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The NMDA/glycine receptor antagonist, L-701,324, produces discriminative stimuli similar to those of ethanol

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Abstract

The ethanol-like discriminative stimulus properties of a novel NMDA glycine receptor antagonist, L-701,324 ((7-chloro-4-hydroxy-3-(3-phenoxy)phenyl-2-(1H)-quinolone), a polyamine receptor antagonist, eliprodil, and a non-competitive NMDA receptor antagonist, MK-801 (dizocilpine), were examined in rats trained to discriminate ethanol from vehicle in a two-lever discrimination procedure. In rats trained to discriminate ethanol from vehicle, L-701,324 and MK-801 substituted for ethanol in a dose-dependent fashion with a complete substitution noted following administration of 7.5 mg/kg L-701,324 and 0.2 mg/kg MK-801, respectively. Full substitution for ethanol was achieved with no alteration in the rate of responding. In contrast, administration of eliprodil (in doses up to 5 mg/kg) showed only a partial, but not dose-dependent, substitution for ethanol. These findings indicate that a reduction of NMDA receptor activity, produced either via a blockade of non-competitive NMDA recognition sites or of NMDA/glycine-sensitive regulatory sites, had discriminative stimulus properties that are similar to those produced by ethanol. Furthermore, the observation that the NMDA/glycine receptor antagonist, L-701,324, was a more effective substitute for ethanol than was the polyamine antagonist, eliprodil, suggests that several NMDA receptor subunits, and thus not only NMDAR2B receptor subunits, are of importance for the discriminative stimulus effects of ethanol. © 1997 Elsevier Science B.V.

Keywords: Ethanol; NMDA/glycine receptor; L-701,324; MK-801; Eliprodil; Drug discrimination; (Rat)

1. Introduction

Much evidence has accumulated to suggest that acute administration of ethanol blocks glutamate receptor activity in the brain. The ethanol-induced reduction of glutamatergic activity appears to be largely mediated through a blockade of glutamate receptors of the *N*-methyl-D-aspartate (NMDA) subtype whereas non-NMDA receptors are reported to be less sensitive to ethanol. Electrophysiological and biochemical studies have shown that ethanol reduces NMDA-induced current in hippocampal neurons, and blocks NMDA-produced stimulation of functional Ca^{2+} responses, intracellular enzyme activity, and neurotoxicity (for references, see Hoffman, 1995; Cebers et al., 1996). In behavioral studies, acutely given ethanol blocks NMDA-convulsions and potentiates the locomotor and/or sedative effects caused by both competitive and non-competitive NMDA receptor antagonists (Kulkarni et al., 1990; Liljequist, 1991a; Robledo et al., 1991; Kuribara, 1994).

While the inhibitory effects of ethanol on various NMDA-induced functional responses have been demonstrated, far less is known about the exact mechanism by which ethanol decreases the activity of NMDA/glutamate receptors. Results from receptor binding studies indicate that ethanol does not directly influence the binding properties of various glutamate receptor agonists or glutamate receptor modulatory agents to their recognition sites (Snell et al., 1993), but some reports suggest that ethanol may alter the kinetics of non-competitive NMDA receptor ligand binding (Snell et al., 1993; Spuhler-Phillips et al., 1995; Michaelis et al., 1996). NMDA/glycine-sensitive sites in the glutamate receptor system may also be involved since application of increasing concentrations of glycine reverses the effects of ethanol (Rabe and Tabakoff, 1990; Woodward and Gonzales, 1990; Dildy-Mayfield and Leslie, 1991; Buller et al., 1995). However, other studies have failed to confirm the existence of a glycine-induced reversal of the inhibitory actions of ethanol (Peoples and Weight, 1992; Woodward, 1994; Chu et al., 1995; Mirshahi and Woodward, 1995; Cebers et al., 1996).

Abundant evidence, obtained in vitro, indicates that

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glycine is a necessary co-agonist for the activation of NMDA receptor-operated ion channels (Johnson and Ascher, 1987; Thomson, 1989). Furthermore, in analogy to the findings obtained with specific NMDA receptor antagonists it has been shown that a blockade of NMDA/glycine-sensitive recognition sites results in inhibition of NMDA receptor activity (Kemp and Leeson, 1993). These observations and the fact that many competitive and non-competitive NMDA receptor antagonists produce various degrees of unwanted, psychotomimetic side effects in vivo in both experimental animals and humans (e.g., Tricklebank et al., 1989; Liljequist, 1991b; Javitt and Zukin, 1991), have prompted vigorous attempts to develop systemically active NMDA/glycine receptor antagonists which are expected to be essentially devoid of psychotomimetic side effects. For example, compounds like 4-hydroxy-2-quinolones and quinoxalinediones represent classes of newly synthetized, systemically active, NMDA/glycine receptor antagonists (Leeson and Iversen, 1994; Nagata et al., 1994; Keana et al., 1995) which have been shown to possess neuroprotective and anxiolytic properties similar to those noted following in vivo administration of traditional NMDA receptor blocking agents (Kulagowski et al., 1994; Priestley et al., 1994; Gill et al., 1995; Tsuchida and Bullock, 1995; Warner et al., 1995 Wiley et al., 1995). Moreover, the NMDA/glycine receptor antagonist used in the present study, L-701,324 (7-chloro-4-hydroxy-3-(3-phenoxy)phenyl-2-(1H)-quinolone, also inhibits K^+-induced spreading depression in vivo (Obrenovitch and Zilkha, 1996) and reduces behavioral stimulation produced by various psychostimulant drugs (Bristow et al., 1994). Furthermore, we have recently demonstrated that oral administration of L-701,324 antagonizes ethanol-induced withdrawal seizures in rats (Kotlinska and Liljequist, 1996).

The activity of NMDA receptors is modulated not only via NMDA/glycine-sensitive recognition sites, but also through recognition sites activated by polyamines (see, e.g., Scatton et al., 1994). Available evidence suggests that polyamines enhance the activity of NMDA receptors via preferential stimulation of certain NMDA receptor subsites, whereas a blockade of NMDAR2B receptor sites by the polyamine antagonists, ifenprodil and eliprodil, respectively, reduces NMDA receptor activity. Furthermore, in analogy to the findings with NMDA and NMDA/glycine receptor antagonists, several polyamine antagonists possess anticonvulsant and neuroprotective properties (for references, see Scatton et al., 1994). There are only a few studies on the involvement of NMDA/polyamine-sites in the effects of ethanol, but some recent reports indicate that ethanol inhibition of NMDA receptors may be at least partially mediated through NMDAR2B subunits (Lovinger, 1995; Fink and Göthert, 1996). Ethanol has also been shown to inhibit the enhancement of NMDA-induced seizures and c-*fos* expression induced by the polyamine agonist, spermidine (Matsumoto et al., 1993). Administration of another polyamine antagonist similar to ifenprodil, eliprodil, attenuates withdrawal seizures in rats chronically treated with ethanol (Kotlinska and Liljequist, 1996) but does not show any stimulus generalization to ethanol in drug discrimination tests (Sanger, 1993).

Although the molecular mechanisms responsible for the ethanol-induced inhibition of NMDA receptor activity remain to be clarified, results from studies using drug discriminative assays indicate that both competitive and non-competitive NMDA receptor antagonists are able to partially or fully substitute for the discriminative properties of ethanol (Grant et al., 1991; Sanger, 1993; Schechter et al., 1993; Shelton and Balster, 1994; Koek et al., 1995; Bienkowski et al., 1996). In the current series of investigations we, therefore, attempted to test the hypothesis that antagonism of NMDA receptor activity produced via a blockade of either glycine- or polyamine-sensitive regulatory NMDA sites, induced by in vivo administration of either the novel NMDA/glycine receptor antagonist, L-701,324, or the polyamine antagonist, eliprodil, will produce discriminative stimulus effects similar to those of ethanol.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats (weighing 320–340 g) were purchased from B&K Universal (Sollentuna, Sweden). Upon arrival the animals were housed in plastic cages in groups of five rats per cage at the animal facilities of the Department of Physiology and Pharmacology at the Karolinska Institute. The animals were allowed 7–10 days to adapt after which time they were housed individually, their food intake was limited to maintain the weight of the animals at approximately 85% of their free-feeding weight before the start of the discriminative training procedures. Throughout, the animals were kept under conditions of constant temperature (25°C) and humidity (about 40%), and on a controlled light–dark cycle (light between 7 a.m. and 7 p.m.). They had continuous access to water (except during discriminative behavior sessions). Their daily food intake (about 15 g) was supplied individually immediately following the completion of the experimental sessions. The investigations were started following approval from the Ethical Committee for the use of Animal Subjects at the Karolinska Institute in Stockholm and were performed in compliance with the current Swedish guidelines for care and use of experimental animals.

2.2. Apparatus

Discriminative training and experimental sessions were held in a separate room equipped with four standard two-lever operant conditioning chambers (MED Associ-

ates, East Fairfield, VT, USA). The chambers were individually housed in a sound-attenuating and ventilated cubicle. Experimental sessions were programmed and data were collected via a 16 port Interface Card for PC computers and specially designed software (MED-PC, version 2) with some modifications. Appropriate lever presses resulted in delivery of a 45 mg food pellet (BioServe, Frenchtown, NJ, USA) into a trough located equidistant between the two levers. The chambers were illuminated by an 8 W house light placed 20 cm above the floor, opposite to the wall with the levers.

2.3. Behavioral procedures

2.3.1. Discriminative training

Pre-training procedures were adapted from the training protocols previously described (Hiltunen and Järbe, 1986; Shelton and Balster, 1994) with some minor modifications. Training sessions were started after the adaptation period (see above). The animals were first randomly placed in an operant conditioning chamber overnight on a fixed-ratio 1 (FR 1) schedule for food pellet delivery. This session was then followed by daily FR 1 training sessions which were continued until the animals displayed reliable responding on both levers. The required FR response for food delivery was then gradually increased from 1 to 10 lever presses (FR 10). The duration of each training session was 15 min. After stabilization of the FR 10 performance, the animals were given either saline or ethanol (1 g/kg; 15% w/v) per os 30 min prior to the training session. The 1 g/kg ethanol dose was chosen as the most effective based upon a series of preliminary investigations when various doses of ethanol were tested (0.5, 0.75, 1.0, 1.25, 1.5 and 2 g/kg). Responding on the 'drug/ethanol lever' (DL) was reinforced following ethanol administration, whereas responding on the 'saline lever' (SL) was reinforced following the injection of saline. Daily training sessions were carried out Monday through Friday according to a double (monthly) alternating schedule (see Koek et al., 1995). Discrimination training was continued until the animals achieved at least 85% correct responses during three consecutive trial sessions before the generalization tests were introduced.

2.3.2. Generalization testing

Drug generalization testing procedures were similar to those described by Willetts and Balster (1989) with some modifications. Drug discrimination tests were performed on Tuesdays and Thursdays, providing that the animals had made the first FR on the correct lever during the two preceding training sessions and that they had maintained 90% correct lever pressing during the two preceding training sessions. If the animal failed to meet these criteria additional training was given until the animal again fulfilled the originally stated requirements. The double alternating sequence of training sessions was continued between the generalization testing sessions. All drugs were administered in increasing doses, one dose per test session in order to establish a dose–response curve for the drugs. The stimulus generalization tests were done with six animals per drug dose and the same animals were used for determining the complete dose range of a given drug. The following drugs were tested in the order given below and with the following doses: ethanol (0.1, 0.2, 0.5, 0.75, 1.0, and 1.5 g/kg, $n = 12$), MK-801 (0.03, 0.05, 0.1, and 0.2 mg/kg, $n = 6$), L-701,324 (1.0, 2.5, 3.25, 4.0, 5.0, and 7.5 mg/kg, $n = 6$), and eliprodil 1.0, 2.0, 4.0, and 5.0 mg/kg, $n = 6$). The drug testing sessions were followed by a re-determination of the ethanol dose–response curve (see above) in order to confirm that the experimental drugs did not alter the discriminative stimulus properties of ethanol. Saline control test sessions were always run prior to the initiation of each dose–response curve.

2.4. Data analysis

The data, expressed as percentage (±S.E.M.) of responses on the ethanol-appropriate lever during the entire 15 min test session, were used to determine the ability of the test drugs to substitute for ethanol (1 g/kg; i.p.). Animals which had a response rate less than 0.05 lever presses/s were not included in the analysis. All responses on both levers (responses/s) were used to calculate drug-induced changes in the rate of responding. ED_{50} values were calculated for drugs which caused more than 50% substitution on the ethanol-appropriate drug lever. The ED_{50} values were calculated using least-square linear regression on the linear portions of the dose–effect curves. Incomplete dose–effect curves were not included in the analysis. A two-sample paired *t*-test was used to compare rates of responding.

2.5. Drugs

The compounds tested in this study were L-701,324 (7-chloro-4-hydroxy-3-(3-phenoxy)phenyl-2(1H)-quinolone sodium salt) and dizocilpine (MK-801) which both were a generous gift from Merck Sharp and Dohme (Harlow, UK), eliprodil (a generous gift from Synthélabo Recherche, Bagneux, France). Ethanol (95% v/v) was purchased from Kemila (Stockholm, Sweden) and diluted in saline to 15% (w/v). L-701,324 was administered per os as a suspension prepared using a 0.5% solution of methyl cellulose. MK-801 was dissolved in slightly warmed saline whereas eliprodil was prepared as a suspension consisting of a few drops of Tween 80 and distilled water. MK-801 and eliprodil were administered intraperitoneally (i.p.).

3. Results

An initial series of experiments was done to obtain the dose–response curve for the discriminative properties of ethanol (also see Section 2). Since the dose–response

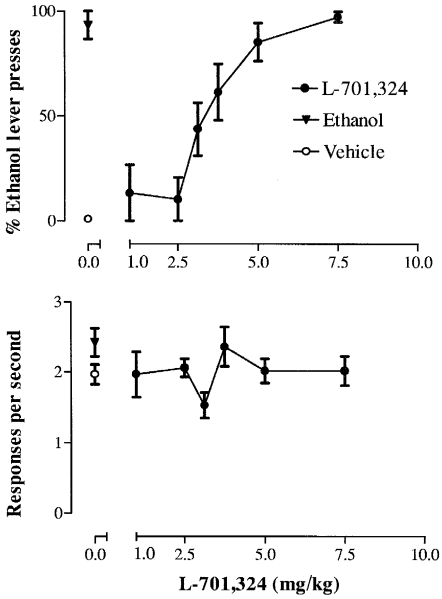

Fig. 1. Effects of oral administration of increasing doses of the glycine/NMDA receptor antagonist, L-701,324, in rats trained to discriminate ethanol (1 g/kg, p.o.) from drug vehicle. Data represent the percentage of rats ($n = 6$) responding on the ethanol- appropriate lever (upper panel). The lower panel shows the response rates as presses/s (means ± S.E.M.).

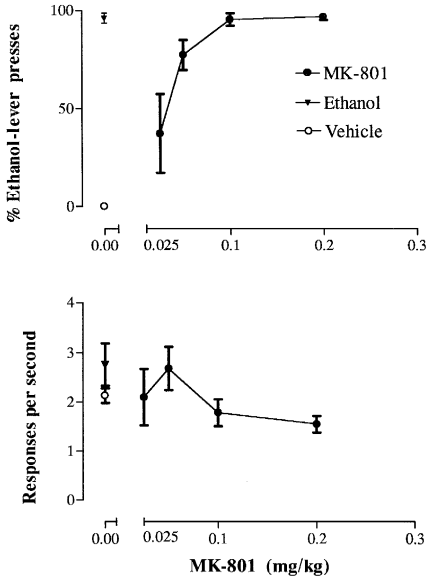

Fig. 2. Effects of increasing doses of the non-competitive NMDA receptor antagonist, MK-801 (−15 min, i.p.), in rats trained to discriminate ethanol (1 g/kg, i.p.) from saline. Data represent the percentage of rats ($n = 6$) responding on the ethanol-appropriate lever (upper panel). The lower panel shows the response rates as presses/s (means ± S.E.M.).

curve for ethanol was very similar to that observed by others (Grant et al., 1991; Grant and Colombo, 1993; Shelton and Balster, 1994), the data are not depicted here. However, in line with earlier reports, it was found that 1 g/kg of ethanol (−15 min; i.p.) was the lowest dose of ethanol which produced a stable discriminative response and that the performance on the ethanol appropriate lever was not further improved following the administration of a higher dose of ethanol (that is up to 2 g/kg).

Fig. 1 shows that oral administration of increasing doses of the specific NMDA/glycine receptor antagonist, L-701,324 (given 30 min prior to the experimental session), dose-dependently increased the amount of responding on the ethanol-appropriate lever in rats trained on 1 g/kg ethanol. The ED_{50} value for substitution for L-701,324 was 3.75 mg/kg and full substitution was reached following oral administration of a dose of 7.5 mg/kg L-701,324. As shown in the lower panel, this dose of L-701,324 did not alter the rate of responding.

Fig. 2 shows that the non-competitive NMDA receptor antagonist, dizocilpine (MK-801; given i.p., 15 min prior to the behavioral recordings), also produced dose-dependent generalization of lever pressing to the ethanol-appropriate lever. The ED_{50} value for substitution for MK-801 was 0.04 mg/kg and full substitution for ethanol was achieved at 0.1 mg/kg of MK-801 which produced a slight, but not significant decrease in the response rate (see lower panel of Fig. 2).

Fig. 3 shows that the polyamine antagonist, eliprodil (−30 min; i.p.), caused only a partial, and not dose-dependent, substitution for ethanol, at all doses tested. Higher doses of eliprodil (> 10 mg/kg) were not used since we had found that they reduce locomotor activity in Sprague–Dawley rats (Kotlinska and Liljequist, 1996).

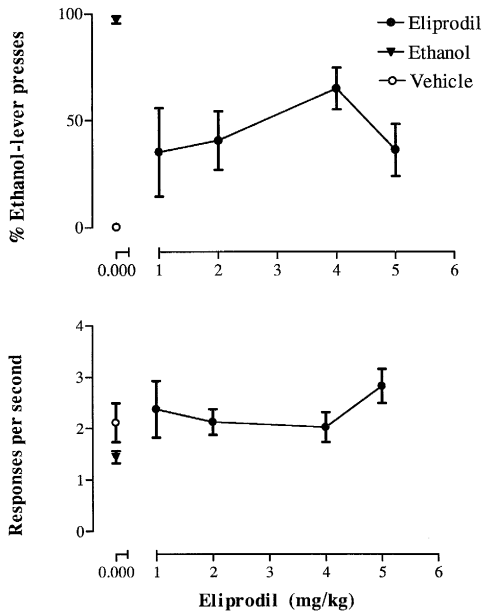

Fig. 3. Effects of increasing doses of the polyamine antagonist, eliprodil (−30 min, i.p.), in rats trained to discriminate ethanol (1 g/kg, i.p.) from drug vehicle. Data represent the percentage of rats ($n = 6$) responding on the ethanol-appropriate lever (upper panel). The lower panel shows the response rates as presses/s (means ± S.E.M.).

4. Discussion

To our knowledge this is the first demonstration to suggest that a systemically administered specific NMDA/glycine receptor antagonist, L-701,324, is able to produce discriminative stimulus effects similar to those of ethanol. Furthermore, we confirmed earlier observations showing that non-competitive NMDA receptor antagonists, such as MK-801, have ethanol-like discriminative properties whereas polyamine antagonists, represented in this study by eliprodil, apparently do not share these effects to the same extent.

In previous drug discrimination studies, non-competitive NMDA receptor antagonists were found to fully substitute for the discriminative stimulus effects of ethanol, whereas competitive NMDA receptor antagonists caused only a partial substitution (Grant et al., 1991; Sanger, 1993; Shelton and Balster, 1994). Those findings have been interpreted to mean that blockade of non-competitive rather than of competitive NMDA receptor sites is involved in the discriminative properties of ethanol (Grant and Colombo, 1993; Shelton and Balster, 1994). Another implication of the same data is that discriminative stimuli effects, caused by a functional reduction of NMDA receptor activity, are experienced as qualitatively different depending on through which subset(s) of NMDA recognition sites the blockade of NMDA channel activity is achieved (Jackson and Sanger, 1988; Willetts and Balster, 1989; Zajaczkowski et al., 1996). However, other observations suggest that both non-competitive and competitive NMDA receptor antagonists are able to substitute for each other as well as for ethanol (Koek et al., 1986; Tricklebank et al., 1987; Bienkowski et al., 1996). Moreover, we now show that the novel NMDA/glycine receptor antagonist, L-701,324, which also blocks functional NMDA receptor responses (see Section 1), is able to fully substitute for the discriminative stimulus effects of ethanol. Together, these findings suggest either that reduction of NMDA receptor activity through various NMDA receptor regulatory sites may generate an array of biochemical changes typically associated with the discriminative stimulus properties of ethanol or, alternatively, that each of the various NMDA/glycine receptor antagonists produces its own unique range of discriminative stimuli also shared by ethanol. Very little is known about the biochemical effects associated with the discriminative stimulus effects of NMDA receptor antagonists and ethanol, respectively. Although the proposal that the stimulus properties of these agents may be determined by the occupation of particular NMDA receptor subsites appears attractive (for Refs., see above), recent data suggest that the situation may be more complicated. Thus it has been demonstrated that ligands which are considered to be full agonists at, e.g., competitive NMDA receptor sites and or NMDA/glycine-sensitive recognition sites in receptor binding assays produce different patterns of allosteric modulations of the NMDA/glutamate receptor complex (see, e.g., Grimwood et al., 1995). Even compounds regarded as specific NMDA/glycine site antagonists exert differential effects on the NMDA receptor complex (e.g., Molnár and Erdo, 1996). Consequently it is suggested that many drug-induced allosteric alterations are determined, not only by which specific set(s) of recognition sites they occupy, but also by some unique features related to the chemical structure of the compound itself. Whether, and to which extent, differential allosteric alterations are accompanied by specific biochemical changes of importance for the discriminative stimulus properties of NMDA receptor antagonists and/or ethanol is not known and needs further study. Furthermore, it should be pointed out that both ethanol and NMDA receptor antagonists exert a variety of effects on many other neurotransmitter systems in the brain (for review, see, e.g., Nevo and Hamon, 1995) which all may contribute to their discriminative stimulus effects and to the degree of stimulus generalization between the various compounds (Gatto et al., 1995).

In our experiments both L-701,324 and MK-801 were able to fully substitute for the discriminative stimulus effects of ethanol without producing a significant reduction in the rate of responding. Our data for MK-801 thus being at variance with results from earlier studies where full substitution for ethanol was seen only at doses of MK-801 that also reduced the rate of responding (e.g., Grant et al., 1991; Shelton and Balster, 1994). A decreased rate of responding was also found in experiments concerning stimulus generalization between ethanol and competitive NMDA receptor antagonists (Bienkowski et al., 1996). We do not yet have a clear explanation for this discrepancy. One suggestion is that genetically determined variations in the pharmacological effects of NMDA receptor antagonists may have contributed to the divergent results (Liljequist, 1991b; Xu and Domino, 1994; Sauter and Rudin, 1995). Another possibility is that a differential development of drug sensitization and/or tolerance to the stimulatory/sedative actions of NMDA receptor antagonists, caused by repeated, intermittent administration of test drugs, could have influenced the behavioral performance of the animals. Differences in training procedures are also known to modulate the discriminative stimulus effects of ethanol (Grant and Colombo, 1993). These factors, however, may not have been relevant for the results obtained with the NMDA/glycine receptor antagonist L-701,324 since this compound has a clearly different pharmacological profile, characterized by its lack of psychotomimetic and sedative side effects (Kotlinska and Liljequist, 1996), compared to many classical NMDA receptor antagonists.

Our current data suggest that modulation of NMDA/glycine-sensitive recognition sites may be involved in the pharmacological actions of ethanol. Previously, Rabe and Tabakoff (1990) as well as Dildy-Mayfield and Leslie (1991 found that the inhibitory actions of

ethanol on NMDA-induced Ca^{2+} fluxes could be antagonized by increasing concentrations of glycine in cerebellar granule cells, whereas Woodward and Gonzales (1990) reported that glycine inhibited the NMDA-evoked release of dopamine in rat striatal brain slices. More recently Buller et al. (1995) presented evidence that both glycine-reversible and glycine-independent mechanisms might be involved. In contrast, other investigators have failed to confirm the involvement of glycine in the ethanol-induced inhibition of NMDA receptor activity either in brain neurons or in recombinant receptor systems (Peoples and Weight, 1992; Woodward, 1994; Chu et al., 1995; Mirshahi and Woodward, 1995; Cebers et al., 1996). Thus it seems that the role of glycine in the inhibitory actions of ethanol on NMDA receptors, at least with regard to findings obtained in various in vitro testing systems, will require further examination. Furthermore, experimental findings from in vitro assays may not necessarily be of immediate relevance for the way in which glycine modulates NMDA-sensitive mechanisms in vivo. Based upon the knowledge that the endogenous concentrations of glycine in cerebrospinal fluid (CSF) is estimated to about 10 μM, it is often assumed that this concentration of glycine always saturates all glycine-sensitive NMDA recognition sites in vivo. However, this assumption may not be consistently valid and has therefore been challenged recently (Wood, 1995). To our knowledge there are no studies available which provide direct evidence for an interaction between NMDA/glycine sites and ethanol under in vivo conditions. Nevertheless, results of some recent studies suggest that the activity of glycine-sensitive NMDA receptors may be involved both in both the acute and the chronic effects of ethanol. For example, D-cycloserine, a partial glycine receptor agonist at the NMDA receptor, enhances the development of rapid tolerance to ethanol (Khanna et al., 1995). Furthermore it was shown in this laboratory that oral administration of L-701,324 attenuates withdrawal seizures induced by cessation of chronic ethanol administration (Kotlinska and Liljequist, 1996). Together with our present findings that L-701,324 possesses discriminative stimulus properties similar to those of ethanol, these observations support the working hypothesis that NMDA/glycine-sensitive sites might be influenced by acute and/or chronic ethanol administration in vivo and that systemically administered NMDA/glycine receptor antagonists can be used for the manipulation of ethanol-induced alterations of NMDA receptor activity in the brain.

Our current data indicating that the polyamine antagonist, eliprodil, can substitute only partially for the discriminative stimulus effects of ethanol are in accordance with previous findings obtained by Sanger (1993). In the present study we investigated the effects of eliprodil only at doses up to 5 mg/kg since higher doses had been found to decrease the locomotor activity of the animals (Kotlinska and Liljequist, 1996). It could, however, be argued that the effects of eliprodil may have been attenuated due to cross tolerance to ethanol. However, this appears less likely since Sanger tested the effects of eliprodil at doses up to 40 mg/kg (i.p.). Another possibility for the partial substitution could be that eliprodil, in contrast to ethanol, was administered i.p., although this treatment route apparently did not influence the discriminative stimulus properties of MK-801. As pointed out in Section 1, recent data suggest that some of the pharmacological actions of ethanol may be at least partially mediated through NMDAR2B, polyamine-sensitive, recognition sites. Although we have previously demonstrated that seizures induced by withdrawal of chronic ethanol treatment can be blocked by eliprodil (Kotlinska and Liljequist, 1996), our current observations only partially support the working hypothesis that NMDAR2B subunits play a preferential role in the discriminative stimulus effects of ethanol. This idea is further substantiated by a recent report showing that L-701,324 does not differ in its affinity for recombinant receptor complexes composed of NMDAR1a/NMDAR2A and NMDAR1b/NMDAR2B subunits, respectively (Priestley et al., 1996).

In summary, our current results demonstrate that systemic administration of NMDA/glycine (i.e., L-701,324) or classical NMDA (i.e., MK-801) receptor antagonists produces discriminative stimulus effects similar to those of ethanol, indicating that a reduction of NMDA receptor activity caused by a blockade of various NMDA receptor sites is involved in the pharmacological actions of ethanol. However, the observation that inhibition of a specific subset of NMDA receptor sites, the NMDAR2B receptor sites, produces only partial stimulus generalization to ethanol suggests that some, but not all, NMDA receptor subsites can fully substitute for the discriminative stimulus effects of ethanol. Additional studies are underway to analyze further the interaction between ethanol and various subtypes of NMDA receptors.

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