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Effects of NMDA receptor antagonists on cocaine-conditioned motor activity in rats

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Abstract

NMDA receptor antagonists have been reported to affect learned behaviors conditioned with abused drugs, with the outcome dependent, in part, on the class of NMDA receptor antagonist used. The present study tested the ability of various site-selective NMDA receptor antagonists to modify cocaine-conditioned motor activity. Two procedures were used for independently assessing drug effects on spontaneous activity and expression of cocaine-conditioned behavior. In the conditioning experiments, rats were administered i.p. injections of cocaine (30 mg/kg) or saline paired with distinctive environments. Spontaneous horizontal activity was dose-dependently enhanced by dizocilpine (0.03–0.3 mg/kg) and memantine (1–30 mg/kg), but not by D-CPPene (3-(2-carboxypiperazin-4-yl)-1-propenyl-1-phosphonic acid; SDZ EAA 494; 1–10 mg/kg), ACEA-1021 (5-nitro-6,7-dichloro-1,4-dihydro-2,3-quinoxalinedione; 3–56 mg/kg), or eliprodil (3–30 mg/kg). Higher doses of memantine, D-CPPene (1–10 mg/kg), eliprodil (3–30 mg/kg), or ACEA-1021 reduced vertical activity. Following five cocaine-environment pairings, rats displayed significant increases in motor activity when exposed to the cocaine-paired environment. The following antagonists were administered prior to the conditioning test: dizocilpine (MK-801; 0.03–0.1 mg/kg), memantine (1–10 mg/kg), D-CPPene (0.3–3 mg/kg), ACEA-1021 (3–10 mg/kg), and eliprodil (1–10 mg/kg). Of these, memantine, ACEA-1021 and, to the lesser degree, eliprodil attenuated expression of cocaine-conditioned motor activity at doses that did not significantly affect spontaneous motor activity. These results show that cocaine-conditioned behaviors can be selectively modulated by some, but not all, NMDA receptor antagonists.

Keywords: Cocaine; Motor activity; Conditioning; Dizocilpine (MK-801); D-CPPene (SDZ EAA 494); Memantine; ACEA-1021; Eliprodil; (Rat)

1. Introduction

The mesolimbic dopamine system is impacted by most abused drugs, and by psychostimulants in particular (Carboni et al., 1989; Chang et al., 1994). Vast glutamatergic projections are co-localized within this system presenting possible targets for neuropharmacological modulations of the effects of abused drugs (Kelley and Domesick, 1982; Kelley et al., 1982; Fuller et al., 1987; Robinson and Beart, 1988). For instance, antagonists acting at the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors attenuate a variety of effects produced by psychostimulants such as seizures (Witkin and Tortella, 1991; Witkin and Acri, 1995; Barat and Abdel-Rahman, 1997; Matsumoto et al., 1997), cardiac and hormonal effects (Hageman and Simor, 1993; Damianopoulos and Carey, 1995), place conditioning (Cervo and Samanin, 1995; Kim et al., 1996), and self-administration (Pulvirenti et al., 1997). Some studies, however, have reported opposite or negative outcomes. For example, competitive NMDA receptor antagonists did not appreciably modify the discriminative stimulus effects of cocaine in rats (Kantak et al., 1998). In addition, cocaine and the non-competitive NMDA receptor antagonist, dizocilpine (MK-801), exert synergistic effects in brain stimulation reward (Ranaldi et al., 1997), intravenous self-administration (Ranaldi et al., 1996) and drug discrimination paradigms (Kantak et al., 1998). De Vries et

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al. (1998) have also shown that dizocilpine reinstates cocaine self-administration behavior following an extinction period. It is possible that different classes of NMDA receptor antagonists differ in their ability to modify stimulant drug effects, accounting for some of these apparently contradictory results.

The functioning of the NMDA receptor complex can be inhibited by drugs acting at various recognition sites. Direct agonists and competitive antagonists bind to a transmitter-recognition site on the receptor complex. There are additional pharmacologically distinct sites at which activity produces alterations in NMDA neurotransmission, including (1) a channel site for noncompetitive antagonists; (2) a strychnine-insensitive glycine co-agonist site; and (3) a polyamine binding site. Antagonists acting at these different modulatory sites possess markedly distinct psychopharmacological profiles (Balster and Willetts, 1996). For instance, a number of studies suggest that dizocilpine has properties consistent with drugs which serve as positive reinforcers and have abuse liability (Corbett, 1989; Beardsley et al., 1990; Balster and Willetts, 1996; Carlezon and Wise, 1996; Ranaldi et al., 1996, 1997) and the psychotomimetic and abuse potential of phencyclidine (PCP) and other PCP-like channel blockers is well recognized (Balster and Willetts, 1996). On the other hand, drugs targeting other modulatory sites (such as glycine and polyamine site antagonists) appear to exert less PCP-like effects, e.g., fail to substitute for PCP in drug discrimination studies and are not self-administered by laboratory animals (Balster and Willetts, 1996; Balster et al., 1994, 1995).

It is likely that the effects of NMDA receptor antagonists on behavioral properties of stimulant drugs which are relevant to their abuse also depend on the specific effect being examined. One class of stimulant drug effects which has been studied is conditioned drug effects, phenomena that are thought to play important roles in reinstating and maintaining drug-seeking behaviors. For example, NMDA receptor antagonists have been shown to block drug-conditioned place preference (Bespalov, 1996; Bespalov et al., 1994; Tzschentke and Schmidt, 1995, 1997; Popik and Danysz, 1997; Popik et al., 1998) as well as conditioned activation of electrical brain stimulation (Bespalov and Zvartau, 1997).

The present study sought to the evaluate effects of several site-selective NMDA receptor antagonists on the expression of cocaine-conditioned motor activity. The selectivity of these effects was assessed by also testing these antagonists for direct effects on activity. The antagonists employed in this study included the high-affinity channel blocker, dizocilpine (Wong et al., 1986), the low-affinity channel blocker, memantine (Parsons et al., 1995), the competitive NMDA receptor antagonist, D-CPPene (Herrling et al., 1997), the glycine site antagonist, ACEA-1021 (Woodward et al., 1995), and the polyamine site antagonist, eliprodil (Carter et al., 1997).

2. Materials and methods

2.1. Subjects

Adult male experimentally naive Wistar rats (200–220 g; ''Rappolovo'', St. Petersburg) were used. Animals were housed in groups of five with standard rodent chow (''Volosovo'', St. Petersburg) and water available ad libitum. Rats were maintained under a 12/12-h light–dark cycle with lights on between 7:00 A.M. and 7:00 P.M. All tests were performed in accordance with the recommendations and policies of the US National Institutes of Health Guidelines for the Use of Animals. Experimental protocols were approved by the Pavlov Medical University's Ethics Committee and Virginia Commonwealth University's Institutional Animal Care and Use Committee.

2.2. Apparatus

Motor activity was measured in five identical boxes ($50 \times 30 \times 30$ cm) with transparent Plexiglas walls, a non-transparent plastic floor and a perforated black plastic lid. Boxes were equipped with eight photocell beams (5 cm off the floor) for measuring horizontal activity and six beams (14 cm off the floor) for vertical components of motor activity. This custom-designed data collection system was controlled by an IBM PC 386 and allowed for differentiation between repetitive and sequential beam breaks. The total number of sequential photocell interruptions during the 60-min test was used as a measure of motor activity.

2.3. Experiment 1: Effects of NMDA receptor antagonists and cocaine on spontaneous motor activity

Prior to the drug tests, rats were habituated to the apparatus by placing them three times in activity boxes for 1 h every other day. Following this initial habituation period, six separate groups of rats ($N = 10$/group) were injected with different doses of dizocilpine (0–0.3 mg/kg; pre-session injection time 15 min), memantine (0–30 mg/kg; pre-session injection time 15 min), D-CPPene (0–10 mg/kg; pre-session injection time 30 min), ACEA-1021 (0–56 mg/kg; pre-session injection time 15 min), eliprodil (0–30 mg/kg; pre-session injection time 15 min) or cocaine (0–30 mg/kg; given immediately pre-session) and placed into the experimental boxes for 60-min observations. Each rat was tested with only one NMDA receptor antagonist or cocaine. Different doses of each drug were administered in a counterbalanced order derived from a Latin Square design. Drug doses and pre-session injection times were chosen based upon preliminary experiments and published data.

2.4. Experiment 2: Cocaine-conditioned motor activity

Experiment 2 consisted of two phases: a conditioning phase (5 consecutive days) and a post-conditioning phase (24 h after the last conditioning session). All animals were habituated to handling for 2 days prior to the start of conditioning.

There was a total of 12 treatment groups in this Experiment. Ten animals were used in each group, a sample size sufficient to detect a cocaine-conditioned increase in activity at least at one dose (30 mg/kg).

For the conditioning phase, rats were randomly assigned to one of three treatment conditions (Paired, Unpaired and Control). The Unpaired group received daily injections of saline (1 ml/kg) immediately before being placed into the experimental boxes for 1 h and then returned to their home cages. Animals were then injected with cocaine (vehicle, 10, 17 or 30 mg/kg) and placed back into the home cage so that the inter-injection intervals were approximately 2 h. Doses of cocaine were those that produced significant increases in motor activity in Experiment 1.

Rats in the Paired group were first given saline (1 ml/kg) and placed back into the home cages. Two h later these animals were injected with cocaine (vehicle, 10, 17 or 30 mg/kg, i.p.) and immediately after that placed in the experimental boxes for 1 h.

Rats from the Control group received exactly the same treatment but were returned to their home cages after both saline and cocaine (vehicle, 10, 17 or 30 mg/kg) injections.

In the post-conditioning phase, rats were injected with saline and 15 min later were placed into the experimental boxes for 60-min observations.

2.5. Experiment 3: Effects of NMDA receptor antagonists on cocaine-conditioned motor activity

The design of Experiment 3 was identical to Experiment 2 with only three exceptions. First, there were only Paired and Unpaired treatment groups in this Experiment. Second, based on the results obtained in Experiment 2, during the conditioning phase, only one dose of cocaine was used (30 mg/kg). Third, for the post-conditioning test, separate groups of rats ($N = 10$ for each group) were injected with dizocilpine (0.03–0.1 mg/kg; pre-session injection time 15 min), memantine (1–10 mg/kg; pre-session injection time 15 min), D-CPPene (0.3–3 mg/kg; pre-session injection time 30 min), ACEA-1021 (3 and 10 mg/kg; pre-session injection time 15 min), eliprodil (1–10 mg/kg; pre-session injection time 15 min) or their vehicles and placed into the experimental boxes for 60-min observations. There was a total of 40 treatment groups in this Experiment ($N = 10$ for each group). Each rat was tested only once.

2.6. Drugs

Cocaine hydrochloride (Central City Pharmacy Station, St. Petersburg, Russia), dizocilpine maleate ((+)-methyl-10,11-dihydro-5H-dibenzo-[a,d]-cyclohepten-5,10-mine maleate; MK-801; Research Biochemicals International, Natick, MA), D-CPPene (3-(2-carboxypiperazin-4-yl)-1-propenyl-1-phosphonic acid; SDZ EAA 494; gift from Novartis Pharma, Basel, Switzerland), eliprodil (gift from Synthelabo Recherche, Bagneux, France), memantine (1-amino-3,5-dimethyl adamantane; gift from Merz, Frankfurt-am-Main, Germany), and ACEA-1021 (5-nitro-6,7-dichloro-1,4-dihydro-2,3-quinoxalinedione; licostinel; gift from CoCensys, Irvine, CA) were obtained from the sources indicated. Cocaine, dizocilpine and memantine were dissolved in physiological saline, ACEA-1021 in 50% dimethylsulfoxide, D-CPPene in equimolar NaOH in saline, and eliprodil in a vehicle of 5% ethanol and 5% Alkamuls EL-620 (castor oil ethoxylated; Rhone-Poulenc, Cranbury, NJ). All drugs and their vehicles were administered intraperitoneally. All injections were delivered in a volume of 1 ml/kg. Doses are based upon the forms of the drugs listed above.

2.7. Data analysis

Data were analyzed using SAS-STAT software (ver. 6.11, SAS Institute, Cary, NC). Since the data were not distributed normally, distribution-free multivariate analysis of variance (ANOVA) was applied. One-way ANOVA with repeated measures on drug dose was applied to Experiments 1 and 2. Two-way ANOVA was applied to Experiments 3 and 4 (factors: drug dose and treatment condition). Dunnett's (Experiment 1) and Tukey's (Experiments 2 and 3) tests were used for post-hoc between-group comparisons whenever a significant main effect was obtained in the ANOVA.

3. Results

3.1. Experiment 1: Effects of NMDA receptor antagonists and cocaine on spontaneous motor activity

Motor activity declined somewhat over three habituation sessions (horizontal: 248 ± 20, 222 ± 15, 203 ± 12; vertical: 24 ± 3, 20 ± 2, 18 ± 3). However, these results were not confirmed by ANOVA (horizontal: $F(2,29) = 2.1$, n.s.; vertical: $F(2,29) = 1.6$, n.s.).

The effects of NMDA receptor antagonists on motor activity are shown in Fig. 1. Different patterns of results were obtained with each of the test drugs. Horizontal activity was dose-dependently increased by dizocilpine ($F(4,43) = 31.9$, $P < 0.01$) and, to the lesser degree, by

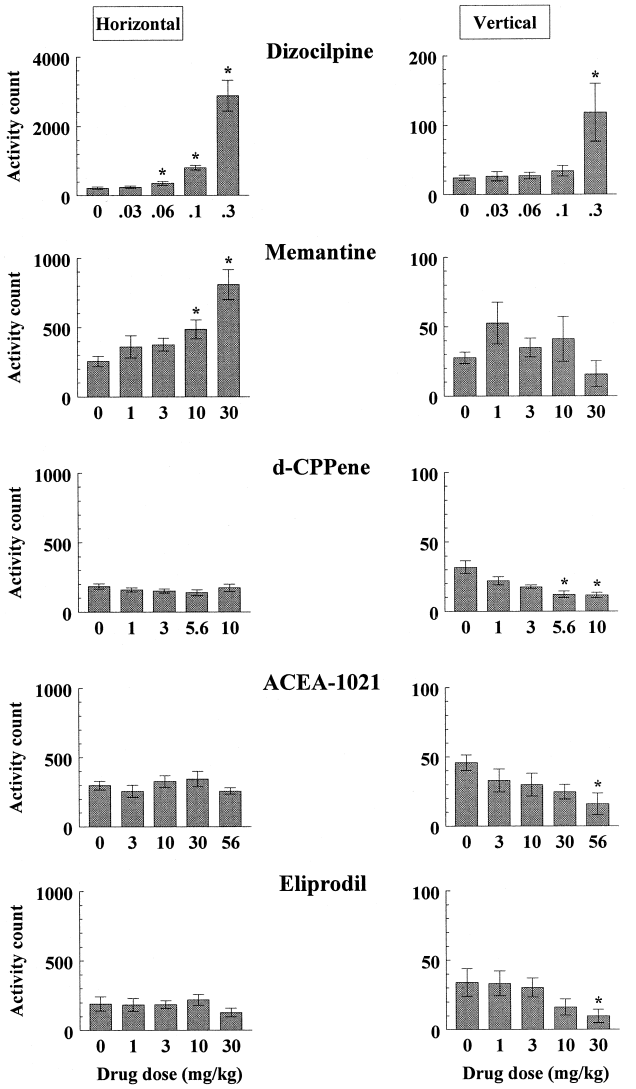

Fig. 1. Effects of NMDA receptor antagonists on spontaneous motor activity. Data represent group mean 60-min activity scores (S.E.M.) for rats pretreated with dizocilpine (0–0.3 mg/kg; pre-session injection time 15 min), memantine (0–30 mg/kg; pre-session injection time 15 min), D-CPPene (0–10 mg/kg; pre-session injection time 30 min), ACEA-1021 (0–56 mg/kg; pre-session injection time 15 min), and eliprodil (0–30 mg/kg; pre-session injection time 15 min). $N = 10$/test drug. $^{*}P < 0.05$ with respect to vehicle treatment (data points above '0'; Dunnett's test).

memantine ($F(4,45) = 7.9$, $P < 0.01$), but not by any other of the antagonists. Dizocilpine stimulated vertical activity ($F(4,43) = 3.3$, $P < 0.05$) while D-CPPene, ACEA-1021 and eliprodil reduced vertical activity counts when administered at higher doses ($F(4,45) = 7.2$, $P < 0.01$, $F(4,45) = 3.4$, $P < 0.05$, $F(4,45) = 4.3$, $P < 0.01$, respectively). Memantine appeared to stimulate vertical activity at lower doses and to reduce it at high doses ($F(4,45) = 3.7$, $P < 0.05$) although post hoc tests did not reveal statistical significance for any individual dose. As expected, cocaine dose-dependently increased horizontal motor activity (Fig. 2; $F(4,43) = 17.0$, $P < 0.01$). The effects on vertical activity were not significant (Fig. 2; $F(4,43) = 0.9$, n.s.) due, in part, to the high variability of the data.

3.2. Experiment 2: Cocaine-conditioned motor activity

Five cocaine-environment pairings were sufficient to establish a conditioned motor activity increase during the post-conditioning test only when the cocaine dose of 30 mg/kg was used during the conditioning phase (Fig. 3). Animals exposed to the cocaine-paired environment did not display stereotypic behaviors (e.g., head bobbing) that are commonly seen after acute challenge with 30 mg/kg of cocaine. ANOVA revealed significant effects of cocaine dose (horizontal: $F(2,89) = 3.6$, $P < 0.05$; vertical: $F(2,89) = 5.0$, $P < 0.01$) and treatment conditions (i.e., Paired, Unpaired and Control groups; horizontal: $F(2,89) = 8.5$, $P < 0.01$; vertical: $F(2,89) = 9.2$, $P < 0.01$). In animals treated with 30 mg/kg of cocaine, effects of conditioning were most pronounced (horizontal: $F(2,29) = 7.9$, $P < 0.01$; vertical: $F(2,29) = 14.8$, $P < 0.01$). Significant differences were revealed between Paired vs. Unpaired and between Paired vs. Control groups ($P < 0.05$, Tukey's test).

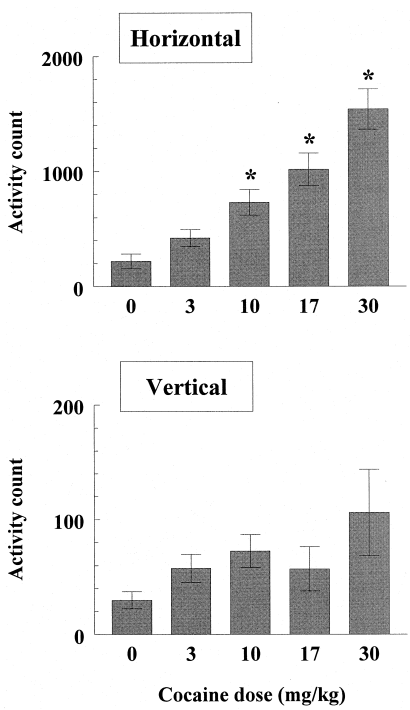

Fig. 2. Effects of cocaine on spontaneous motor activity. Data represent group mean 60-min activity scores (S.E.M.) for rats pretreated with cocaine (0–30 mg/kg) immediately prior to the test session. $N = 10$. $^{*}P < 0.05$ with respect to vehicle treatment (data points above '0'; Dunnett's test).

3.3. Experiment 3: Effects of NMDA receptor antagonists on cocaine-conditioned motor activity

The conditioned motor activity increases after training with 30 mg/kg cocaine were reliably shown in Experiment 3 (values above the 0 mg/kg doses shown in Fig. 4) as confirmed by ANOVA (dizocilpine: $F(1,72) = 17.1$, memantine: $F(1,72) = 18.9$, D-CPPene: $F(1,72) = 28.8$, ACEA-1021: $F(1,72) = 32.5$, eliprodil: $F(1,72) = 18.9$, $P < 0.01$). Cocaine-conditioned motor effects were attenuated by pre-treatment with dizocilpine, memantine, D-CPPene, ACEA-1021, and eliprodil (Fig. 4). Overall, these suppressive effects were observed for both horizontal and vertical components of conditioned motor response and were replicated with at least two doses of each NMDA receptor antagonist (except for eliprodil). However, there were certain differences among the various antagonists. For example, the effects of dizocilpine (horizontal activity) and ACEA-1021 (vertical activity) were not clearly dose-dependent whereas for the others greater attenuation of conditioned effects was obtained at higher test doses. Most importantly, for the higher doses of dizocilpine and, to the lesser degree, for memantine, inhibition of cocaine-conditioned horizontal activity was associated with clear evidence for these drugs' general motor stimulatory properties (dark bars; dizocilpine: $F(3,72) = 50.7$, $P < 0.01$; memantine: $F(3,72) = 3.2$, $P < 0.05$).

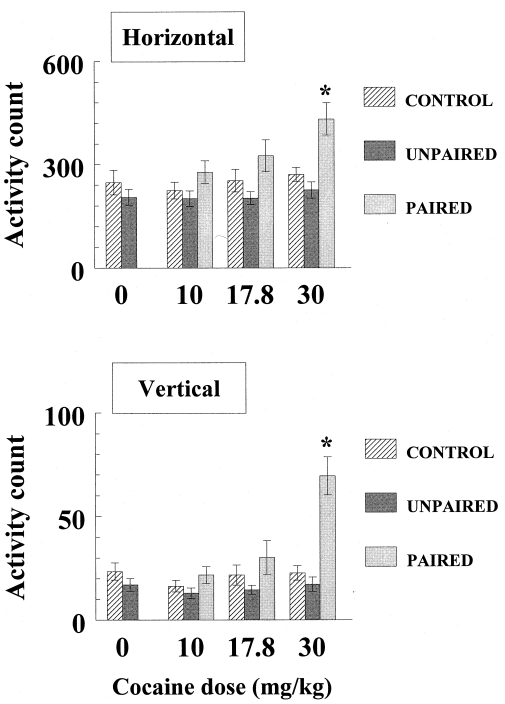

Fig. 3. Cocaine-conditioned motor activity. During the conditioning period rats received injections of saline (dark bars; Unpaired) or different doses of cocaine (light bars; Paired) prior to the placement into the experimental boxes while the second daily injection of saline (light bars; Paired) and cocaine (dark bars; Unpaired) was followed by the placement back into the home cages. Control groups (hatched bars) were returned to home cages after each saline or cocaine injection. Data represent group mean 60-min activity scores (S.E.M.) during the post-conditioning test. $N = 10$/group. $^{*}P < 0.05$ with respect to Unpaired and Control groups (Tukey's test).

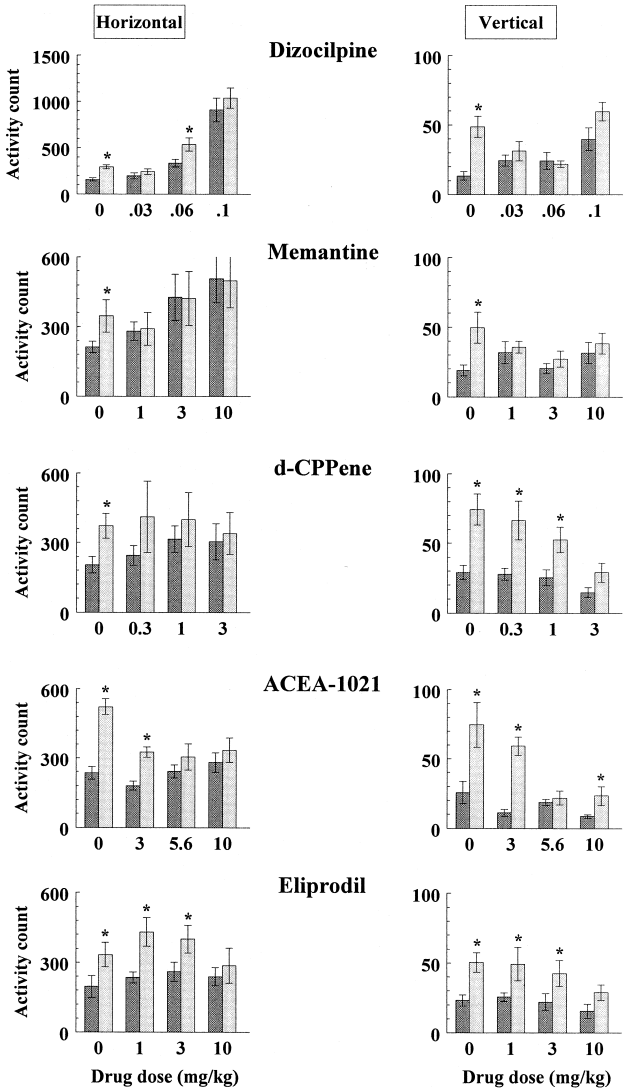

Fig. 4. Effects of NMDA receptor antagonists on motor activity conditioned with cocaine. During the conditioning period rats received injections of saline (dark bars) or cocaine (light bars) prior to the placement into the experiment boxes while the second daily injection of saline (light bars) and cocaine (dark bars) was followed by the placement back into the home cages. Data represent group mean 60-min activity scores (S.E.M.) during the post-conditioning test in rats pretreated with dizocilpine (0–0.1 mg/kg), memantine (0–10 mg/kg), D-CPPene (0–3 mg/kg), ACEA-1021 (0–10 mg/kg), or eliprodil (0–10 mg/kg). $N = 10$/test drug. $^{*}P < 0.05$ with respect to saline-conditioned group (dark bars; Tukey's test).

4. Discussion

In the present study spontaneous motor activity was dose-dependently increased by dizocilpine and memantine,

but not by D-CPPene, ACEA-1021 or eliprodil. Higher doses of D-CPPene, eliprodil or ACEA-1021 reduced vertical activity. These data are consistent with earlier reports on motor effects of NMDA receptor antagonists (Witkin, 1993; Witkin and Acri, 1995; Danysz et al., 1994). The low affinity channel blocker, memantine, increased motor activity but only at high doses that are known to produce brain concentrations well above those needed for NMDA receptor blockade (Parsons et al., 1995; Danysz et al., 1997).

Although rats in this study were tested with only one drug, they were tested with all doses and the vehicle for each drug in a counterbalanced order. It is possible that this design influenced the direct effects of the NMDA receptor antagonists on motor activity since behavioral sensitization and tolerance have been reported to occur in animals repeatedly exposed to PCP-like channel blockers and competitive antagonists (e.g., Boast et al., 1988; Wolf and Khansa, 1991; Balster and Willetts, 1996). No such evidence is available for other classes of NMDA receptor antagonists such as glycine or polyamine site antagonists. Acute motor effects of these antagonists were re-evaluated in Experiment 3 (Unpaired groups) and comparisons between motor effects in Experiments 1 and 3 do not provide support for the role of behavioral sensitization / tolerance in the present results.

Consistent with previous reports (e.g., Stewart et al., 1984), the cocaine-paired environment elicited increases in motor activity following five pairings with cocaine. This phenomenon can be considered an instance of classical conditioning although alternative explanations have been offered to account for the pattern of results obtained in this study. For example, a lack of habituation to the novel environment offered by the test chambers has been proposed as a mechanism (see introduction sections in Ahmed et al., 1996; Tirelli and Terry, 1998). According to this hypothesis, hyperactivity observed in the cocaine-paired environment is identical to the hyperactivity observed in a novel environment. It could be argued that cocaine administration disrupts habituation to the environment, sparing its novelty. Thus, the post-conditioning test (conducted in a drug-free state) reveals the typical activity increasing response to a novel environment. Generally speaking, it is quite difficult to argue against this hypothesis since several classical conditioning phenomena may also have an impact on the habituation process. For example, pre-exposure to the environment that is to be paired with a drug could be expected to decrease both the magnitude of the conditioned response (latent inhibition) and the novelty response. Nevertheless, there were several reports that provided findings incompatible with the habituation hypothesis (Ahmed et al., 1996; Tirelli and Terry, 1998). Experiment 2 was designed to demonstrate that the magnitude of the cocaine-conditioned response is higher than motor activity in a non-habituated environment. This Experiment included a non-habituated control group (rats were returned to home cages after each saline or cocaine injection) as well as control groups that did not receive cocaine injections at all. The results suggested that the cocaine-paired group exhibited significantly higher level of motor activity than any other corresponding control group, including those that were exposed to a ''novel'' environment.

Interestingly, conditioned activation was observed for both horizontal and vertical activity, although cocaine itself only significantly increased horizontal activity. The interpretation of these data comparing conditioned vs. unconditioned motor activity is difficult because unconditioned effects of cocaine were assessed using a within-subjects design (i.e., rats were repeatedly treated and tested with different doses of cocaine). It is plausible that repeated cocaine exposures is an important variable affecting responses to both vehicle and cocaine.

On the other hand, higher doses of cocaine produced marked elevation of horizontal activity that may have negatively affected vertical activity. As a result, in some animals, cocaine seemed to fail to produce increases in vertical activity as partially reflected by a high degree of variability of these data (Fig. 2). Nevertheless, the cocaine-environment conditioning resulted in significant increases in vertical activity (conditioned response). It is not unusual that conditioned responses are evident when there was no observable unconditioned response (e.g., see Mackintosh, 1974, p. 80).

The main finding of these studies is that all NMDA receptor antagonists that were tested altered the expression of cocaine-conditioned motor activation. Nonetheless, differences were also evident in the pattern of effects produced by the individual drugs as seen in the Unpaired groups and in Experiment 1. In the cases of dizocilpine, memantine and D-CPPene, the attenuation of the differences between motor activity in the Paired and Unpaired groups can be attributable in part to their own direct activity increasing effects. This was clearly evident for the effects of 0.1 mg/kg dizocilpine; however, at the lowest tested dose of 0.03 mg/kg, it did not produce motor stimulation but still eliminated the difference between cocaine-conditioned and pseudo-conditioned groups.

For the horizontal activity measures, D-CPPene and higher doses of memantine mimicked dizocilpine in producing motor stimulation in some of the subjects resulting in greater variability of the group data and loss of the difference between cocaine-conditioned and pseudo-conditioned groups. These results are not surprising since it is established that PCP-like effects may develop after administration of either competitive NMDA receptor antagonists (Herrling et al., 1997) or high doses of low-affinity channel blockers (Nicholson et al., 1998).

Meanwhile, lower doses of memantine, as well as ACEA-1021, attenuated cocaine-conditioned horizontal motor activity at doses that did not significantly suppress spontaneous motor activity. These results confirm well-

known differences between various classes of NMDA receptor antagonists (e.g., Balster and Willetts, 1996). It is especially appealing that lower doses of memantine and ACEA-1021 are devoid of PCP-like activity (Balster et al., 1994; Nicholson et al., 1998), do not produce motor stimulation and yet are capable of producing selective decrements in cocaine-conditioned motor activity. Interestingly, memantine, ACEA-1021, D-CPPene as well as lower doses of dizocilpine inhibited vertical conditioned motor activity suggesting that differences between classes of NMDA receptor antagonists are less evident when this type of cocaine-conditioned response is studied.

Eliprodil inhibited both horizontal and vertical components of cocaine-conditioned motor activity although this effect was evident only at the dose level (10 mg/kg) that tended to directly decrease vertical activity. Eliprodil is also devoid of PCP-like effects (Balster et al., 1994). In this study, eliprodil appeared to be less effective than memantine, D-CPPene or ACEA-1021. Such differences may be attributed either to NMDAR2B subunit-selectivity of eliprodil (Carter et al., 1997) or to the degree of functional antagonism exerted by polyamine site antagonists in general (e.g., dependence on glycine site saturation; Carter et al., 1997).

The finding that the effects of dizocilpine on cocaine-conditioned activity could not be readily distinguished from its direct effects on behavior confirmed earlier reports of failures to get selective effects. Cervo and Samanin (1996) reported that, although dizolcipine blocked the development of cocaine-induced conditioned motor activity, it did not modify its expression. Negative results were also obtained by Druhan and Wilent (1999) who administered the competitive antagonist CPP into the lateral ventricles prior to the post-conditioning test. Cocaine conditioned motor activity was not modified by CPP at doses that did not affect spontaneous motor activity. However, it is unclear how these data relate to the results obtained with systemic administration of NMDA receptor antagonists because of the possibility that intracerebroventricular and systemic injections target different brain areas according to a partially overlapping but not identical pattern. For instance, NMDA receptors in the nucleus accumbens were demonstrated to modulate intravenous cocaine self-administration (Pulvirenti et al., 1992) and also the effects of cocaine on extracellular dopamine levels (Pap and Bradberry, 1995), while administration of NMDA receptor antagonists into the nucleus accumbens septi attenuated amphetamine-conditioned motor activity (Bespalov and Zvartau, 1996).

Overall, information on the role of NMDA receptors in the mechanisms underlying drug-conditioned behaviors is very limited. NMDA receptor antagonists were shown to block morphine-and amphetamine-conditioned place preferences (Bespalov, 1996; Bespalov et al., 1994; Tzschentke and Schmidt, 1995, 1997; Popik and Danysz, 1997), while expression of a cocaine-conditioned place preference was not modified by dizocilpine (Cervo and Samanin, 1996). The negative results with cocaine need to be interpreted in the context of synergistic effects of dizocilpine and cocaine (Ranaldi et al., 1996, 1997; Kantak et al., 1998), since it is known that expression of conditioned place preference may be enhanced by drug administration prior to the post-conditioning test (Bozarth, 1987; Bespalov et al., 1999). Similar phenomenon could, at least in part, have contributed to the outcome of the studies where dizocilpine was shown to reinstate responding for cocaine following an extinction period (De Vries et al., 1998).

In conclusion, expression of cocaine-conditioned motor activity is differentially affected by antagonists acting at different recognition sites on the NMDA receptor complex. The low-affinity channel blocker (memantine) as well as glycine (ACEA-1021) and, to the lesser degree, polyamine (eliprodil) site antagonists more selectively attenuated expression of cocaine-conditioned motor responses than did the high-affinity channel blocker (dizocilpine). Thus, NMDA receptors may have a role in the expression of cocaine-conditioned motor activity and these results imply that NMDA receptor antagonists may be useful in the treatment of drug-cue reactivity in drug abusers. Different types of NMDA receptor antagonists need to be evaluated for the selectivity of their effects.

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