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Place conditioning of mice with the NMDA receptor antagonists, eliprodil and dizocilpine

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Abstract

Effects of noncompetitive and competitive NMDA receptor antagonists have been repeatedly characterized using place conditioning models. The present study aimed to characterize the effects in mice of another NMDA receptor antagonist acting at polyamine binding site, eliprodil. Five-day conditioning with eliprodil (1–30 mg/kg, i.p.) resulted in a dose-dependent avoidance of an eliprodil-paired compartment during post-conditioning tests. These effects were: (i) observed both with eliprodil and without drug, and (ii) less pronounced in individually housed mice subjected to repeated social defeats and mild footshocks prior to and during the conditioning period (compared to group-housed and individually housed nonstressed mice). In a parallel set of experiments, the effects of dizocilpine (MK-801; 0.03–0.3 mg/kg, i.p.) were evaluated using the same study design as for eliprodil. Conditioned place preference was established with the dizocilpine dose of 0.3 mg/kg and this effect was not affected by housing/stressing or drug exposures during the test.

Keywords: NMDA receptor antagonist; Eliprodil; Dizocilpine; Place conditioning; Social interaction; (Mouse)

1. Introduction

Place conditioning procedures are frequently used in studies aiming to characterize the abuse potential or aversive properties of drugs. There is a substantial body of evidence suggesting that the results of place conditioning should be analyzed in conjunction with data obtained from other experimental approaches. Ability of a drug to establish conditioned place preferences does not infer an abuse potential of this drug unless corresponding conclusions are drawn from experiments with intravenous self-administration, drug discrimination and/or electrical brain stimulation. For instance, conditioned place preferences were reportedly induced by an opioid antagonist, diprenorphine (Beaman et al., 1984), and a well-known anxiogenic compound, pentylenetetrazol (Gauvin et al., 1991). Place preferences and place aversions can sometimes be secondary to other effects of a drug as was demonstrated by establishing conditioned place aversion to a voltage-sensitive calcium channel blocker, nimodipine (Martin-Iverson et al., 1997).

The present study evaluated the outcome of place conditioning with two NMDA receptor antagonists, eliprodil (Avenet et al., 1997) and dizocilpine (MK-801; Wong et al., 1986). The abuse potential and psychotomimetic properties of NMDA receptor channel blockers such as phencyclidine and dizocilpine are well established (Balster and Willetts, 1996), while other NMDA receptor antagonists are thought to have a different behavioral profile. For instance, eliprodil acting at the polyamine site of the NMDA receptor complex, is not self-administered by rhesus monkeys, has no phencyclidine (PCP)-like discriminative stimulus properties in rats (Balster et al., 1994) and does not produce psychotomimetic effects in humans (Patat et al., 1994). Meanwhile, eliprodil retains some of the behavioral effects, such as antidepressant-like activity, described for PCP-like NMDA receptor antagonists (Layer et al., 1995).

Since no information is available for eliprodil effects in a place conditioning model, this study was aimed at comparing the effects of eliprodil and dizocilpine. The effects of both drugs were to be evaluated for a range of behaviorally active doses in mice maintained under different environmental conditions (housing, exposures to stress). Housing conditions are known to affect the outcome of

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place conditioning with various drugs (e.g., Wongwitdecha and Marsden, 1995). Results of earlier studies suggested that the behavioral consequences of the housing and stressing procedure used in the present study were sensitive to traditional antidepressant treatments (Poshivalov and Verbitskaya, 1989; Verbitskaya, 1992). Thus, taking into account the antidepressant-like activity of NMDA receptor antagonists (eliprodil: Layer et al., 1995; dizocilpine: Papp and Moryl, 1994; see also Panconi et al., 1993), the outcome of place conditioning with NMDA receptor antagonists may depend on the environmental conditions under which the experimental subjects are maintained. In addition, standard resident–intruder tests were conducted: (a) to characterize the behavior of mice kept under different environmental conditions, and (b) to relate behavioral alterations produced by eliprodil and dizocilpine to the outcome of place conditioning with these drugs.

2. Materials and methods

2.1. Animals

Adult male albino SHR mice (22–30 g; State Breeding Farm 'Rappolovo', St. Petersburg) were used. Animals were kept in groups of five or individually in plastic cages with food and water ad libitum. All experiments were conducted during the light period of a 12 h/12 h light–dark cycle (0900–2100 h). The experiments were approved by the Institutional Ethics Committee of Pavlov Medical University and were performed in accordance with the recommendations and policies of the US National Institutes of Health Guidelines for the Use of Animals.

2.2. Drugs

The drugs used were as follows: dizocilpine maleate ((+)-MK-801; Research Biochemicals International, Natick, MA) and eliprodil (gift from Synthélabo Recherche, Bagneaux, France). Dizocilpine was prepared in physiological saline, eliprodil in a vehicle of 5% ethanol and 5% Alkamuls EL-620 (castor oil ethoxylated; Rhone-Poulenc, Cranbury, NJ). Both drugs and their vehicles were administered intraperitoneally. All injections were delivered in a volume of 10 ml/kg. Dosages are based upon the forms of the drugs listed above.

2.3. Apparatus

Experiments were performed in eight identical shuttle boxes ($30 \times 30 \times 30$ cm). Each shuttle box was divided into two compartments of equal size by a sliding partition. These compartments were distinguished by color (white vs. black) and floor texture (wire mesh in the black compartment vs. rubber pad in the white compartment). Illumination of the white and the black compartments was 240 and 220 lx, respectively. The general light intensity in the animal facility and experimental room was approximately 350–370 lx. A partition was placed between the compartments, which could either restrict movement to one compartment only or allow movement between the compartments through a 10×8-cm opening. Pyroelectric infrared detectors (FOTON-6, Rielta, St. Petersburg) based on a Lhi 954 sensing element (EG&G Heimann, Germany) were mounted above each of the compartments. The infrared detectors were interfaced to a custom designed PC-based data acquisition system that recorded transitions mice made between compartments and, thereby, their position within the apparatus.

2.4. Place conditioning procedure

Two different pools of mice were used in these experiments. First, full dose–effect relationships for both eliprodil and dizocilpine were estimated in group-housed mice. Second, effects of the highest doses of dizocilpine and eliprodil were assessed in isolated mice (stressed and nonstressed).

Immediately after arrival from the breeding center, mice were housed in groups or individually. Housing conditions were stable for three weeks prior to and throughout the conditioning and testing. All mice were screened in a standard resident–intruder test one day after their arrival from the breeding center and one day before the conditioning was commenced. During the 4-min test, a nonaggressive intruder was placed in the home cage of the resident (experimental mouse; see below for additional details). Only mice that did not show any aggressive patterns (bites, attacks, tail rattling) towards an intruder were used in subsequent experiments. Later, the behavior of the mice was re-evaluated twice using the same set-up—before the first stress session and two weeks later.

The stress procedure consisted of either footshocks or social defeats once daily for two weeks prior to and throughout place conditioning. Footshocks and social confrontations were presented according to the randomly alternating daily schedule. Sixty footshocks (0.15 mA, 1.0 s) were delivered within the 10-min session. On alternating days, experimental mice were placed as intruders into a cage of an aggressive resident mouse (randomly selected from a pool of 18 mice housed in isolation). Each resident–intruder confrontation lasted 10 min. There were 20–25 attacks displayed by an intruder within one confrontation session. Stress exposures took place 2 to 3 h prior to place conditioning sessions.

The place conditioning procedure consisted of conditioning and post-conditioning periods. The conditioning period consisted of 30-min experimental sessions run twice a day for five consecutive days (Days 1–5). Each day, the

animals received a saline injection before being confined to one compartment, and then were injected with drug 1 h later, before placement in the opposite compartment. Injections were performed 2 min before sessions. For each treatment group, half the mice received drug injections before placement into the white compartment, while the rest of mice were placed into the black compartment after the drug injection.

Fifteen-minute post-conditioning tests were conducted on Days 6 and 7. Half the animals in each experimental group were injected with drug prior to the first post-conditioning test and saline was injected prior to the second post-conditioning test. For the other half of each group, injections were administered in the opposite order. During post-conditioning tests, the animals were allowed to explore both compartments freely. Each post-conditioning session began with initial placement of the mouse in the white compartment. Shuttle boxes were deodorized with H_2O_2 solution after each animal placement.

Our pilot experiments had demonstrated that preconditioning tests which are often employed in place conditioning studies dramatically reduced the magnitude of place conditioning with several classical agents such as morphine. Thus, the present study was based on an experimental design consisting of only two phases—conditioning and post-conditioning. To control for possible initial place preferences caused by apparatus or light conditions, 9 groups of 10 mice each were formed from a separate pool of experimentally and drug-naive mice. For each of these groups, a 15-min test was conducted, in which the animals were allowed to explore both compartments freely.

Different groups of group-housed mice were trained with eliprodil (1, 3.2, 10, 17.3, 30 mg/kg), dizocilpine (0.03, 0.1, 0.3 mg/kg) or their vehicles as described above. The eliprodil dose of 30 mg/kg and the dizocilpine dose of 0.3 mg/kg were also tested in isolated nonstressed and isolated stressed mice.

2.5. Resident–intruder procedure

Behavioral observations were done in the home cages ($300 \times 200 \times 200$ mm) covered with a transparent plastic lid and containing 10 g of standard food chow ($d = 9$–10 mm) spread all over the cage and mixed with sawdust bedding. After a 1-min adaptation period, a group-housed nonaggressive male intruder was placed into the home cage of an experimental mouse. During the next 4 min of observation, sequence, frequency ([amount of times the element was expressed/total number of behavioral counts per session] $\times$ 100%), and duration ([cumulative time of the element expression/session duration] $\times$ 100%) of 40 items of the resident's behavior (acts and postures) were recorded by means of the customized PC-based data acquisition system. After the resident–intruder test was completed, the intruder was returned to its home cage, while the experimental mouse was removed from the home cage (i.e., the observation arena) and kept in a holding cage until the end of the testing of the other animals with which it shared the home cage.

The behavioral inventory was as follows: (i) agonistic behaviors (aggressive behavior—threats, attacks, bites; ambivalent behavior—tail rattling, circling; defensive behavior—sideway postures, upright postures, pushing, freezing, shrivelling, retreats, supine back), (ii) sociability (nose sniffing, body sniffing, genital sniffing, grooming of the partner, huddling, passive contact, self-exposing for grooming, approaching, climbing over the partner, crawling under the partner), and (iii) individual behaviors (forward and backward locomotion, rotation, rearing, digging, forward and backward digging, jumping, eating, self-grooming, scratching, nodding, shaking, stretching, sitting with [exploratory] sniffing, static sitting, lying).

Thirty minutes prior to the test, different groups of mice were pre-treated with eliprodil (1, 3.2, 10 mg/kg), dizocilpine (0.03, 0.1, 0.3 mg/kg) or their vehicles.

2.6. Data analysis

During each post-conditioning session, time spent in the drug-paired compartment was recorded. For the resident–intruder test, duration and frequency of each behavioral item or group of items was calculated. For the sake of clarity and brevity, the results of the analysis are presented using only relative durations of the selected clustered elements (i.e., sociability, locomotion and defense) for display rather than all elements item by item.

Statistical analysis was conducted using SAS-STAT software (release 6.11, SAS Institute, Cary, NC). Analysis of the descriptive statistics demonstrated that some of the data were not distributed normally (Wilks–Shapiro's test). Following rank transformation, the data were subjected to analysis of variance for unbalanced design with unequal group sizes. Wilcoxon's rank-sum test was conducted for pairwise between-group comparisons. Although repeated testing is known to attenuate drug-induced conditioned place preference (Bardo et al., 1986), no differences were found between the results, based on order of the two post-conditioning tests. Hence, average values are used for presentation of the data.

3. Results

3.1. Place conditioning experiments

Preliminary tests indicated that there were no significant initial place preferences for drug- and experimentally naive mice allowed to explore the shuttle boxes freely. The mean ($\pm$S.E.M.) time spent in the white compartment was 466 ± 13 s ($N = 90$) with individual group means ranging from 385 to 522 s.

Table 1
Place conditioning with eliprodil, dizocilpine and vehicles

Treatment group	*N*	Time spent on the treatment side	Percentage of animals preferring treatment side
Saline	18	436.7 ± 27.9	38.9
Alkamuls EL-620	12	528.2 ± 59.2	75
Ethanol	12	435.7 ± 51.1	41.7
Ethanol/Alkamuls	17	451.8 ± 40.5	52.9
Eliprodil (1 mg/kg)	11	433.7 ± 39.7	36.4
Eliprodil (3 mg/kg)	12	277.8 ± 40.1[a]	16.7
Eliprodil (10 mg/kg)	11	234.6 ± 24.1[a]	0
Eliprodil (17.3 mg/kg)	12	224.8 ± 23.6[a]	0
Eliprodil (30 mg/kg)	11	104.3 ± 21.8[a]	0
Dizocilpine (0.03 mg/kg)	12	440.5 ± 34.0	25
Dizocilpine (0.1 mg/kg)	12	521.3 ± 43.4	66.7
Dizocilpine (0.3 mg/kg)	12	595.2 ± 43.4[b]	75

[a,b] $P < 0.05$ (Wilcoxon's rank-sum test), compared to Ethanol/Alkamuls and Saline treatment groups, respectively.

Five drug-place pairings with eliprodil in group-housed mice resulted in dose-dependent avoidance of the shuttle box compartment associated with eliprodil injections (Table 1; $F(9,118) = 9.9$, $P < 0.01$). Administration of either vehicle or its components (ethanol, Alkamuls EL-620) failed to result in any significant place conditioning (Table 1).

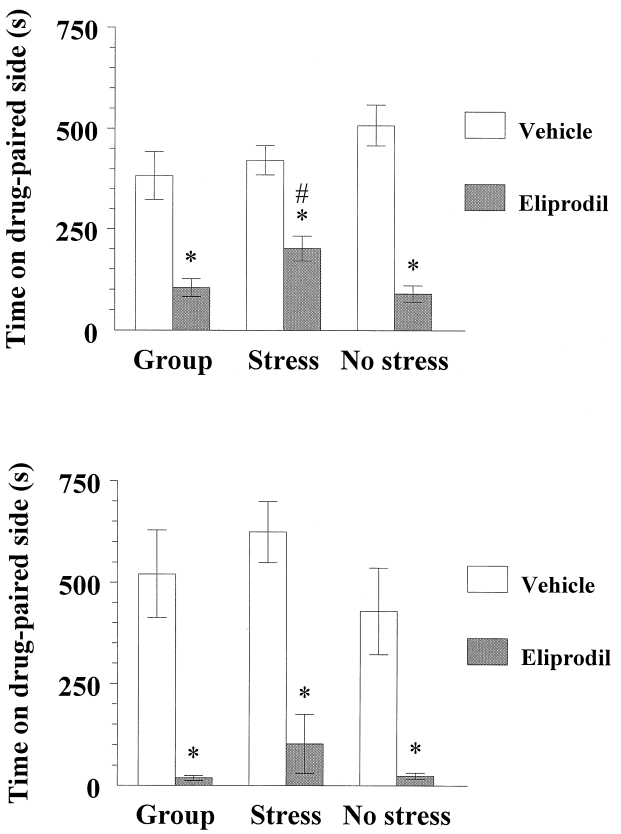

Fig. 1. Effects of eliprodil in place conditioning set-up. Mean (±S.E.M.) time (s) spent in the drug-paired compartment during the post-conditioning test. Group: group-housed mice; No stress: individually housed mice with no stress exposures; Stress: individually housed mice repeatedly exposed to electric footshocks and social confrontations. During the conditioning period, mice received five drug-place pairings with 30 mg/kg of i.p. eliprodil or its vehicle. Prior to the post-conditioning test, mice were injected with either vehicle (upper panel) or with eliprodil (lower panel; 30 mg/kg, i.p.). Each point represents data from 11–12 mice. * $P < 0.05$ (Wilcoxon's rank-sum test), compared to vehicle-conditioned group.

The effects of the eliprodil dose of 30 mg/kg were also tested in mice housed individually (Fig. 1). Resident–intruder tests with these mice (Table 2) revealed that repeatedly stressed mice exhibited an almost three-fold increase in the display of defensive acts and postures and a corresponding decrease in both horizontal and vertical locomotor activity.

The place conditioning tests (Fig. 1) showed no differences between eliprodil effects in group- and individually housed mice. However, individually housed mice subjected to repeated stress exposures showed a significantly less pronounced aversion to the eliprodil-paired compartment ($F(2,32) = 3.9$, $P < 0.05$). Eliprodil-induced place aversion was more pronounced when the tests were held after eliprodil (30 mg/kg) injection compared to that in tests done during the drug-free state ($F(1,32) = 10.6$, $P < 0.01$). Post-hoc tests showed statistically significant between-group differences only for data from drug-free tests (Fig. 1, upper panel).

Table 2
Behavioral characteristics of individually housed mice prior to the conditioning (resident–intruder set-up)

	Nonstressed	Stressed
Defense	7.8 ± 1.4	23.3 ± 4.2[a]
Sociability	28.9 ± 2.8	30.9 ± 3.7
Walking	11.8 ± 0.8	6.5 ± 0.7[a]
Rearing	17.9 ± 1.9	9.1 ± 1.6[a]
Static forms	24.7 ± 1.8	26.9 ± 3.0

[a] $P < 0.05$ (Wilcoxon's rank-sum test), compared to nonstressed group. $N = 24$.
Data are presented as mean percent duration per session (±S.E.M.). Defense: defensive upright and sideways postures, escape and shriveling. Sociability: nose, body and genital sniffing, grooming of the partner. Static forms: sitting, sitting with sniffing.

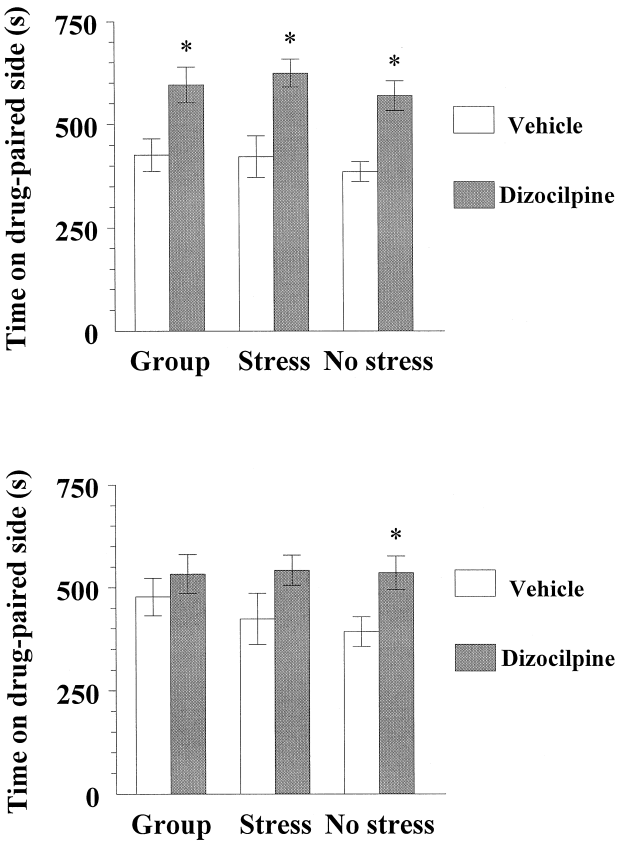

Fig. 2. Effects of dizocilpine in place conditioning set-up. Mean (±S.E.M.) time (s) spent in the drug-paired compartment during the post-conditioning test. Group: group-housed mice; No stress: individually housed mice with no stress exposures; Stress: individually housed mice repeatedly exposed to electric footshocks and social confrontations. During the conditioning period, mice received five drug-place pairings with 0.3 mg/kg of i.p. dizocilpine or its vehicle. Prior to the post-conditioning test, mice were injected with either vehicle (upper panel) or with dizocilpine (lower panel; 0.3 mg/kg, i.p.). Each point represents data from 10–12 mice. $* P < 0.05$ (Wilcoxon's rank-sum test), compared to vehicle-conditioned group.

Following place conditioning with dizocilpine, group-housed mice showed a moderate, but statistically significant preference for the dizocilpine-associated compartment ($F(3,53) = 4.2$, $P < 0.01$). The effects of the dizocilpine dose of 0.3 mg/kg were also tested in mice housed individually (Fig. 2). No main effect of housing and stressing was found ($F(2,68) = 0.4$, $P = 0.66$). Mice spent more time in dizocilpine-paired compartments both when drug-free and dizocilpine-treated ($F(1,68) = 34.0$, $P < 0.01$, $F(1,68) = 8.1$, $P < 0.01$, respectively), although dizocilpine pretreatment prior to the test tended to decrease the magnitude of the preference for dizocilpine-paired compartment ($F(1,31) = 3.6$, $P = 0.07$).

3.2. Resident–intruder tests

As displayed in Fig. 3, administration of eliprodil to group-housed drug-naive mice resulted in a dose-dependent increase in expression of defensive acts and postures ($F(3,43) = 10.5$, $P < 0.01$) accompanied by decreased locomotor activity ($F(3,43) = 12.8$, $P < 0.01$) and sociability ($F(3,43) = 21.7$, $P < 0.01$).

In contrast to eliprodil, dizocilpine altered the behavior of the mice only at the dose level where marked ataxia was noted. Ataxia was observed in all mice treated with 0.3 mg/kg of dizocilpine. At the dose of 0.3 mg/kg, dizocilpine-treated mice (Fig. 4) displayed significantly less defensive behavior ($F(3,43) = 5.9$, $P < 0.01$), while the overall (i.e., per session) intensity of locomotor activity and social contacts was not affected ($F(3,43) = 1.5$, $P = 0.21$, $F(3,43) = 0.3$, $P = 0.86$). A tendency to an increased locomotor activity correlated negatively with decreased defensiveness (partial correlation coefficient derived from multivariate analysis of variance matrix: $r = -0.5$, $df = 43$, $P < 0.01$).

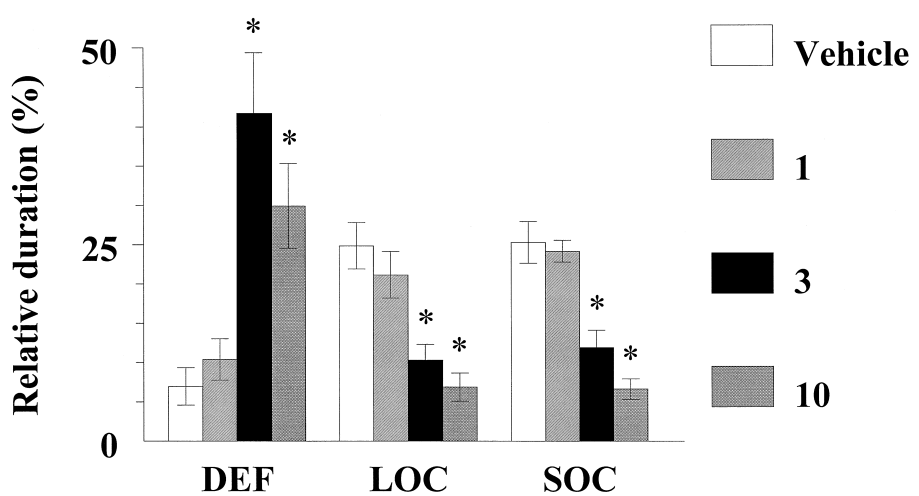

Fig. 3. Effects of eliprodil in social interaction set-up. Mean (±S.E.M.) relative duration per session (%) of defensive behaviors (DEF), locomotion (LOC) and social contacts (sociability, SOC). Resident–intruder tests were conducted 30 min after the injection of eliprodil (1–10 mg/kg, i.p.) or vehicle. $* P < 0.05$ (Wilcoxon's rank-sum test), compared to vehicle-treated group. $N = 10–11$.

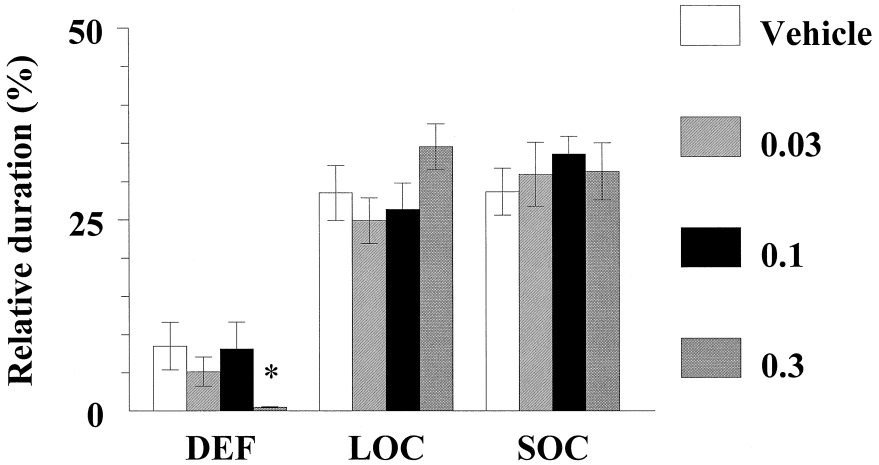

Fig. 4. Effects of dizocilpine in social interaction set-up. Mean (±S.E.M.) relative duration per session (%) of defensive behaviors (DEF), locomotion (LOC) and social contacts (sociability, SOC). Resident–intruder tests were conducted 30 min after the injection of dizocilpine (0.03–0.3 mg/kg, i.p.) or vehicle. $* P < 0.05$ (Wilcoxon's rank-sum test), compared to vehicle-treated group. $N = 10–11$.

There were no significant behavioral alterations found in mice pre-treated with either the eliprodil vehicle or the vehicle's components such as ethanol or Alkamuls EL-620 (data not shown; defense: $F(3,40) = 0.3$, $P = 0.86$; locomotion: $F(3,40) = 0.3$, $P = 0.86$; sociability: $F(3,40) = 1.1$, $P = 0.36$).

4. Discussion

The main finding of the present study was that eliprodil induced conditioned place aversion. In contrast, place conditioning with dizocilpine resulted in more time spent in the dizocilpine-paired compartment. The effects of dizocilpine in place conditioning studies are well documented (Layer et al., 1993; Steinpreis et al., 1995; Papp et al., 1996) although certain concerns arise due to lack of dose-dependence (Hoffman, 1994) and stereoselectivity (Del Pozo et al., 1996). Following the place conditioning with phencyclidine, conditioned place aversion is a likely outcome unless low doses of PCP and/or subjects with a history of PCP administration are used (Iwamoto, 1986; Acquas et al., 1989; Marglin et al., 1989; Kitaichi et al., 1996).

Together with the ability of NMDA receptor antagonists to induce conditioned taste aversions (Jackson and Sanger, 1989), the above data suggest that eliprodil-induced conditioned place aversion may be characteristic of NMDA receptor antagonists other than phencyclidine-like channel blockers such as dizocilpine. In fact, eliprodil's discriminative stimulus effects are markedly different from those of noncompetitive NMDA receptor antagonists (Balster et al., 1994). Eliprodil does not possess the anxiolytic activity demonstrated for other NMDA receptor antagonists (Wiley, personal communication; see also Sanger and Jackson, 1989) and there is no evidence of either psychotomimetic or abuse potential (Balster et al., 1994; Patat et al., 1994). Interestingly, eliprodil may act preferentially at subtypes of NMDA receptors assembled from NR1 and NR2B subunits (Avenet et al., 1997) and this selectivity may account at least in part for the unparalleled behavioral profile of eliprodil. The existence of behavioral differences between eliprodil and dizocilpine was also confirmed by the resident–intruder data where eliprodil, but not dizocilpine, facilitated the display of defensive acts and postures in group-housed mice.

The expression of eliprodil-induced place aversion was affected by several factors. First, the place aversions were potentiated when the post-conditioning tests were held with mice pre-treated with eliprodil. There are earlier reports of similar trends in conditioned place aversions induced by a substance P analogue (Elliott, 1988), cholecystokinin (Swerdlow et al., 1983), methamphetamine (Cunningham and Noble, 1992), FG7142, lithium chloride (Oberling et al., 1993), and naloxone (Bespalov et al., in press; Oberling et al., 1993). Interestingly, no such drug state-induced facilitation of the expression of place conditioning was found for dizocilpine in the present study. Moreover, dizocilpine pretreatment prior to the test tended to decrease the magnitude of the preference for the dizocilpine-paired compartment. It should be noted that the locomotor effects of either eliprodil or dizocilpine were unlikely to affect the outcome of place conditioning tests. For instance, drugs that reduce locomotor activity (e.g., pentobarbital) exert no effect on the expression of amphetamine conditioned place preference (Hiroi and White, 1991). Furthermore, rats demonstrate conditioned place preference even when their activity is restrained (Carr et al., 1988).

Second, eliprodil-induced place aversion was reduced in mice housed individually and repeatedly stressed before and throughout the conditioning. These mice expressed some behavioral abnormalities (increased defense; reduced exploratory activity) when tested in the resident–intruder

set-up. It is of potential importance that earlier data obtained in this laboratory suggested that the housing/stressing procedure described in the present study is sensitive to traditional antidepressant treatment (tricyclics, trazodone, etc.; Poshivalov and Verbitskaya, 1989; Verbitskaya, 1992). However, an antidepressant-like activity of eliprodil can hardly be responsible for the results of place conditioning with eliprodil. First of all, the preference for the dizocilpine-associated compartment was not significantly affected by housing/stressing although antidepressant effects were described for both dizocilpine (Papp and Moryl, 1994; see, however, Panconi et al., 1993) and eliprodil (Layer et al., 1995). Second, eliprodil facilitated the display of defensive acts and postures in group-housed mice, while similar behavioral alterations were observed in repeatedly stressed mice.

Repeated exposure to stressing factors is known to affect the individual's sensitivity to drug effects. For instance, defeats in the social confrontations produced selective tolerance to morphine-induced analgesia (Miczek and Winslow, 1987). Thus, it can be argued that, in the present study, repeatedly stressed mice developed tolerance to aversive effects of eliprodil as evidenced by the results of place aversion tests.

In conclusion, eliprodil-induced place aversion data are consistent with the low abuse potential of polyamine NMDA receptor antagonists. Taken together with social interaction data (resident–intruder tests), the present results indicated that effects produced by the polyamine site antagonist, eliprodil, are different from those of noncompetitive NMDA receptor channel blockers.

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