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BLOCKADE OF THE ACQUISITION OF ETHANOL-INDUCED CONDITIONED PLACE PREFERENCE BY *N*-METHYL-D-ASPARTATE RECEPTOR ANTAGONISTS

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Abstract — We have examined the influence of two different *N*-methyl-D-aspartate (NMDA) receptor antagonists on acquisition of the reinforcing properties of ethanol measured in the conditioned place preference (CPP) paradigm in rats. After receiving 15 daily injections of ethanol (0.5 g/kg, i.p.) before the conditioning trials, rats acquired the preference to the compartment paired with ethanol injections during conditioning. Both dizocilpine (0.1 mg/kg, i.p.), a non-competitive antagonist of the NMDA receptor, and L-701,324 (5 mg/kg, per os), an antagonist acting at the strychnine-insensitive glycine site of NMDA receptor complex, when co-administered repeatedly with ethanol, prevented the acquisition of ethanol-induced CPP. Dizocilpine alone provoked the development of CPP, having some intrinsic rewarding properties. In contrast, L-701,324 alone did not affect the CPP. These results suggest that the rewarding properties of ethanol could be, at least in part, due to its action at the NMDA receptor complex. Additionally, we can speculate that NMDA receptor antagonists can be useful in the treatment of ethanol dependence. Glycine receptor antagonists having no abuse potential might have advantages in terms of safety compared to non-competitive NMDA receptor antagonists.

INTRODUCTION

The conditioned place preference (CPP) paradigm has been used as a model for studying the reinforcing effects of drugs with dependence liability (Carr *et al.*, 1989). In this paradigm, one of two distinctive places is repeatedly paired with a drug injection and the other with a vehicle. On the test day when no drug is given an increase in the time spent by animals in the compartment previously associated with the drug injection is taken as a measure of the rewarding properties of this drug. A variety of drugs that are abused by humans have been shown to support the CPP (e.g. morphine, heroin, cocaine, amphetamine) (Carr *et al.*, 1989). These reinforcing effects may be due to their common property of facilitating dopamine (DA) transmission in mesolimbic and mesocortical DA neurons. The DA system has been postulated to be a critical link in all rewards including natural rewards such as food and water (Spyraki *et al.*, 1982*a*; Guyon *et al.*, 1993). Studies regarding the effect of ethanol (EtOH) on CPP are controversial. Some demonstrate EtOH-induced place preference, whereas others show no effect or even a place aversion (Van der Kooy *et al.*, 1983; Reid *et al.*, 1985; Bozarth, 1989; Bieńkowski *et al.*, 1996*a*). In order to establish a CPP using EtOH, extensive conditioning trials are necessary. With repeated exposure to EtOH, tolerance to aversive effects may develop, thus revealing the rewarding effects. EtOH is a weak but positive reinforcer in rats, so failure in demonstrating its rewarding effects with the CPP methods may be due to an insufficient number of conditioning trials or to an inadequate exposure to the drug. In the earlier reports, EtOH-induced CPP has been demonstrated in rats that had previously consumed a 6% EtOH solution daily for 26 days (Reid *et al.*, 1985), or after prolonged daily conditioning trials (Bozarth, 1989; Bieńkowski *et al.*, 1996*a*), or if rats were offered food in the pairing compartment (Steward and Grupp, 1981).

There is considerable evidence that activation of mesolimbic DA pathways is critical for EtOH-induced reinforcement (Brodie *et al.*, 1990; Yoshimoto *et al.*, 1991), but also many other neurotransmitter systems are involved. For example,

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some anatomical and pharmacological studies have illustrated a synaptic interaction between DA and the excitatory amino acid glutamate, especially within the striatum and the nucleus accumbens (Clow and Jhamandas, 1989; Krebs *et al.*, 1991). Given these close functional relationships, a glutamatergic influence in some of the behavioural actions of EtOH is possible. DA release in many brain areas is controlled by the *N*-methyl-D-aspartate (NMDA) receptors and glutamatergic mechanisms probably through the presynaptic NMDA receptors located on the DA neurons.

Glutamate is now considered to be the major excitatory neurotransmitter in the mamalian central nervous system (CNS). The NMDA receptor is the most clearly characterized subtype of glutamatergic amino acid receptor and appears to be a complex of multiple binding and modulatory sites including the glutamate, strychnine-insensitive glycine and polyamine sites. The NMDA receptors might be involved in the neuronal and behavioural changes resulting from chronic administration of many drugs of abuse. NMDA receptor antagonists have been found to influence the development of tolerance, sensitization and physical dependence to a variety of psychoactive drugs, including psychostimulants, opioids, nicotine and ethanol (Schenk *et al.*, 1993; Bristow *et al.*, 1994; Trujillo and Akil, 1995; Kim *et al.*, 1996). These results indicate an important role of NMDA receptors in drug-induced behavioural plasticity. Many biochemical and pharmacological investigations have shown that EtOH, acutely, is a potent and selective inhibitor of the actions of NMDA subtype of glutamate receptors (Hoffman and Tabakoff, 1993). In some behavioural studies, EtOH given acutely blocked NMDA-induced convulsion and potentiated the locomotion provoked by NMDA receptor antagonists (Kuribara, 1994). Chronic EtOH exposure might have provoked a compensatory response of neurons, i.e. the development of greater numbers of excitatory amino acid receptors or the production of receptors with increased affinity (Rossetti and Carboni, 1995). Non-NMDA receptors are reported to be less sensitive to EtOH. Some reports regarding the site of action for EtOH point to its influence on the NMDA/glycine co-agonist site. Glycine has been shown to be a necessary co-agonist for the activation of NMDA receptor-operated ion channels and it has been demonstrated that increasing concentration of glycine can reverse some of the effects of ethanol (Woodward and Gonzales, 1990). Like the NMDA receptor antagonists, glycine receptor antagonists may have blocked many of the acute and chronic actions of EtOH including EtOH withdrawal seizures (Kotlińska and Liljequist, 1996) and the reinforcing properties of EtOH measured using the self-administration procedure (Rassnick *et al.*, 1992). It has been shown that glycine receptor antagonists share many of the pharmacological actions of NMDA receptor antagonists (e.g. antidepressant, antianxiety, anticonvulsant, neuroprotective) (Tricklebank *et al.*, 1989; Kotlińska and Liljequist, 1998). In contrast, they seem to be devoid of psychomimetic-like effects.

Taken together, the aim of the present study was to investigate the influence of two NMDA receptor antagonists: dizocilpine (MK-801), a non-competitive NMDA-receptor antagonist, and L-701,324, a novel strychnine-insensitive glycine site antagonist, systemically active, on the acquisition of EtOH-induced CPP in rats. In addition, we have intended to demonstrate if these compounds, given alone, in the doses used, could have some intrinsic rewarding properties measured in the CPP paradigm.

MATERIALS AND METHODS

Animals

The experiments were carried out on male Wistar rats (Farm of Laboratory Animals, Szostak, Warszawa) weighing 250–350 g, kept under standard laboratory conditions (4–6 per cage, 12 h/12 h light/dark cycle) with free access to tap water and lab chow (Bacutil, Motycz, Poland). The animals were adapted to the laboratory conditions for at least 1 week. The rats were handled once daily for 4 days before the start of the experiments.

Apparatus

The testing apparatus was similar to that used by Spyraki *et al.* (1982*a*,*b*). Each of four rectangular wooden boxes (60 × 35 × 30 cm) was divided into three compartments: two large compartments (25 × 35 cm) were separated by removable guillotine doors from a small central area (10 × 10 cm). One of them had its walls painted white, the walls of the other were painted black. The central small

compartment was painted grey. The testing boxes were kept in a soundproof room with a neutral masking noise and constant light provided by a 40 W lamp.

Procedure

The CPP procedure with ethanol was similar to that described by Bieńkowski *et al.* (1996*a*). It was preceded by 15 single daily injections of 10% (v/v) EtOH (0.5 g/kg, i.p.) or distilled water each day for 15 days. The CPP paradigm consisted of three phases: pre-conditioning, conditioning and post-conditioning (preference test). During the first habituation phase (pre-conditioning), each rat was placed in the central grey area and allowed to explore three compartments of the testing boxes for 15 min (each day for 2 days). The time spent by each animal in the two large compartments was recorded manually on the second day. The initially non-preferred compartment was paired with EtOH (0.5 g/kg) during the second (conditioning) phase. During this phase (8 days), the rats were pretreated with dizocilpine (0.1 mg/kg) or L-701,324 (5 mg/kg) respectively before EtOH injection and, after 5 min, they were confined to the non-preferred compartment for 30 min. On alternate days, the rats were exposed for 30 min to the preferred compartment after the injection of distilled water. The control group received distilled water every day. During the third phase (post-conditioning), the guillotine doors were removed and each rat was allowed to explore the entire apparatus. The time spent by each animal in the two large compartments was measured manually over a 15-min period. As a general rule, neither drug nor water was injected on this test day.

Drugs

The drugs used in this study were: ethanol (Polmos, Poland, 95% v/v), L-701,324 [7-chloro-4-hydroxy-3-(3-phenoxy)phenyl-2(1H)-quinolone; a generous gift from Merk Sharp and Dohme, Rahway, NJ, USA]; dizocilpine {[+]-5methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine hydrogen maleate; RBI, Natick, MA, USA}. Ethanol was prepared for injections by diluting 95% ethanol in distilled water to obtain a concentration of 10% (v/v). L-701,324 was prepared as a suspension using a 0.5% solution of methylcellulose and administered per os in a volume of 5 ml/kg, 30 min before EtOH administration. Dizocilpine was diluted in distilled water and administered i.p. in a volume of 2 ml/kg 15 min before each of the i.p. ethanol injections.

Statistics

Data were expressed as group means (± SEM) of time (in s) spent by animals in the drug-paired compartment after conditioning. Statistical analysis was carried out by one-way analysis of variance (ANOVA) followed by the Bonferroni test. The confidence limit of $P < 0.05$ was considered as statistically significant.

RESULTS

On the pre-conditioning test day, the rats spent significantly more time in the black compartment (>8 min) than in the white compartment (<1 min). These side preferences were not significantly different between groups. The natural preferences of rats were not changed by saline injections during the conditioning sessions.

Effects of L-701,324 on acquisition of the CPP produced by ethanol

As shown in Fig. 1, rats treated chronically with 0.5 g/kg of EtOH exhibited preference to the initially non-preferred compartment paired with EtOH injections ($P < 0.001$). Pretreatment with L-701,324 (5 mg/kg) inhibited EtOH-induced place preference ($P < 0.05$) (Fig. 1). L-701,324 given alone during the conditioning trials failed to affect the CPP (Fig. 1).

Effects of dizocilpine on acquisition of the CPP induced by ethanol

Pairing of dizocilpine (0.1 mg/kg) with each injection of EtOH during the conditioning sessions completely abolished the acquisition of the EtOH-induced CPP ($P < 0.001$) (Fig. 2). Dizocilpine by itself, however, elicited a significant preference for the drug-paired compartment ($P < 0.01$) (Fig. 2).

DISCUSSION

Using the place conditioning paradigm (biased procedure) we have shown that, after prolonged pre-exposure to EtOH, rats acquired significant place preference to the compartment paired with

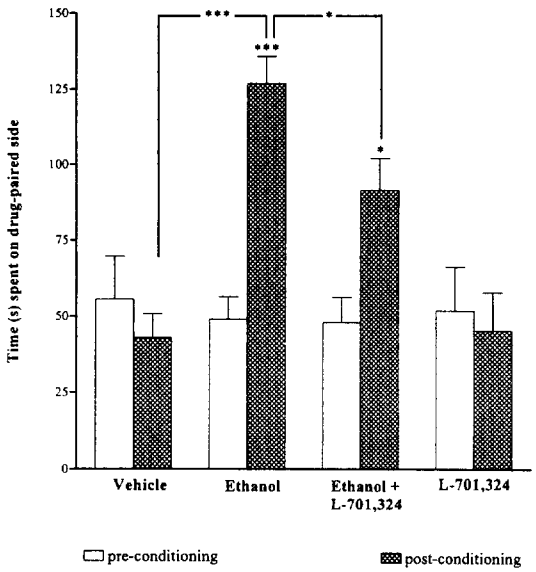

Fig. 1. Effect of L-701,324 on acquisition of conditioned place preference induced by ethanol.

The columns show the times (means ± SEM, bars) spent in the initially non-preferred (white) compartment during pre-conditioning and post-conditioning (n = 6–12). $^{*}P < 0.05$; $^{***}P < 0.001$.

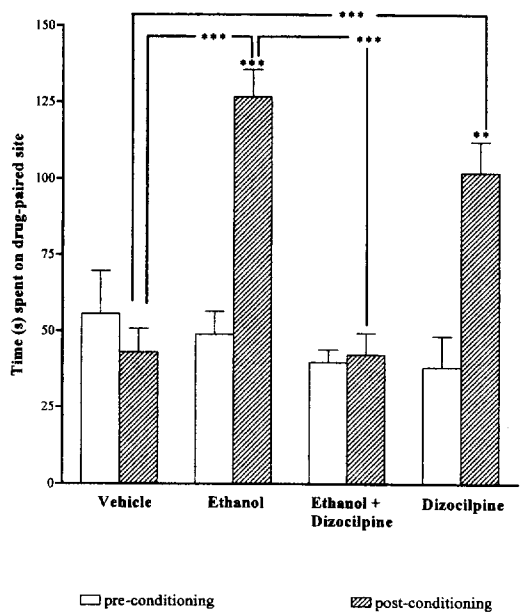

Fig. 2. Effect of dizocilpine on acquisition of the conditioned place preference induced by ethanol.

The columns show the times (means ± SEM, bars) spent in the initially non-preferred (white) compartment during pre-conditioning and post-conditioning (n = 6–12). $^{**}P < 0.01$; $^{***}P < 0.001$.

EtOH injections. These rewarding properties of EtOH depend, at least partially, on NMDA receptor activity, as we have demonstrated that two different NMDA antagonists, dizocilpine (a non-competitive antagonist) and L-701,324 (an NMDA/glycine receptor antagonist), blocked the acquisition of EtOH-induced CPP. In our study, only one dose of dizocilpine and L-701,324 was tested. In line with earlier reports, it was found that 0.1 mg/kg of dizocilpine (given i.p. 15 min prior to the behavioural recording) was the dose which produced a stable behavioural response without psychomimetic effects. Moreover, it was found that L-701,324 given at a dose of 5 mg/kg 30 min prior to the experimental session substituted for ethanol in a two-lever discrimination procedure in rats. At the doses of 2.5 mg/kg and 5 mg/kg (–30 min) L-701,324 also had some anxiolytic properties and had no influence on the locomotor activity of the animals (Kotlińska and Liliequist, 1998).

Studies on the effects of EtOH on CPP in rats have generated conflicting data. Our results are in agreement with previous findings indicating that the rewarding properties of relatively low doses of EtOH can be shown in the CPP paradigm (Reid *et al.*, 1985; Bieńkowski *et al.*, 1996*a*). It is more difficult to observe reinforcement by EtOH in naive laboratory animals than it is with other substances commonly consumed by humans. Only the prolonged treatment and pre-exposure to EtOH can reduce its ability to produce conditioned place aversion, unmasking its rewarding properties. Additionally, it has been demonstrated that multiple exposures can facilitate i.v. self-administration of EtOH in rats (Numan, 1981). In our experiments, rats after receiving a total of 15 daily injections of EtOH before the beginning of conditioning trials showed a significant preference for the EtOH-paired compartment on the test day. Earlier reports suggested a development of sensitization

to EtOH's rewarding effects after prolonged administration of small doses (Bieńkowski *et al.*, 1996*a*). As low doses of EtOH are known to increase DA release (Gessa *et al.*, 1985), it can be speculated that DA mechanisms underlie the development of this sensitization.

Overall the results suggest that NMDA receptors play an important role in the action of many psychoactive drugs. It has previously been reported that the NMDA/glycine receptor antagonist R-(+)-HA-966 attenuates amphetamine-induced activation of mesocortico-limbic DA neurons (Hutson *et al.*, 1991; Bristow *et al.*, 1994). Dizocilpine, a non-competitive NMDA receptor antagonist, can attenuate the acquisition of cocaine self-administration i.e. the establishment of cocaine as a positive reinforcer (Schenk *et al.*, 1993). Dizocilpine can also prevent the development of opiate and EtOH tolerance, dependence and behavioural sensitization to psychostimulants (Trujillo and Akil, 1991; Khanna *et al.*, 1993; Wu *et al.*, 1993; Wessinger, 1994). A number of studies *in vitro* and *in vivo* have demonstrated that acute and chronic EtOH exposure can also affect central glutamate neurotransmission (Rassnick *et al.*, 1992; Diana *et al.*, 1993). In a drug discrimination procedure, it has been shown that the competitive NMDA receptor antagonist CGP 40116 and the D-stereoisomer of CGP 37849 completely substituted for EtOH and caused only moderate suppression of the response rate. In this procedure, dizocilpine substituted partially for EtOH at doses that also reduced the rate of responding (Bieńkowski *et al.*, 1996*b*). In the generalization tests, the non-competitive NMDA antagonists acting at the ion channel (dizocilpine, memantine and phencyclidine) dose-dependently generalized for EtOH (Hundt *et al.*, 1998). It has also been demonstrated that NMDA receptors could play a role in EtOH withdrawal (Rossetti and Carboni, 1995). Using microdialysis in the striatum of EtOH-dependent rats, elevated extraneuronal glutamate output has been shown within 12 h from withdrawal. These findings can reflect the hyperactivity of excitatory amino acid neurotransmission during EtOH withdrawal (Rossetti and Carboni, 1995). Non-competitive NMDA receptor antagonists reduced both the physical signs of withdrawal and glutamate output (Valverius *et al.*, 1990). Some of these responses of brain neurons in animals chronically exposed to EtOH may include the development of increased numbers or enhanced sensitivity of glutamate receptors (i.e. up-regulation).

In the present experiments, EtOH-induced CPP was significantly altered by pretreatment with dizocilpine and this effect may also suggest a possible involvement of NMDA receptors in the mechanism of action of EtOH. Previously, it has been shown that these receptors play an important role in the acquisition of a number of learned behaviours (Morris, 1989; Malenfant *et al.*, 1991; Maurice *et al.*, 1994). Dizocilpine binds with high affinity to the phencyclidine (PCP) binding site located inside the ion channel associated with the NMDA type of glutamate receptor. Dizocilpine can act as the non-competitive antagonist of NMDA receptor by binding to this PCP receptor and blocking the NMDA receptor-gated ion channel. After systemic injection, dizocilpine stimulates locomotor activity and increases the firing of DA neurons (Löscher *et al.*, 1991; French *et al.*, 1993; Layer *et al.*, 1993). Like dizocilpine, other non-competitive NMDA antagonists can activate DA systems by increasing synthesis, release and metabolism of DA in various brain areas, predominantly in the nucleus accumbens, striatum and prefrontal cortex (French and Ceci, 1989; Bubster *et al.*, 1992). It should be emphasized that this effect is not a general characteristic of all NMDA receptor antagonists. It has been shown that dizocilpine facilitates intracranial self-stimulating reward and is self-administered in rhesus monkeys, so it might also be rewarding and have some abuse potential (Corbett, 1989; Herberg and Rose, 1989; Beardsley *et al.*, 1990; Wessinger, 1994). In our study, dizocilpine produced a significant preference for the drug-paired compartment and this finding is consistent with previous results demonstrating a marked place conditioning effect of dizocilpine in rats (Layer *et al.*, 1993; Papp *et al.*, 1996). We failed to show an additive effect of dizocilpine and EtOH despite similar increases in preference for drug-paired place. On the contrary, dizocilpine blocked the rewarding properties of EtOH. It may be suggested that dizocilpine-induced reinforcing properties measured in the CPP paradigm do not seem to be strictly dependent on ion channel blockade within the NMDA receptor.

In the second part of our study, we examined the effect of L-701,324, which acts as an antagonist at the strychnine-insensitive glycine site on the NMDA receptor complex. Glycine may act as

co-agonist at the NMDA receptor and is necessary for channel opening, so that it can be speculated that a blockade of NMDA/glycine-sensitive sites results in inhibition of NMDA receptor activity. We have demonstrated that, like dizocilpine, L-701,324 can prevent the acquisition of the EtOH-induced CPP, but this effect is less significant. So it is possible that EtOH can exercise at least some of its reinforcing effects by acting at the NMDA/glycine co-agonist site. Many other behavioural studies have shown that glycine-sensitive NMDA co-agonist sites may be involved in both the acute and chronic actions of EtOH. For example, L-701,324 was able to fully substitute for the discriminative stimulus effects of EtOH (Kotlińska and Liljequist, 1997). Furthermore, D-cycloserine, a partial glycine receptor agonist, enhances the development of rapid tolerance to EtOH (Khana *et al.*, 1995). In addition, we have demonstrated that L-701,324 alone did not change the time spent by rats in the drug-paired compartment, so, unlike dizocilpine, L-701,324 seems to be devoid of intrinsic rewarding properties in animals. In contrast to many other currently available NMDA receptor antagonists, L-701,324 does not modulate the spontaneous activity of DA neurons and it does not produce psychomimetic or sedative side-effects. Moreover, some recent reports even indicate that L-701,324 can inhibit amphetamine-induced locomotor stimulation in rats and this suggests its antagonistic influence on DA neurotransmission in brain (Bristow *et al.*, 1996). Recently, it has been demonstrated that oral administration of L-701,324, at doses which do not alter the locomotor activity of rats, blocked EtOH withdrawal-induced audiogenic seizures (Kotlińska and Liljequist, 1996) so that systemically active glycine receptor antagonists may be useful in the treatment of the EtOH withdrawal syndrome in man. In addition to the treatment of EtOH withdrawal syndrome, the NMDA receptor antagonists of various NMDA receptor sites could also be useful to block the alteration of NMDA receptor activity induced by chronic exposure to EtOH, i.e. in the development of EtOH dependence.

It should be noted that, in our experiments, we used a biased CPP procedure in which the natural preference of rats was relatively strong for one side of the chamber. Possible involvement of the anxiolytic properties of all the compounds used cannot be excluded. However, L-701,324 which has been reported to have some anxiolytic activity in the Vogel's test did not induce conditioned place preference when given alone. The present data would also indicate that NMDA/glycine receptor antagonists might have advantages in terms of therapeutic safety, compared to the non-competitive NMDA antagonists.

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