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Differential effects of agents acting at various sites of the NMDA receptor complex in a place preference conditioning model

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Abstract

A conditioned place preference paradigm was used to assess the potential rewarding properties of the uncompetitive NMDA receptor antagonist, MK-801 (dizolcipine), the two competitive NMDA receptor antagonists, CGP 37849 (DL-(*E*)-2-amino-4-methyl-5-phosphono-3-pentonoic acid) and its (*R*)-enantiomer CGP 40116, as well as the partial agonist at strychnine-insensitive glycine receptors, ACPC (1-aminocyclopropanecarboxylic acid). MK-801 (0.3 mg/kg), CGP 37849 (1.25–10 mg/kg) and CGP 40116 (1.25–10 mg/kg), administered in association with either the initially non-preferred or initially preferred side of the two-arm chamber, caused a significant increase in the time spent on that side in a post-conditioning test. In contrast, ACPC did not support the conditioned place preference. Thus, the time spent on the drug-associated side following conditioning with ACPC (50–400 mg/kg) did not significantly differ from that measured in the pre-conditioning test, irrespective of whether it was associated with the initially non-preferred black side or the initially preferred white side. These results are consistent with both clinical and pre-clinical data demonstrating differences in psychopharmacological properties among compounds acting at the multiple, allosteric regulatory sites on the NMDA receptor complex. Moreover, these results indicate that the abuse potential of ACPC, which acts as a functional NMDA receptor antagonist, may be lower than that of either uncompetitive or competitive NMDA receptor antagonists.

Keywords: Conditioned preference; Reward; NMDA receptor; Glycine site; MK-801; CGP 37849; CGP 40116; ACPC (1-aminocyclopropanecarboxylic acid)

1. Introduction

N-Methyl-D-aspartate (NMDA) receptors have been linked to a variety of central nervous system disorders and NMDA receptor antagonists have been proposed for the treatment of neuronal damage associated with stroke and head trauma (Collingridge and Singer, 1990; Meldrum and Garthwaite, 1990; Szatkowski and Attwell, 1994), epilepsy (Gean and Shinnick-Gallaher, 1988; Patel et al., 1990; Turski et al., 1990), anxiety (Dunn et al., 1989; Kehne et al., 1991; Rupniak et al., 1993) and depression (Maj et al., 1992; Paul et al., 1993, 1994, Papp and Moryl, 1994a). However, both uncompetitive and competitive NMDA receptor antagonists have been reported to produce severe psychomimetic-like effects which would likely preclude their use in chronic therapy (Beardsley et al., 1990; Carter, 1995; Faden and Salzman, 1992; Koek and Woods, 1988; Koek et al., 1988; Olney et al., 1990; Willetts et al., 1990). These predictions, based on pre-clinical data, are further corroborated by clinical trials in which severe adverse side-effects were reported in patients undergoing pharmacotherapy with the competitive NMDA receptor antagonists D-CPP-ene and CGS 19755 (Grotta et al., 1995; Sveinbjornsdottir et al., 1993). Therefore, in recent years, intensive studies have been carried out to identify compounds which retain NMDA receptor antagonistic properties but are devoid of unwanted side-effects. As a result of these studies, it has been found that compounds acting at NMDA receptors produce a wide spectrum of behavioural effects which depend on both the specific site of interaction with the NMDA receptor complex and the intrinsic activity of the compound. For example, several reports suggest that, due to apparent co-requirement for glycine to operate NMDA receptor-gated cation channels (Kleckner and Dingledine, 1988), ligands acting at strychnine-insensitive glycine receptors can also act as functional NMDA receptor antagonists under conditions in which synaptic

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concentrations of glycine are presumed to be at or near saturation (Carter, 1992; Fossom et al., 1995). According to this concept, glycine receptor antagonists and partial agonists (i.e., compounds with a lower intrinsic activity than glycine) have been found to share many of the pharmacological actions of both uncompetitive and competitive NMDA receptor antagonists (e.g., neuroprotective, anticonvulsant, antianxiety, antidepressant) without having their psychomimetic-like effects (Anthony and Nevins, 1993; Dunn et al., 1992; Faiman et al., 1994; Kehne et al., 1995; Nowak et al., 1993; Rundfeldt et al., 1994; Trullas and Skolnick, 1990; Trullas et al., 1989, 1991; Von Lubitz et al., 1992).

In view of the above data, the purpose of the present study was to compare the effects of four ligands acting at different loci on the NMDA receptor complex in a place preference conditioning model which is frequently used to evaluate the potential rewarding properties of drugs. Typically, in this paradigm animals are exposed to an apparatus with at least two distinctive environments. One environment is repeatedly associated with drug administration while the other is paired with vehicle. Following training, the animals, usually drug-free, are allowed to freely explore both environments and the change in the time spent on the drug-paired side is measured. It is assumed that the animals learn to approach stimuli associated with the reward and, if they spend more time on the drug-paired side, the choice is attributed to the rewarding properties of the drug. This interpretation is consonant with the finding that most drugs that induce conditioned preference are also active in other models, such as self-administration and intracranial self-stimulation (Carr et al., 1989; Goudie, 1991). Since the notion of reward is essential to many theories of abuse and dependence, the conditioned place preference paradigm is extensively used to detect the abuse potential of psychoactive drugs and most drugs that are abused by humans (e.g., psychostimulants, opiates, benzodiazepines, alcohol) have been shown to support the conditioned preference while drugs with little or no potential for abuse (e.g., antihistaminergic, neuroleptics) are generally inactive in this model (for reviews, see Carr et al., 1989; Schechter and Calcagnetti, 1993).

In this study, we compared the rewarding properties of the uncompetitive NMDA receptor antagonist, MK-801 (dizolcipine), and the two competitive NMDA receptor antagonists, CGP 37849 (DL-(*E*)-2-amino-4-methyl-5-phosphono-3-pentonoic acid) and its (*R*)-enantiomer CGP 40116, with those of 1-aminocyclopropanecarboxylic acid (ACPC), a high-affinity partial agonist at strychnine-insensitive glycine receptors (Marvizon et al., 1989). We found that, while both MK-801 and the CGP compounds significantly increased the time that the animals spent on the drug-associated side, the glycine receptor partial agonist ACPC was inactive in the place preference conditioning model. The failure of ACPC to support the conditioned preference suggests that this functional NMDA receptor antagonist is devoid of rewarding properties and, therefore, may have no abuse potential in humans.

2. Materials and methods

2.1. Subjects

Male Wistar rats (250 g; Gorzkowska, Warszawa, Poland) were housed in groups of five in plastic cages ($40 \times 25 \times 15$ cm), with food and water freely available. The rats were maintained on a 12-h light/dark cycle (lights on at 08:00 h), at a temperature of 22 ± 2°C.

2.2. Apparatus

The animals were trained and tested in five identical wooden chambers consisting of white and black arms ($30 \times 20 \times 25$ cm) with a different floor texture (plain wood or wire mesh) and a gray central area ($12 \times 20 \times 25$ cm). Black and white compartments were separated from the gray one by guillotine doors.

2.3. Procedure

On the first 3 days, the animals were placed in the central area; after 5 s, the guillotine doors were raised and each rat was allowed freely to explore the whole chamber for 10 min/day. On day 4 that procedure was repeated, but this time the amount of time spent by animals in each arm was manually recorded (through a mirror located 1.5 m above the chambers) in a 10-min pre-conditioning test. This measure was used to establish initial preference for either of the two arms of the chamber. Only those animals that showed clear preference for the black arm of the chamber were used for drug evaluation. Group means for those animals were ≈ 470 s in the preferred (black) arm and ≈ 60 s in the non-preferred (white) arm. These pre-conditioning scores did not differ significantly among the groups (see below). On days 5–10, the animals ($n = 7$–10 rats/group) were confined on alternate days for 60 min to either of the two arms (white or black), following injection of an active drug or vehicle. In the first series of experiments, the animals were injected with MK-801 (0.3 mg/kg), CGP 37849 (1.25–10 mg/kg), CGP 40116 (1.25–10 mg/kg) or ACPC (50–400 mg/kg) prior to confinement to the white arm (initially non-preferred) and with vehicle prior to confinement to the black arm (initially preferred). In another series of experiments, these contingencies were reversed: MK-801 (0.3 mg/kg), CGP 37849 (5.0 mg/kg), CGP 40116 (5.0 mg/kg) or ACPC (200 and 400 mg/kg) was administered prior to confinement to the black arm (initially preferred) and vehicle prior to confinement to the white arm (initially non-preferred). All injections were IP in a volume of 1 ml/kg body weight and were administered 30 min (MK-801, ACPC) or 60 min (the CGP compounds) before confinement to the

apparatus. Changes in place preference were measured drug-free on day 11. The animals were placed in the central area and, after 5 s, the guillotine doors were raised and the time spent in each arm was measured manually in a 10-min post-conditioning test.

2.4. Statistics

The results were analyzed by the two-way analysis of variance, with test (pre- and post-conditioning) and treatment (saline and drug) as grouping variables and the time spent on the conditioned side as a dependent variable. Fisher's least significant difference (LSD) test was used for post-hoc comparisons of the means.

2.5. Drugs

The following agents were used in the study: (+)-MK-801 (Research Biochemicals, Natick, MA, USA), CGP 37849 and CGP 40116 (Ciba-Geigy, Basel, Switzerland) and ACPC (Symphony Pharmaceuticals, Malvern, PA, USA). All agents were dissolved in distilled water, which was used for vehicle injections.

3. Results

In the pre-conditioning test, the times spent on the initially non-preferred (white) and initially preferred (black) sides did not significantly differ between groups (white side: $F(16,133) = 0.638$; N.S., black side: $F(3,33) = 0.719$; N.S.) and the initial side preferences were not significantly affected by saline injections in the conditioning chamber (white side: $F(5,54) = 0.619$; N.S., black side: $F(1,18) = 0.773$; N.S.).

As shown in Fig. 1, MK-801 administered in association with the initially non-preferred side caused a signifi-

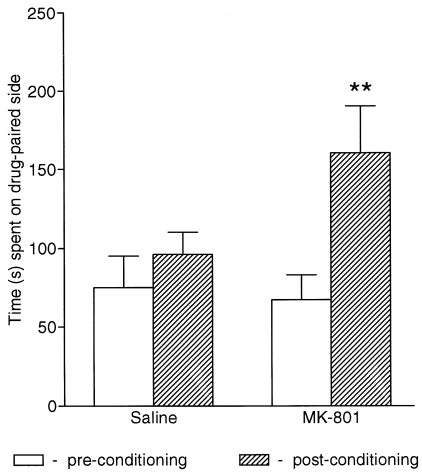

Fig. 1. The conditioned place preference induced by MK-801 (0.3 mg/kg). Values are means ± S.E.M. of time spent on the drug-associated side before (open bars) and after (hatched bars) conditioning. ** $P < 0.02$; relative to pre-conditioning scores.

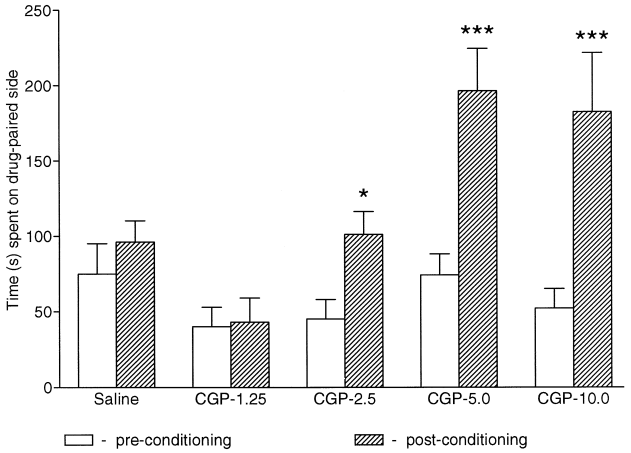

Fig. 2. The conditioned place preference induced by CGP 37849 (1.25, 2.5, 5.0 and 10 mg/kg). Values are means ± S.E.M. of time spent on the drug-associated side before (open bars) and after (hatched bars) conditioning. * $P < 0.05$, *** $P < 0.001$; relative to pre-conditioning scores.

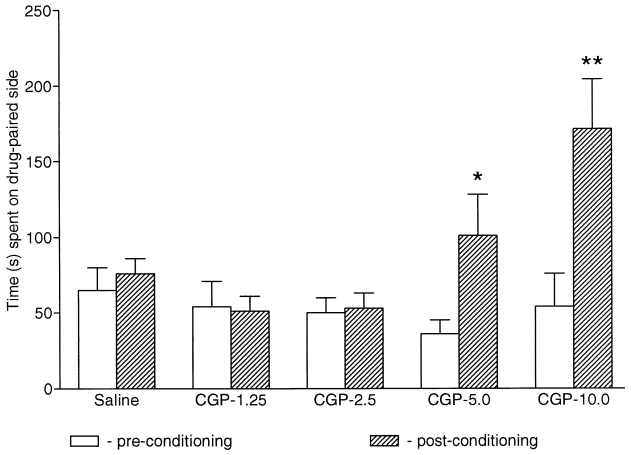

Fig. 3. The conditioned place preference induced by CGP 40116 (1.25, 2.5, 5.0 and 10 mg/kg). Values are means ± S.E.M. of time spent on the drug-associated side before (open bars) and after (hatched bars) conditioning. * $P < 0.05$, ** $P < 0.02$; relative to pre-conditioning scores.

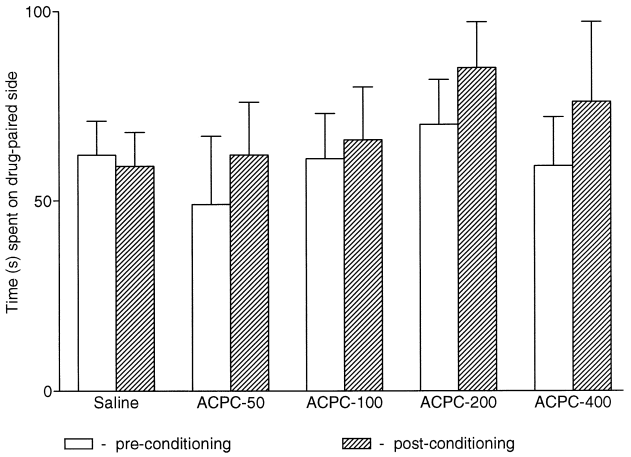

Fig. 4. The effect of ACPC (50, 100, 200 and 400 mg/kg) on the conditioned place preference. Values are means ± S.E.M. of time spent on the drug-associated side before (open bars) and after (hatched bars) conditioning.

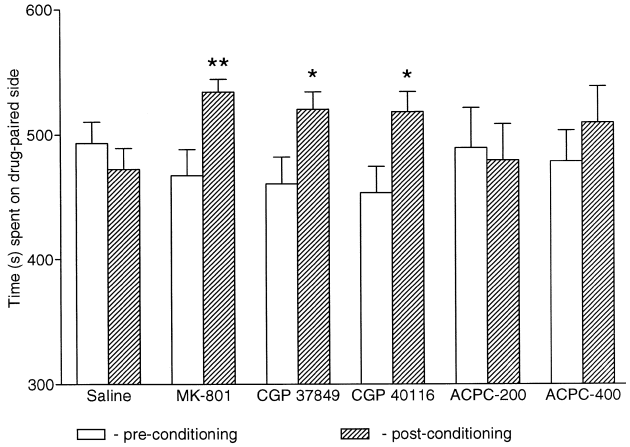

Fig. 5. The effect of MK-801 (0.3 mg/kg), CGP 37849 (5 mg/kg), CGP 40116 (5 mg/kg) and ACPC (200 and 400 mg/kg) on conditioned place preference. All compounds were paired with the initially preferred (black) side of the conditioning chamber. Values are means ± S.E.M. of time spent on the drug-associated side before (open bars) and after (hatched bars) conditioning. * $P < 0.05$, ** $P < 0.02$; relative to pre-conditioning scores.

cant increase in the time spent on the conditioning side in the post-conditioning test ($F(1,36) = 7.512$; $P < 0.01$). MK-801 also caused an increase in place preference when paired with the initially preferred side ($F(1,36) = 6.171$; $P < 0.02$, Fig. 5). The times spent on the initially non-preferred side before and, after conditioning with CGP 37849 and CGP 40116, are shown in Figs. 2 and 3. Both compounds caused a significant and dose-dependent increase in place preference (CGP 37849: $F(4,80) = 5.499$; $P < 0.001$, CGP 40116: $F(4,70) = 3.692$; $P < 0.01$). A similar shift towards the drug-paired side was observed when CGP 37849 and CGP 40116 were associated with the initially preferred side (CGP 37849: $F(1,36) = 5.000$; $P < 0.05$, CGP 40116: $F(1,30) = 3.954$; $P < 0.05$, Fig. 5).

In contrast, ACPC did not support the conditioned place preference. As shown in Fig. 4, the time spent on the initially non-preferred side following conditioning with four doses of ACPC (50, 100, 200 and 400 mg/kg) did not significantly differ from that measured in the pre-conditioning test ($F(4,80) = 1.377$; N.S.). Similarly, when administered in association with the initially preferred side, ACPC (200 and 400 mg/kg) did not cause a significant increase in place preference ($F(2,54) = 0.405$; N.S., Fig. 5).

4. Discussion

The place preference conditioning paradigm has been demonstrated to have high predictive validity for detecting compounds with an abuse potential in humans (Carr et al., 1989; Goudie, 1991). The present data show that, in addition to a number of drugs active in this model (Carr et al., 1989; Schechter and Calcagnetti, 1993), also MK-801, CGP 37849 and CGP 40116 can produce a significant place conditioning effect, increasing the subsequent preference for an environment in which these compounds were administered. In contrast, ACPC, at doses well within the range that produce anticonvulsant, neuroprotective, anxiolytic and antidepressant actions in rodents (Anthony and Nevins, 1993; Faiman et al., 1994; Nowak et al., 1993; Trullas and Skolnick, 1990; Trullas et al., 1991; Von Lubitz et al., 1992) failed to elicit a conditioned place preference.

It should be noted that in these experiments we used a biased apparatus in which animals showed strong, unconditioned preference for one side. Thus, in the pre-conditioning test, the rats spent significantly more time in the black arm of the chamber (> 6 min) than in the initially non-preferred, white arm (< 2 min). If the tested compounds were active on one side only (i.e., initially non-preferred), changes in the side preference could be attributed to their antiaversive or antianxiety activity (see Carr et al., 1989). This issue is particularly important for interpretation of the present results, since all the compounds used in this study have been shown to be active in several animal models of anxiety (Anthony and Nevins, 1993; Dunn et al., 1989; Faiman et al., 1994; Kehne et al., 1991; Rupniak et al., 1993; Trullas et al., 1989). However, possible involvement of the anxiolytic properties of MK-801, CGP 37849 and CGP 40116 can be excluded, since increases in the time spent on the drug-associated side were observed not only when MK-801 and the CGP compounds were administered on the initially non-preferred side, but also, to a lesser extent due to a ceiling effect, when they were paired with the initially preferred side. Moreover, ACPC, which has also been reported to have anxiolytic activity (Anthony and Nevins, 1993; Faiman et al., 1994; Trullas et al., 1989, 1991), did not support conditioned place preference, irrespective of whether it was associated with the initially non-preferred black side or the initially preferred white side. Thus, the observation that the conditioned effects of MK-801 and the CGP compounds were qualitatively similar, regardless of the side of the apparatus in which they were administered, suggests that these compounds have rewarding properties.

The ability of MK-801, an uncompetitive NMDA receptor antagonist, to induce conditioned place preference, also demonstrated in previous studies (Hoffman, 1994), is consistent with other data showing that this compound facilitates intracranial self-stimulation, may be self-administered under certain circumstances and shares many behavioural and biochemical effects with phencyclidine, a drug with well-established reinforcing and psychotomimetic properties in both animals and humans (Beardsley et al., 1990; Herberg and Rose, 1989; Koek et al., 1988; Koek and Woods, 1988). Similar effects of competitive NMDA receptor antagonists have not been previously demonstrated. Recently, CGP 37849 was found to be active in the preference conditioning paradigm (Tzschentke and Schmidt, 1995); unfortunately in this study only one dose

was tested. The present results confirm this finding and show that CGP 37849 and its (*R*)-enantiomer, CGP 40116, can produce conditioned place preference in a dose-dependent manner. Together, these data provide strong evidence that these competitive NMDA receptor antagonists may also have rewarding properties. Further studies are required to establish definitively whether such a conclusion can be extended to all competitive NMDA antagonists.

The mechanism of the rewarding effect of MK-801, CGP 37849 and CGP 40116 is not clear. MK-801 has been shown to stimulate the activity of the dopaminergic mesolimbic system (Bubser et al., 1992; French and Ceci, 1990; Löscher et al., 1993), which is consistent with the substantial literature implicating this system in the rewarding effects of drugs in the place conditioning paradigm (see Carr et al., 1989). However, only a few reports have shown that CGP 37849 and CGP 40116 cause similar effects (Löscher et al., 1993; Wedzony et al., 1994, 1996). In other biochemical and electrophysiological studies, systemic administration of competitive NMDA receptor antagonists did not affect the activity of dopaminergic neurons (e.g., Bubser et al., 1992; French et al., 1991). In our preliminary studies, we found that acquisition, but not expression, of the conditioned preference induced by MK-801 and the CGP substances was abolished by haloperidol (Papp and Moryl, 1994b). These data suggest the involvement of dopaminergic neurons in the rewarding activity of both uncompetitive and competitive NMDA receptor antagonists; however, they also indicate that the involvement of other neurotransmitter systems cannot be excluded. The possibility that dopaminergic neurons can mediate the above effects of both classes of NMDA receptor antagonists is further corroborated by the failure of ACPC to support conditioned preference. Although no effects of ACPC on dopamine release have been reported, other glycine receptor partial agonists and antagonists (e.g., HA-966, D-cycloserine, 7-Cl-KA) do not modulate the spontaneous activity of dopaminergic neurons (Layer et al., 1993; Gandolfi et al., 1994).

The inactivity of ACPC in the place preference conditioning model suggests that this compound has no rewarding properties in animals, a finding consistent with both pre-clinical and clinical analyses demonstrating that, in contrast to other classes of NMDA receptor antagonists, ACPC does not produce psychomimetic-like side-effects in either animals or humans (Cherkofsky, 1995). Recently, Bespalov et al. (1994) reported that kynurenic acid, a non-selective glycine receptor antagonist, is also ineffective in the conditioned place preference model, suggesting that the above conclusion may also refer to other functional NMDA receptor antagonists. Nevertheless, further studies with other selective glycine receptor partial agonists and full antagonists are needed to verify this hypothesis.

In conclusion, the results presented in this article confirm that NMDA receptors are involved in brain mechanisms of reward and that uncompetitive and competitive NMDA receptor antagonists have rewarding properties in animals, which may indicate their abuse liability in humans. ACPC, a functional NMDA receptor antagonist which acts through strychnine-insensitive glycine receptors, may be devoid of such undesirable behavioural effects.

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