, non-significant decrease in sucrose intake in experiment 1 ($F(5,84) = 0.92$; NS). This modest effect was essentially absent in experiment 2 ($F(5,84) = 0.48$; NS), nor had it been observed in similar experiments performed under comparable conditions in this and other laboratories (see Papp et al., 1996; Willner et al., 1992). In

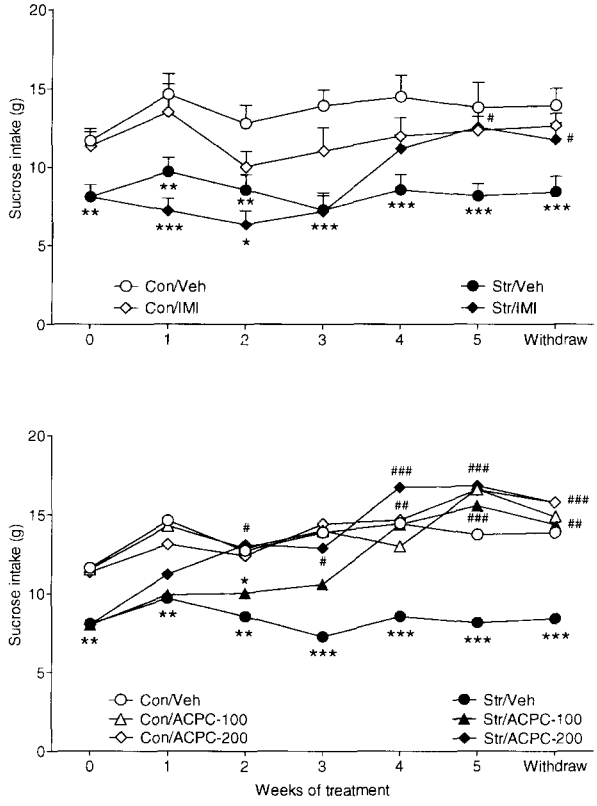


Fig. 1. The effect of chronic treatment with imipramine (IMI, 10 mg/kg i.p.; upper panel) and ACPC (ACPC, 100 and 200 mg/kg i.p.; lower panel) on the consumption of a 1% sucrose solution in controls (Con) and animals exposed to chronic mild stress (Str). Treatment commenced after 3 weeks of stress. In the lower panel standard errors have been omitted for clarity. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$; relative to controls. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$; relative to Week 0 scores.

stressed animals, imipramine produced a gradual increase in sucrose intake, resulting in a significant Treatment × Weeks interaction (experiment 1: $F(5,84) = 2.89$; $P < 0.05$; experiment 2: $F(5,84) = 3.38$; $P < 0.001$]. The onset of action of imipramine varied between experiments 1 and 2, and the first statistically significant increase in sucrose consumption was obtained after five and three weeks of treatment, respectively. These time-course values for imipramine (as well as other tricyclics) are consistent with values obtained in most other studies with the chronic mild stress model (see Papp et al., 1996; Willner et al., 1992). In both experiments, the consumption of sucrose solution in imipramine-treated control and stressed animals was maintained at a similar level for one week after withdrawal from the drug (see Figs. 1 and 2).

Chronic treatment with ACPC had no significant effect on sucrose intake in control animals ($F(10,126) = 0.47$; NS), but in stressed animals this compound caused a gradual recovery of performance, resulting in a significant Treatment effect ($F(2,126) = 18.76$; $P < 0.001$) and Treatment × Weeks interaction ($F(10,126) = 2.05$; $P < 0.05$). As shown in Fig. 1, the action of ACPC was dose-dependent; four weeks of treatment with the low dose

regimen (100 mg/kg) was required to produce the first significant increase in sucrose consumption whilst animals receiving the high dose regimen (200 mg/kg) recovered from chronic mild stress-induced deficits in sucrose intake within the first two weeks of treatment. Analysis of the data obtained from the two ACPC-treated stressed groups revealed a significant Treatment × Weeks interaction ($F(6,98) = 4.43$; $P < 0.01$), confirming that the dose of 200 mg/kg has faster therapeutic effects on the chronic mild stress-induced decrease of the consumption of sucrose solution. Despite the dose-dependent differences in the onset of action of ACPC, the magnitude of its effect was similar; at the end of the treatment period (Week 5) the sucrose consumption in stressed animals treated with the two doses of ACPC did not significantly differ from intakes of the drug-treated control (i.e., non-stressed) animals (Treatment × Group interaction: $F(1,28) = 0.11$; NS). As was observed in imipramine-treated rats, the effect of ACPC persisted for at least one week after cessation of treatment in the stressed group, and sucrose consumption was not significantly altered in the ACPC-treated control groups ($F(1,28) = 0.08$; NS) (Fig. 1).

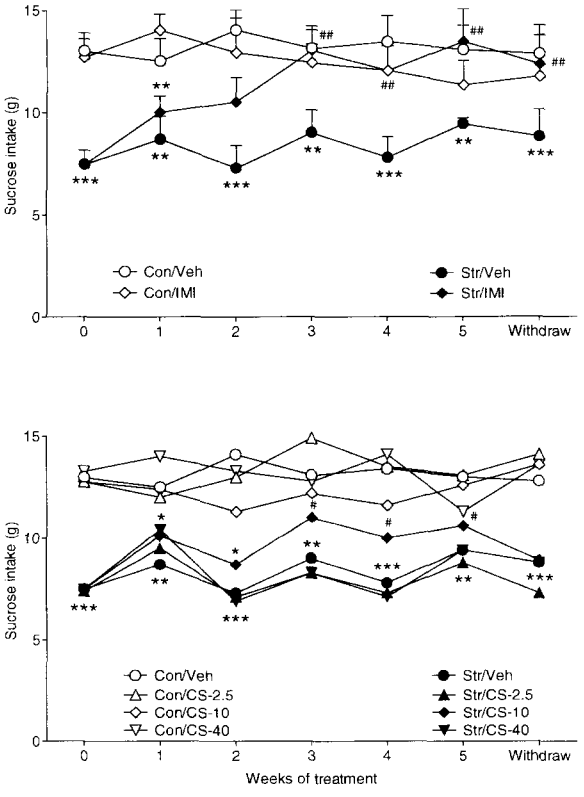


Fig. 2. The effect of chronic treatment with imipramine (IMI, 10 mg/kg i.p.; upper panel) and D-cycloserine (D-cycloserine, 2.5, 10 and 40 mg/kg i.p.; lower panel) on the consumption of a 1% sucrose solution in controls (Con) and animals exposed to chronic mild stress (Str). Treatment commenced after 3 weeks of stress. In the lower panel standard errors and the effect of D-cycloserine administered at inactive dose of 100 mg/kg have been omitted for clarity. $^{**}$ $P < 0.01$, $^{***}$ $P < 0.001$; relative to controls. $^{\#}$ $P < 0.05$, $^{\#\#}$ $P < 0.01$; relative to Week 0 scores.

Table 1
Body weight (g) measured at the end of the treatment period (Week 5)

| | Controls | Stressed |
|---|---|---|
| Experiment 1 | | |
| Vehicle | 468 ± 19 | 483 ± 20 |
| Imipramine | 453 ± 13 | 446 ± 14 |
| ACPC 100 | 499 ± 22 | 464 ± 18 |
| ACPC 200 | 496 ± 14 | 475 ± 11 |
| Experiment 2 | | |
| Vehicle | 456 ± 13 | 423 ± 18 |
| Imipramine | 419 ± 18 | 403 ± 10 |
| D-cycloserine 2.5 | 446 ± 14 | 439 ± 14 |
| D-cycloserine 10 | 436 ± 16 | 424 ± 11 |
| D-cycloserine 40 | 423 ± 16 | 421 ± 11 |
| D-cycloserine 100 | 386 ± 12 [a] | 418 ± 10 |

[a] $P < 0.01$; relative to vehicle-treated group.

Chronic administration of D-cycloserine had no significant effect on the sucrose intake in control animals ($F(20,210) = 0.63$; NS) (Fig. 2). In stressed animals, the four doses of D-cycloserine used produced inconsistent effects, with only one of the intermediate doses (10 mg/kg) significantly increasing consumption of sucrose solution intake compared to Week 0 scores (Treatment effect: $F(1,84) = 5.96$; $P < 0.05$). However, even at this dose, D-cycloserine was less effective than imipramine and ACPC. Thus, although the increase in sucrose consumption reached statistical significance ($P < 0.05$) after three weeks of treatment, this effect was not further increased, remaining intermediate to those of control and vehicle-treated stressed rats for the remainder of the treatment period. Moreover, the effect of D-cycloserine was no longer observed one week after withdrawal from the drug (Fig. 2). At the lower (2.5 mg/kg) and higher (40 and 100 mg/kg) doses, D-cycloserine had no significant effect on the sucrose intake throughout the whole treatment period (Treatment × Weeks interaction: $F(15,168) = 0.13$; NS) (Fig. 2).

As shown in Table 1, chronic mild stress had no significant effect on body weight in either experiment 1 or 2. In addition, chronic treatment with ACPC and imipramine did not alter body weight in either the stressed ($F(3,28) = 0.94$; NS) or control groups ($F(3,28) = 1.69$; NS). In contrast, five weeks of treatment with D-cycloserine caused a decrease of the body weight in control ($F(4,35) = 3,18$; $P < 0.05$), but not in stressed animals ($F(4,35) = 0.37$; NS). This effect of D-cycloserine was dose-dependent, and reached statistical significance ($P < 0.02$) at the highest dose (100 mg/kg) employed.

## 4. Discussion

The present study demonstrates that chronic administration of glycine receptor partial agonists reverse the reduc-

tion in consumption of a palatable sucrose solution produced by chronic mild stress. Based on the absolute requirement for glycine in the operation of NMDA receptor coupled cation channels (Kleckner and Dingledine, 1988), it had been hypothesized that glycine receptor partial agonists could act as functional NMDA receptor antagonists if synaptic glycine concentrations were at or near saturation (Trullas et al., 1989; Skolnick et al., 1989). The finding that ACPC (and, to a lesser extend D-cycloserine) mimic the effects of uncompetitive and competitive NMDA receptor antagonists to reverse the chronic mild stress-induced anhedonia supports this 'functional antagonist' hypothesis. Moreover, the ability of ACPC to reverse the behavioural deficit produced in an animal model of depression with face, construct, and predictive validity (see Papp et al., 1996; Willner et al., 1992) is consistent with previous reports demonstrating that acute administration of this glycine receptor partial agonist mimics the effects of antidepressant drugs in the forced swim and tail suspension tests in 'normal' animals. (Trullas and Skolnick, 1990; Trullas et al., 1991). While chronic treatment with functional NMDA receptor antagonists (including ACPC) also down regulates $\beta$-adrenoceptors and produces adaptive changes in radioligand binding to NMDA receptors (Klimek and Papp, 1994; Layer et al., 1995; Nowak et al., 1993; Paul et al., 1992), the efficacy of ACPC and AP-7 (a competitive NMDA receptor antagonist) have been reported to wane in the forced swim test following chronic administration (Skolnick et al., 1992), raising the possibility that these compounds could be false positives. However, the finding that ACPC is active in the chronic mild stress model (and that like with other antidepressants, this activity is sustained for at least one week after cessation of treatment) indicates that the utility of the forced swim test may be limited to its predictive validity in detecting antidepressant-like compounds.

ACPC appears to be as efficacious as imipramine in the chronic mild stress model, since like the latter antidepressant, a complete reversal of deficits in sucrose consumption was obtained (Fig. 1). This finding is consistent with the observation that ACPC reduces immobility in the forced swim test to the same extent as imipramine (Trullas and Skolnick, 1990). Moreover, ACPC exhibited a dose dependence in the chronic mild stress model, manifested as a significant dose $\times$ time interaction (Fig. 1). Thus, significant increases in sucrose consumption were first observed following two and four weeks of high (200 mg/kg) and low (100 mg/kg) dose regimens of ACPC, respectively. All other drugs and compounds tested in the chronic mild stress model require at least three to five weeks of treatment before they can normalize the behaviour of stressed animals (see Willner et al., 1992; Papp et al., 1996; Przegalinski et al., 1995), and to our knowledge, a complete reversal of chronic mild stress-induced suppression of sucrose consumption following two weeks of drug treatment has not been previously reported. These findings may have important clinical implications, since they indicate that the onset of antidepressant action of ACPC may be substantially faster than that of other antidepressants. Although, imipramine was tested only at one dose of 10 mg/kg per day, in earlier studies this drug was administered at a dose of 20 mg/kg per day and caused similar effects, both in terms of the magnitude and the time-course (Papp and Moryl, 1994). Also other drugs (e.g., buspirone, citalopram) were not more effective against the chronic mild stress-induced anhedonia when their doses were increased above the threshold active ones (Przegalinski et al., 1995; unpublished data). We previously demonstrated that the uncompetitive NMDA receptor antagonist dizocilipine and the competitive antagonists CGP 37849 and CGP 40116 were active in the chronic mild stress model, but like other antidepressants, required 3 to 4 weeks of treatment to produce a significant increase in sucrose consumption (Papp and Moryl, 1994). This study also employed a fixed dose of each compound, and dose ranging studies with these compounds will be required to determine if the apparent rapid onset of action produced by ACPC is a common feature of NMDA receptor antagonists. However, if adaptive changes in NMDA receptors are required for antidepressant action (Paul et al., 1994; Skolnick et al., 1996) then the fast reversal of the chronic mild stress-induced anhedonia observed with ACPC may be the result of a direct (and hence more rapid) adaptation in this family of ligand-gated ion channels. While speculative, this hypothesis merits further investigation.

The effect of ACPC on sucrose consumption was confined to stressed animals (Fig. 1), which is a characteristic feature of all antidepressant drugs examined to date in the chronic mild stress model (see Papp et al., 1996; Willner et al., 1992). The inability of antidepressant drugs to increase sucrose consumption in control animals may correspond to the failure of these drugs to elevate mood in non-depressed human subjects (Pillard and Fisher, 1978). This observation, together with the lack of effect of ACPC on body weight is consistent with preclinical and clinical toxicological studies demonstrating that this compound is devoid of any serious adverse effects (Cherkofsky, 1995). Several reports have demonstrated that ACPC (as well as other classes of NMDA receptor antagonists) are active in animal models of anxiety (Anthony and Nevins, 1993; Faiman et al., 1994; Trullas et al., 1989, 1991; Winslow et al., 1990). Since antidepressant drugs are also active in some forms of anxiety (Kahn and Van Praag, 1992), it could be argued that these putative anxiolytic properties of ACPC (as well as other antidepressants) are responsible for the reduction in the stress-induced deficits in sucrose consumption. However, this is unlikely since the non-antidepressant anxiolytic chlordiazepoxide (5 mg/kg per day, for 8 weeks) is completely ineffective in the chronic mild stress model of depression (Muscat et al., 1992).

While D-cycloserine is a glycine receptor partial agonist, its profile in the chronic mild stress model differed

significantly from ACPC (Fig. 2) and other functional NMDA receptor antagonists (Papp and Moryl, 1994). Thus, D-cycloserine reversed stress-induced deficits in sucrose consumption, but this was partial (albeit statistically significant), observed only at a mid-range dose (10 mg/kg), and not sustained following cessation of treatment (Fig. 2). The effect of this compound in the chronic mild stress model appears to have an inverted U-shaped dose-response pattern, characteristic of a partial agonist. Similar U-shaped dose-response relationships have been demonstrated for some other pharmacological actions of D-cycloserine such as punishment procedures (but not in fear-potentiation of startle response paradigm) (Anthony and Nevins, 1993; Faiman et al., 1994) and anticonvulsant activity (Baran et al., 1994; Rundfeldt et al., 1994). While ACPC also exhibits an U-shaped dose response curve in some of its actions (e.g., anticonvulsant and neuroprotective: Skolnick et al., 1989; Fossom et al., 1995), the doses used in the present study would fall on the ascending part of this curve. The intrinsic activity of D-cycloserine has been reported to range from 40% to 70% of that of glycine (Henderson et al., 1990; Hood et al., 1989) and ACPC has been reported to range from 20% to 80% (Fossom et al., 1995; Watson and Lanthorn, 1990). The efficacies of these compounds relative to glycine are clearly measure-dependent, and this in turn may depend on the NMDA receptor subunit composition. Based on these observations, it may be postulated that the efficacy of D-cycloserine at NMDA receptors that presumably mediate the effects in the chronic mild stress model is higher than that of ACPC, resulting in a modest effect of the former and robust effect of the latter in these measures. Irrespective of the mechanism of action, ACPC produces a full and rapid resolution of stress-induced anhedonia in the chronic mild stress model. Late stage clinical trials with this compound will determine whether the chronic mild stress model can predict rapid onset of action of antidepressant drugs as well as their antidepressant activity.

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