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Antidepressant-like Actions of the Polyamine Site NMDA Antagonist, Eliprodil (SL-82.0715)

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LAYER, R. T., P. POPIK, T. OLDS AND P. SKOLNICK. *Antidepressant-like actions of the polyamine site NMDA antagonist eliprodil (SL-82.0715).* PHARMACOL BIOCHEM BEHAV **52**(3) 621-627, 1995.—Functional *N*-methyl-D-aspartate (NMDA) antagonists including competitive antagonists, glycine partial agonists, and use-dependent channel blockers exhibit antidepressant-like actions in preclinical models. The present study examined the effects of eliprodil (SL-82.0715), an NMDA antagonist acting at polyamine sites, in behavioral and neurochemical tests predictive of antidepressant activity. In mice, eliprodil produced a dose-dependent reduction in immobility in the forced swim test, but was inactive in the tail suspension test. Chronic treatment with eliprodil produced both a significant downregulation of β-adrenoceptors and a reduction in the potency of glycine to inhibit [^{3}H]5,7-dichlorokynurenic acid binding to strychnine-insensitive glycine receptors in neocortical membranes. In toto, these data indicate that like other NMDA antagonists, eliprodil possesses antidepressant-like actions in preclinical tests predictive of clinical efficacy.

Eliprodil SL-82.0715 Antidepressants NMDA receptors β-adrenoceptors Forced swim test

THE NMDA (*N*-methyl-D-aspartate) subtype of glutamate receptor is constituted as a heterooligomer, containing discrete but allosterically coupled recognition sites for glutamate, glycine, divalent cations, and polyamines (45). Eliprodil (SL 82.0715) and ifenprodil are structurally related piperidine ethanols that exhibit NMDA antagonist actions both in vitro (38) and in vivo (2,9,28,40). Converging lines of evidence (3,11, 34,36,37) indicate that the NMDA antagonist properties of eliprodil and ifenprodil are effected at polyamine sites associated with this family of ligand-gated ion channels [reviewed in (48)].

NMDA antagonists mimic many of the behavioral effects produced by clinically active antidepressants [reviewed in (16)]. Thus, like many clinically effective antidepressants, competitive NMDA antagonists (AP-7, CGP 37849, and CGP 39551) (17,43), a use-dependent channel blocker (dizocilpine) (18,43), and a glycine partial agonist (1-aminocyclopropanecarboxylic acid; ACPC) (43) reduce immobility in rat and mouse variations of the forced swim test (FST) (30,31). Papp and Moryl (23,24) also demonstrated that both a competitive antagonist (CGP 37849) and a use-dependent channel blocker (dizocilpine) mimic the effect of antidepressants to reverse the reduction in sucrose consumption produced by chronic, mild stress. In addition to this mimicry, chronic treatment with NMDA antagonists reduces the density of cortical β-adrenoceptors (15,26), a phenomenon that is among the most consistent neurochemical actions produced across antidepressant therapies (44,51). Moreover, chronic treatment with clinically active antidepressants produces region-specific, adaptive changes in radioligand binding to NMDA receptors (21,25), and similar effects have been noted following chronic treatment with dizocilpine and ACPC (21).

The objectives of the present study were to determine whether an NMDA antagonist acting at polyamine sites would produce antidepressant-like actions in both behavioral and neurochemical measures. We report that like other classes of NMDA antagonists, eliprodil produced a significant reduction in the duration of immobility in the FST. In addition, chronic treatment with eliprodil resulted in both a downregulation of β-adrenoceptors and a reduction in the potency of glycine to

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inhibit [^{3}H]-5,7-dichlorokynurenic acid (5,7-DCKA) binding to strychnine-insensitive glycine receptors in neocortical membranes.

METHODS

Animals

Male NIH-Swiss or C57Bl/6 mice (25–35 g) were obtained from the Veterinary Resources Branch (Bethesda, MD). Mice were housed 10/cage in a temperature controlled (23 ± 1°C) room with a 12 L : 12 D cycle (lights on 0700 h) with free access to food and water.

Drug Administration

For behavioral assays, mice were moved to the testing area and allowed to adapt for at least 1 h before drug administration. Behavioral assays were conducted 0.5–1 h after drug administration as indicated. For neurochemical assays, mice were injected with drugs or vehicle for 14 days on a daily or twice-daily regimen as indicated. All injections were administered intraperitoneally in a volume of 0.2 ml. Twenty-four hours after the last injection, animals were decapitated and the cerebral cortices removed. Tissues were stored at −70°C until assayed. Imipramine HCl and *d*-amphetamine sulfate were dissolved in saline; eliprodil was dissolved in a solution of 10% Alkamuls EL-620 (Rhône-Poulenc, Cranbury, NJ), 10% ethanol, and 80% saline.

Forced Swim Test

The duration of immobility in the forced swim test was measured in NIH-Swiss mice as described elsewhere (31,41). One hour after drug administration, mice were placed in transparent lucite cylinders (diameter 10 cm, height 25 cm) filled with room temperature water to a depth of 6 cm. The duration of immobility was quantitated with the PORSOLT program (Infallible Software, Research Triangle Park, NC) during the last 4 min of a 6-min test. Water was changed after each test, and each animal was tested once.

Locomotor Activity

Time ambulating, distance traveled, and vertical movements were measured in NIH Swiss mice in a 42 × 42 × 20-cm activity chamber (Columbus Instruments, Columbus, OH) under dim light (41). Activity was monitored for 5 min commencing 1 h after drug administration. Each animal was tested once.

Tail Suspension Test

The duration of immobility in the tail suspension test (TST) was measured in C57/Bl6 mice as described elsewhere (43). Mice were suspended 75 cm above a tabletop by adhesive tape placed 1 cm from the tip of the tail. During the procedure, subjects were visually isolated from other animals. Testing commenced 0.5 or 1 h after drug treatment. The duration of immobility was recorded for 6 min using the PORSOLT program (Infallible Software). Each animal was tested once.

[^{3}H]Dihydroalprenolol Binding

[^{3}H]Dihydroalprenolol (DHA) binding to β-adrenoceptors was assayed using a modification of a previously described method (26). Cortices were thawed in 50 vol. of ice-cold 5 mM Hepes/4.5 mM tris (HTS) buffer (pH 7.4) and homogenized with a Brinkman Polytron (setting 6, 20–30 s, Westbury, NY). Homogenates were centrifuged at 20,000 × *g* for 20 min at 4°C and the supernatants discarded. Pellets were resuspended in 50 vol. of ice-cold assay buffer [50 mM Tris HCl buffer (pH 7.9) containing 1 mM $MgCl_2$ and 57 μM ascorbic acid] and recentrifuged at 20,000 × *g* for 20 min at 4°C. The supernatants were discarded and the pellets were resuspended in ice-cold assay buffer at a concentration of 5–10 mg original wet wt. tissue/ml. Membrane suspensions (~0.1 mg protein) were incubated (25°C) with 0.1–4 nM [^{3}H]DHA (109 Ci/mmol; NEN-Dupont, Boston, MA) in a total volume of 0.5 ml. Serotonin HCl (10 nM) and pargyline HCl (20 μM) were included to diminish nonspecific binding. Nonspecific binding was defined with 100 μM isoproterenol bitartrate. Assays were terminated after 60 min by rapid filtration through Whatman GF/B filters (Whatman Int'l Ltd., Maidstone, Kent, UK) presoaked in 0.03% polyethylenimine. The filters were rinsed twice with a total of 2 ml ice-cold assay buffer. The radioactivity retained by the filters was measured in a Beckman LS 5801 liquid scintillation counter (Fullerton, CA). Protein determinations were made using the bicinchoninic acid method with kits supplied by Pierce (Rockford, IL). Data were analyzed by iterative curve fitting (Inplot 4.0, San Diego, CA).

[^{3}H]5,7-DCKA Binding

[^{3}H]5,7-DCKA binding to strychnine-insensitive glycine receptors was assayed essentially as described (21). Cortices were thawed in 50 vol. of ice-cold HTS buffer and homogenized with a Brinkman Polytron (setting 6, 20–30 s). Homogenates were centrifuged at 20,000 × *g* for 20 min (4°C) and the supernatants discarded. Pellets were resuspended in 50 vol. of ice-cold HTS containing 1 mM EDTA and recentrifuged. The pellets were resuspended in HTS-EDTA and recentrifuged, and the resulting pellets resuspended in 10 vol. HTS, frozen on solid CO_2, and stored at −70°C for at least 2 days before assay. On the day of assay, tissues were thawed and resuspended in 50 vol. of HTS and centrifuged at 20,000 × *g* for 20 min at 4°C. The pellets were resuspended in ice-cold 50 mM Hepes-KOH buffer (pH 8.0) at 5–10 mg/ml. Membrane suspensions (~0.1 mg protein) were incubated (total vol., 1 ml) with 20 nM [^{3}H]5,7-DCKA (16.9 Ci/mmol; NEN-Dupont) in 50 mM Hepes-KOH for 90 min (0–4°C). Nonspecific binding was defined by using 1 mM glycine. Eight concentrations of glycine (10^{-9}–10^{-3} M) were used to construct displacement curves. Incubations were terminated by centrifugation (20,000 × *g* for 20 min, 0–4°C). The supernatants were aspirated and pellets superficially washed with 1 ml 50 mM Hepes-KOH buffer, dissolved in 250 μl tissue solubilizer (TS-2, Amersham Corp., Des Plains, IL), and neutralized with 25 μl glacial acetic acid. Scintillation cocktail (Cytoscint; ICN Biomedicals, Inc., Irvine, CA) was added and the radioactivity was measured in a Beckman LS 5801 liquid scintillation counter. Data were analyzed by iterative curve fitting (Inplot 4.0).

Statistical Analysis

Data were expressed as the mean ± SEM and evaluated by one-way analysis of variance followed by Dunnett's test, with $p < 0.05$ accepted as significant.

Materials

Imipramine HCl, serotonin HCl, and glycine were purchased from Sigma Chemical Co. (St. Louis, MO). *d*-Amphetamine sulfate was obtained from NIDA (Rockville,

MD). Pargyline was purchased from Research Biochemicals, Inc. (Natick, MA). Eliprodil was the generous gift of Synthelabo (Bagneux, France). Other materials and reagents were obtained from standard sources.

RESULTS

Effects of Eliprodil in the Forced Swim, Tail Suspension, and Locomotor Activity Tests

Eliprodil produced a dose-dependent reduction in the duration of immobility in the FST, with a statistically significant effect first manifested at 20 mg/kg (Fig. 1). The magnitude of this reduction was comparable to that produced by the tricyclic antidepressant, imipramine (15 mg/kg) (Fig. 1). Doses of eliprodil that produced significant reductions in immobility in the FST also suppressed locomotor activity in an open field (Table 1). Thus, at 20 and 40 mg/kg, eliprodil (administered 1 h before testing) significantly reduced time ambulating, distance travelled, and number of vertical movements compared to vehicle-injected mice (Table 1).

Consistent with previous findings (43), imipramine (15 mg/kg) significantly reduced immobility in the TST administered to C57Bl/6 mice 0.5 h before testing (Fig. 2). Under identical conditions, eliprodil did not significantly affect immobility when administered 0.5 or 1 h before the TST (Fig. 2). Whereas locomotor activity was not quantitated in C57Bl/6 mice, eliprodil appeared to reduce motor activity in this strain, and a profound ataxia was observed at 40 mg/kg (unpublished observations).

TABLE 1

EFFECT OF TREATMENT WITH ELIPRODIL ON LOCOMOTOR ACTIVITY

Treatment	Time Ambulatory (s)	Distance Traveled (cm)	Vertical Movements
Vehicle	156.3 ± 5.9	2303 ± 141	43.9 ± 12.6
Eliprodil			
10 mg/kg	140.7 ± 4.1	1917 ± 58	48.0 ± 13.2
20 mg/kg	111.0 ± 8.4*	1424 ± 124*	17.3 ± 7.4
40 mg/kg	60.1 ± 10.1*	652 ± 114*	2.3 ± 1.4†

NIH Swiss mice were treated with eliprodil and placed in an activity chamber 1 h later. Locomotor activity was assessed for 5 min. Data represent the mean ± SEM of eight to ten mice per group. *d*-Amphetamine included as a positive control, increased ambulatory time, distance traveled and vertical movements (185.8 ± 6.6, 2886 ± 241, and 75.9 ± 11.9, respectively). Data were analyzed by ANOVA [$F(4, 43) = 40.5$, $p < 0.01$ for time ambulatory; $F(4, 43) = 36.3$, $p < 0.01$ for distance traveled; $F(4, 43) = 7.4$, $p < 0.01$ for vertical movements). * $p < 0.01$, † $p < 0.05$ vs. vehicle (Dunnett's test).

Effects of Chronic Eliprodil on [^{3}H]DHA Binding

Chronic (14-day) treatment of NIH Swiss mice with eliprodil effected a significant reduction in the maximum num-

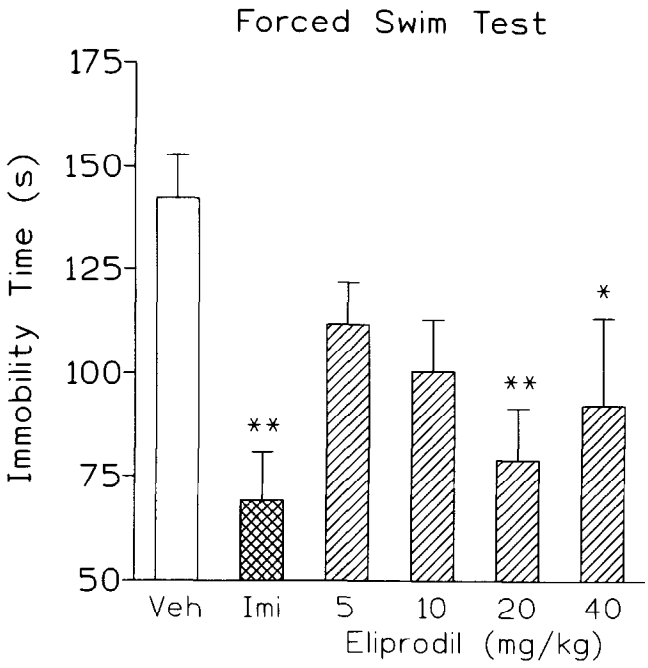

FIG. 1. Effects of imipramine and eliprodil on immobility in the forced swim test. Male NIH-Swiss mice were administered vehicle (Veh, open bar), imipramine (15 mg/kg, IP; Imi, cross-hatched bar), or eliprodil (5–40 mg/kg, IP; hatched bars). Immobility was measured 1 h later in the forced swim test as described in Methods. Values represent means ± SEM of five to 16 mice per group. Data were analyzed by ANOVA [$F(5, 59) = 5.63$, $p < 0.01$; *$p < 0.05$; **$p < 0.01$, Dunnett's test].

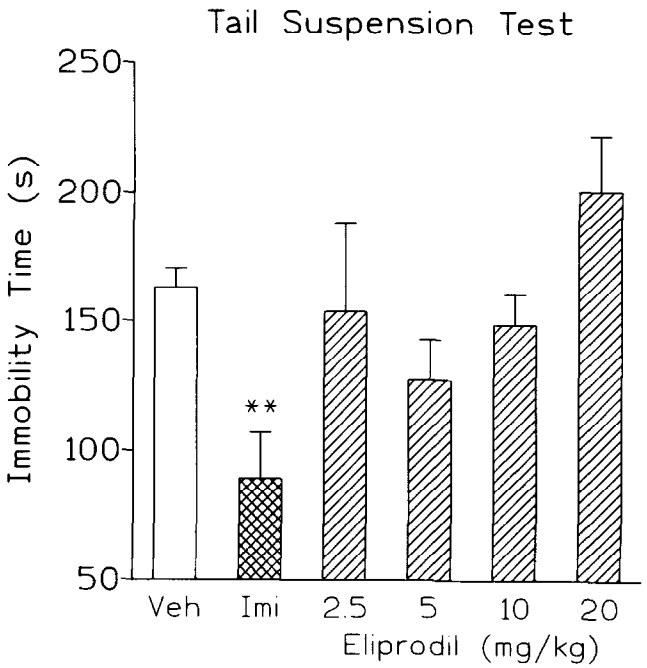

FIG. 2. Effects of imipramine and eliprodil on immobility in the tail suspension test. Male C57Bl/6 mice were administered vehicle (Veh, open bar), imipramine (15 mg/kg, IP; Imi, cross-hatched bar), or eliprodil (2.5–20 mg/kg, IP; hatched bars). Immobility was measured 30 min later in the tail suspension test as described in Methods. Values represent means ± SEM of five to 16 mice per group. Data were analyzed by ANOVA [$F(5, 42) = 5.06$, $p < 0.01$]. In addition, eliprodil (10 and 20 mg/kg, IP) administered 1 h before the test did not reduce immobility [immobility times for vehicle, 10 and 20 mg/kg groups were 159.4 ± 6.3, 163.9 ± 11.6, and 178.4 ± 10.6, respectively; $F(2, 25) < 1$]. **$p < 0.01$, Dunnett's test.

ber of [^{3}H]DHA binding sites (B_{max}) in cortical membranes (Table 2). This effect was statistically significant using dosing regimens of 20 mg/kg twice daily and 40 mg/kg once or twice daily, with the maximum effect (~30% decrease; $p < 0.05$) produced by administering 40 mg/kg daily. A significant reduction in the K_d was observed only in mice treated with the 40 mg/kg of eliprodil twice daily.

Effects of Chronic Eliprodil on [^{3}H]5,7-DCKA Binding

Chronic administration with eliprodil (40 mg/kg, twice daily) produced a statistically significant reduction (~1.6-fold; $p < 0.05$) reduction in the potency of glycine to displace [^{3}H]5,7-DCKA binding in cortical membranes. By comparison, imipramine (15 mg/kg, IP, daily) reduced the potency of glycine to displace [^{3}H]5,7-DCKA by ~1.9-fold ($p < 0.05$) (Table 3). None of the treatment regimens reduced basal [^{3}H]5,7-DCKA binding (Table 3).

DISCUSSION

Competitive NMDA antagonists, use-dependent channel blockers, and a partial agonist at strychnine-insensitive glycine receptors mimic the effects of clinically active antidepressants in both behavioral and neurochemical measures [reviewed in (16)]. The present studies were initiated to determine whether this mimicry would also occur for functional NMDA antagonists acting at polyamine sites, because the pharmacologic profile of eliprodil (and the structurally related ifenprodil) differs significantly from both use-dependent channel blockers and competitive NMDA antagonists (8,27,28,36). Although the mechanism(s) responsible for such differences are unknown, studies with recombinant homomeric and heteromeric receptors indicate that the ability of polyamines and polyamine antagonists may be capable of modulating a limited number of NMDA receptor subtypes (47,49,50,52).

Eliprodil (5–20 mg/kg) produced a dose-dependent reduction in immobility in the FST. The doses of eliprodil required to produce statistically significant reductions in this measure (≥20 mg/kg) are higher than those producing a neuroprotective action in rodent models of ischemia (36), but are in accord with the ED_{50} of eliprodil (26 mg/kg) to block NMDA-induced convulsions (36). The present findings are also consistent with a recent report (7) demonstrating no significant effects of eliprodil in the FST at doses of up to 10 mg/kg. Although the maximum reduction in immobility produced by eliprodil was comparable to that produced by a standard dose of imipramine (Fig. 1), a higher dose (40 mg/kg) produced a more modest, albeit statistically significant reduction in immobility in the FST (Fig. 1). The reduced efficacy observed at the higher dose of eliprodil may be attributable to a profound reduction in motor activity (Table 1). It has been suggested that the efficacy of NMDA antagonists such as dizocilpine in the FST may be due to a nonspecific increase in motor activity rather than an antidepressant-like action (22). However, the ability of eliprodil to reduce immobility in the FST at doses that inhibit spontaneous locomotor activity is inconsistent with this hypothesis. In addition, the competitive NMDA antagonists CGP 37849 and CGP 39551 reduce immobility in the FST at doses that inhibit locomotor activity (17). In contrast to its actions in the FST, eliprodil did not reduce immobility in the TST (Fig. 2). C57Bl/6 mice were used because this strain exhibits a high basal immobility in the TST (42) and is responsive to both imipramine (Fig. 2) (43) and ACPC (43). Although the effects of eliprodil on motor activity were not measured in this strain, we noted a marked suppression in motor activity of eliprodil-treated C57Bl/6 mice (unpublished observations). In view of the U-shaped dose response curve produced by eliprodil in the TST, it is possible that motor depression and ataxia may have masked a positive response. Several other potential antidepressant compounds, including levo-protiline and rolipram, display efficacy in the FST but not the TST (32).

Chronic treatment with eliprodil effected a significant reduction in the number of β-adrenoceptors in mouse cerebral cortex (Table 2). Although the pharmacologic relationship of β-adrenoceptor downregulation to antidepressant action is unknown, this phenomenon is among the more consistent neurochemical changes produced by chronic treatment with clinically effective antidepressants [for review, see (44,51)].

TABLE 2

EFFECT OF CHRONIC TREATMENT WITH ELIPRODIL ON THE AFFINITY AND DENSITY OF [^{3}H]DHA BINDING TO B-ADRENOCEPTORS IN MOUSE NEOCORTICAL MEMBRANES

Treatment	K_d (nM)	B_{max} (fmol/mg)
Vehicle	0.92 ± 0.06	116.5 ± 5.0
Eliprodil		
20 mg/kg (1)	0.81 ± 0.08	91.0 ± 6.1
20 mg/kg (2)	0.57 ± 0.16	88.8 ± 9.4*
40 mg/kg (1)	0.59 ± 0.05	80.8 ± 5.2†
40 mg/kg (2)	0.46 ± 0.05*	82.2 ± 4.0†

NIH Swiss mice were treated once or twice daily (indicated by numbers in parentheses) with eliprodil (20 or 40 mg/kg IP). Neocortical membranes were assayed with [^{3}H]DHA as described in Methods. Data were fit to a single component rectangular hyperbolic function (Inplot 4.0). Data represent the mean ± SEM for each group. Data were analyzed by ANOVA [$F(5, 68) = 4.27$, $p < 0.01$ for K_d; $F(5, 68) = 5.49$, $p < 0.01$ for B_{max}.
*$p < 0.05$, †$p < 0.01$ vs. vehicle, (Dunnett's test).

TABLE 3

EFFECT OF CHRONIC TREATMENT WITH ELIPRODIL ON THE POTENCY OF GLYCINE TO INHIBIT [^{3}H]5,7-DCKA BINDING TO MOUSE NEOCORTICAL MEMBRANES

Treatment	IC_{50} (nM)	B_0 (fmol/mg)
Vehicle	262.7 ± 18.7	1044.3 ± 42.4
Eliprodil		
20 mg/kg (1)	263.8 ± 28.9	1198.1 ± 64.5
20 mg/kg (2)	322.9 ± 26.2	989.3 ± 48.2
40 mg/kg (1)	323.4 ± 28.5	1054.3 ± 102.0
40 mg/kg (2)	419.3 ± 40.2*	915.3 ± 61.9

NIH Swiss mice were treated once or twice daily (indicated by numbers in parentheses) with eliprodil (20 or 40 mg/kg IP). Neocortical membranes were assayed using 20 nM [^{3}H]5,7-DCKA as described in methods. Data were fit to a one component sigmoid curve function (Inplot 4.0). Values represent the mean ± SEM for each group and were analyzed by ANOVA [$F(6, 77) = 5.54$, $p < 0.01$ for IC_{50}; $F(6, 77) = 2.0$, NS, for B0)]. Chronic imipramine (15 mg/kg, IP once daily), included as a positive control, produced a significant increase in IC_{50} (503.3 ± 66.2 nM) and no change in B_0 (977.4 ± 38.1 fmol/mg protein). No differences were found between means of Hill slopes which ranged from 0.76 to 1.07. * $p < 0.05$ vs. vehicle, (Dunnett's test).

β-Adrenoceptor downregulation has also been observed following chronic treatment with dizocilpine and ACPC (15,26), and the ability of eliprodil to produce this effect is consistent with the hypothesis that NMDA antagonists possess antidepressant actions.

Chronic but not acute administration of a wide variety of clinically effective antidepressants produce region-specific adaptive changes in the radioligand binding properties of NMDA receptors [(25); reviewed in (16)]. These changes include a reduction in the potency (increased IC_{50}) of glycine to inhibit [^{3}H]5,7-dichlorokynurenic acid (DCKA) binding to strychnine-insensitive glycine receptors and a reduction in the proportion of high-affinity glycine sites inhibiting [^{3}H]CGP 39653 binding to NMDA receptors. The ability of a chronic drug treatment to produce such adaptive changes is a more robust predictor of antidepressant activity than either β-adrenoceptor downregulation or activity in the FST (25). Chronic administration of eliprodil produced a significant (~60%) increase in the IC_{50} of glycine to inhibit [^{3}H]5,7-DCKA binding (Fig. 2) to strychnine-insensitive glycine receptors, although this effect was manifested only at the highest dose tested (40 mg/kg, twice daily). By comparison, imipramine (15 mg/kg) increased the IC_{50} of glycine by ~90% in this measure (Table 3). These adaptive changes appear to be both time- and dose-dependent (25), and it is possible that longer treatment with lower doses of eliprodil would have resulted in similar or more robust changes.

Eliprodil (and ifenprodil) have also been reported to affect a variety of other neurotransmitter systems that could contribute to the antidepressant-like actions demonstrated in the present study. Thus, eliprodil is an α_1 adrenoceptor antagonist that potently (IC_{50} ~ 110 nM) inhibits [^{3}H]prazosin binding (4). Several clinically effective antidepressants (e.g. amitriptyline, mianserin, maprotiline) also possess α_1 antagonist properties (35). Nonetheless, other α antagonists (e.g., prazosin, yohimbine, phenoxybenzamine, phentolamine) are inactive or increase immobility in the FST (10,29,33). Moreover, mianserin does not downregulate β-adrenoceptors following chronic treatment (25). Ifenprodil and eliprodil are also high-affinity σ-receptor ligands (IC_{50} 10–40 nM to inhibit [^{3}H](+)3-PPP binding) (5,14). Several antidepressants, including the tricyclics imipramine and amitriptyline (46) and the MAO A inhibitors clorgyline and deprenyl (13), also exhibit high affinities for σ receptors. However, other high-affinity σ-receptor ligands (such as haloperidol and pentazocine) are inactive in the FST (6). Ifenprodil has also been shown competitively to inhibit both MAO-A and MAO-B (K_i of 75 and 110 μM, respectively) (1). Eliprodil bears a close structural similarity to ifenprodil, and although its effects on MAO have not been reported, these piperidine ethanol derivatives have similar effects in most experimental systems. If eliprodil is an MAO inhibitor, it could be argued that the antidepressant-like neurochemical and behavioral effects described here are attributable to this action. However, MAO inhibitors capable of mimicking these preclinical actions of eliprodil are ~ ≥2 orders of magnitude more potent inhibitors of this enzyme than ifenprodil (20). In toto, this information leads us to conclude that the NMDA antagonist properties of eliprodil provides the parsimonious explanation for the antidepressant-like actions described here.

In conclusion, eliprodil exhibits antidepressant-like actions in both behavioral and neurochemical measures with good predictive validity for clinical efficacy. These findings are consistent with previous reports demonstrating that other classes of NMDA antagonists (15–18,23,24,43) produce this same spectrum of behavioral and neurochemical actions. The side-effect profiles of competitive NMDA antagonists and use-dependent channel blockers that would appear to limit the use of these classes of compounds to all but life-threatening situations (19,39) are consistent with this view. However, the preclinical behavioral (28,36) profile of eliprodil differs from other NMDA antagonists, and this polyamine site antagonist has been reported not to produce the cortical neurotoxicity (vacuolization in retrosplenial and cingulate cortices) common to competitive NMDA antagonists and use-dependent channel blockers (8). If long-term trials with eliprodil confirm the lack of psychotomimetic, amnesic, or motor-impairing actions following a single dose in young male volunteers (12), then this compound may represent the prototype of a novel class of antidepressant agents.

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