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Ifenprodil influences changes in mouse behaviour related to acute and chronic ethanol administration

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Abstract

The aim of the present study was to examine the influence of ifenprodil (a non-competitive NMDA receptor antagonist which also blocks 5-HT_3 receptors and α_1-adrenoceptors) on the effects of ethanol in the mouse in vivo and to elucidate the role of various receptors in these actions. The ethanol (4 g/kg i.p.)-induced sleeping time was shortened by ifenprodil 1 mg/kg but was not affected by ifenprodil 0.3 mg/kg, the 5-HT_3 receptor antagonist ondansetron 0.03 mg/kg and the non-competitive NMDA receptor antagonist MK-801 ((+)-5-methyl-10,11-dihydro-5*H*-dibenzo(*a*,*d*)cycloheptan-5,10-imine maleate) 0.01 mg/kg. Ifenprodil 10 mg/kg mimicked the α_1-adrenoceptor antagonist prazosin 1 mg/kg in that it prolonged the hypnotic response to ethanol (no additive effect when both drugs were given in combination); this is compatible with an involvement of α_1-adrenoceptors in this effect of ifenprodil. Chronic exposure to ethanol (7%) induced physical dependence. The severity of ethanol withdrawal was suppressed by ifenprodil 1 and 10 mg/kg. In conclusion, ifenprodil influences ethanol-related changes in mouse behaviour and may prove to be useful in the treatment of alcoholism.

Keywords: Ethanol; Ifenprodil; Ethanol withdrawal; Behavioral sleep; NMDA receptor; 5-HT_3 receptor

1. Introduction

The mechanisms of the depressant action of ethanol on the central nervous system (CNS) are still not completely understood. In recent years, electrophysiological, neurochemical and behavioral studies provided increasing evidence that several ligand-gated ion channels are especially sensitive to ethanol at concentrations compatible with social drinking. These ethanol-sensitive ion channels include NMDA receptors and 5-HT_3 receptors (for review, see Kostowski, 1996; Hoffman and Tabakoff, 1996; Lovinger, 1997).

Ethanol, when administered acutely, inhibits NMDA-induced ion currents in vitro (Lovinger et al., 1989) and in vivo (Simson et al., 1991), Ca^{2+} influx, cyclic GMP production (Hoffman et al., 1989), neurotransmitter release (Göthert and Fink, 1989) and reduces NMDA-evoked neurotoxity (Chandler et al., 1993). In contrast, chronic exposure to ethanol enhances NMDA receptor function (Iorio et al., 1993) by an increase in the number of NMDA binding sites (Grant et al., 1990) and therefore potentiates NMDA-induced neurotoxicity (Chandler et al., 1993; Iorio et al., 1993). Consequently, NMDA receptor antagonists [e.g., MK-801 ((+)-5-methyl-10,11-dihydro-5*H*-dibenzo(*a*,*d*) cycloheptan-5,10-imine maleate) and CGP 39551 [D,L-(*E*)-2-amino-4 methyl-5-phosphonopentoate carboxy-ethylester)] decrease the severity of ethanol withdrawal reaction (Grant et al., 1990; Liljequist, 1991; Danysz et al., 1992).

In contrast to NMDA receptors, ethanol potentiates the action of serotonin (5-hydroxytryptamine; 5-HT) at central 5-HT_3 receptors. Thus, Lovinger and White (1991) and Barann et al. (1995) reported a facilitatory effect of ethanol

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on responses mediated via 5-HT_3 receptors in isolated adult mammalian neurons and on N1E-115 neuroblastoma cells, respectively. A number of behavioral studies revealed that various 5-HT_3 receptor antagonists [e.g., ondansetron, ICS 205-930 (tropisetron), MDL 72222 (tropanserin) or zacopride)] reduce ethanol consumption and/or preference in humans (Sellers et al., 1997) and rats (Kostowski et al., 1993) and are able to modify the intensity of withdrawal seizures in rats withdrawn from ethanol (Costall et al., 1990; Kostowski et al., 1993; Grant et al., 1994).

Ifenprodil has been developed as a cerebral antiischemic agent (Gotti et al., 1988). It is not only a noncompetitive antagonist at the polyamine recognition site of the NMDA-gated ion channels (Carter et al., 1989) but also blocks 5-HT_3 receptors (McCool and Lovinger, 1995; Molderings et al., 1996; Barann et al., 1998) and α_1-adrenoceptors (Gotti et al., 1988). Ifenprodil is a structurally unique modulator of the NMDA receptors which exhibits subunit-specific affinity for NMDA receptors with a high affinity for the NMDA receptor containing the NMDAR-2B subunit and a low affinity for NMDA receptors containing NMDAR-2A subunit (Williams, 1993). The NMDAR-2B subunit may be an obligatory component of an NMDA isoreceptor sensitive to ethanol. Indeed, in vitro studies of NMDA-stimulated neurotransmitter release (Fink and Göthert, 1996) and Ca^{2+} influx (Engblom et al., 1997) as well as electrophysiological experiments in vitro (Lovinger, 1995) and in vivo (Yang et al., 1996) have indicated that NMDA receptors with the highest ethanol sensitivity are also sensitive to ifenprodil. Moreover, chronic exposure of cortical slices to ethanol increased the sensitivity of neurons to low concentration of ifenprodil, suggesting an enhanced density of ifenprodil-sensitive NMDA receptors (Blevins et al., 1995). It was therefore the aim of our study to examine the influence of ifenprodil on behavioral changes related to acute and chronic ethanol administration in mice. Moreover, we decided to elucidate the role of NMDA receptors, 5-HT_3 receptors and α_1-adrenoceptors blockade in this action.

Preliminary accounts of the present results were given at congresses (Malinowska et al., 1997; Buczko et al., 1998).

2. Material and methods

2.1. Animals

All experiments were performed on male Swiss Webster mice weighing 17–32 g. The animals were allowed 1 week of acclimation upon arrival at our animal facilities. During this time they were kept under conditions of constant temperature (20–22°C) and on a controlled 12:12 h light:dark cycle. The animals had free access to standard lab chow and water.

2.2. Acute experiments

2.2.1. Ethanol-induced ''sleeping'' time

The loss of the righting reflex, measured and expressed in min, was used as index of sedation. Mice received an intraperitoneal (i.p.) injection of ethanol 4 g/kg which was administered as a 15% w/v solution and 5 min later, an i.p. injection of ifenprodil, ondansetron, MK-801, prazosin or their solvent (water). In some experiments, ethanol was injected i.p. 5 min after ifenprodil. Water-pretreated control animals were always studied simultaneously in order to eliminate day to day variation in sleeping time. The ethanol-induced sleeping time was defined as the time period between the loss and the recovery of the righting reflex (i.e., three rightings within 1 min). Some mice received water instead of ethanol in order to determine the influence of the receptor antagonists on behaviour.

2.2.2. Determination of ethanol level in blood and brain

Ethanol and ifenprodil were injected as described above. Ethanol level was determined by the method of head-space gas chromatography. Blood and brain tissues were obtained after decapitation. Mixed arterial and venous flow was collected into ice-cold plastic tubes and complemented with water 1:10 (v/v). Brains were quickly removed, weighed and homogenized in 2 ml of ice-cold 0.6 M perchloric acid. One millilitre aliquots of the homogenate or blood sample were pipetted into 2 ml flasks. Flasks were sealed and incubated at 60°C for 30 min. Subsequently, 200 μl of the headspace was chromatographed onto GC Hewlett Packard 5890 and analysed for the content of ethanol.

2.3. Chronic experiments

2.3.1. Induction of physical dependence on ethanol

For chronic ethanol treatment the mice were housed individually in cages ($15 \times 19 \times 25$). Mice were given a measured amount of liquid diet containing 7% (v/v) ethanol and vitamin supplement as their sole nutrient source. The mice were gradually introduced to the ethanol diet as follows: 1st–3rd day: 2.3%; 4th–6th day: 4.7% and from the 7th to 13th day: 7% ethanol diet, respectively. Every 24 h, the amount of diet consumed was measured and replaced with fresh ethanol-containing or control liquid diet. The pair-fed control mice were given the same volume of ethanol-free liquid diet (with sucrose substituted in isocaloric quantities for ethanol) as the ethanol-exposed mice had consumed the previous day. Every 12 h, the drinking tubes were checked for easy passage of the liquid diet. The mice were rated for signs of gross behavioral intoxication every evening. Briefly, an intoxication rating of 0 indicated normal behaviour. A rating of 1 corresponded to decreased activity and abnormal, widened gait. A rating of 2 corresponded to a pronounced decrease in activity and staggering when prodded. Finally, a rating of

3 indicated a loss of righting reflex. The same investigator rated all mice without knowledge of how much diet the animals had consumed.

2.3.2. Measurement of ethanol withdrawal reaction

Withdrawal was initiated at 8:00 a.m. of the day 14 by removing the ethanol-containing diet and replacing it with ethanol-free diet. All ethanol-exposed mice were counterbalanced into the various treatment groups on the basis of the intoxication ratings and body weight gathered over the course of the chronic ethanol treatment. Handling-induced withdrawal seizures were rated on a scale of 0 to 4, modified from a scale described previously (Ritzmann and Tabakoff, 1976). Briefly, the mice were picked up by the tail and rated as follows: 0 corresponded to little or no reaction; 1 corresponded to a mild reaction, usually limited to a slight jerkiness upon handling; 2 corresponded to an initial jerkiness escalating into a clonic–tonic seizure within 5 s; 3 corresponded to either a spontaneous seizure or an instantaneous clonic–tonic seizure upon being handled; and 4 corresponded to death as the result of a seizure. Two investigators, blind to the drug conditions, were present at every rating, although only one of the investigators rated the mice for seizure severity. The ratings took place at 2-h intervals for the first 6 h of withdrawal (2, 4 and 6 h of withdrawal), then every hour until 11 h of withdrawal had passed (7th, 8th, 9th, 10th and 11th h of withdrawal) and a final observation was made at 24 h. Ifenprodil or its solvent was administered by an i.p. injection three times during the course of withdrawal: at 0, 3 and 7 h of withdrawal.

2.4. Calculations and statistics

Results are given as mean ± S.E.M. Differences in the ratings of handling-induced convulsive behaviour for each time point were determined with a Kruskall–Wallis nonparametric ANOVA, followed by a Wilcoxon signed rank test when appropriate. Student's *t*-test for paired or unpaired data (followed by Dunnett's test when appropriate) was used in other cases for comparison of mean values. *P*-value less than 0.05 was considered statistically significant.

2.5. Drugs used

Ifenprodil, MK-801 (RBI, USA), ondansetron (Glaxo, UK), prazosin (Sigma, Germany), ethanol (98%, Polmos, Poland), control and ethanol liquid rat diets (Bio-Serv, USA). All substances were dissolved in distilled water and injected i.p. at a volume of 0.5 ml/20 g. When two antagonists were administered together, they were injected in a volume of 0.5 ml/20 g each.

3. Results

3.1. Acute experiments

3.1.1. Ethanol-induced sleeping time

Injection of ethanol (4 g/kg i.p.) to mice caused loss of the righting reflex within 2 min. The ethanol-induced sleeping time in the various control groups ranged between 30 and 45 min (Figs. 1 and 2). Ifenprodil given i.p. 5 min before ethanol at a dose of 1 mg/kg tended to diminish the hypnotic action of ethanol and at a dose of 10 mg/kg prolonged it by about 100% (Fig. 1A). The same doses of ifenprodil administered 5 min after ethanol significantly decreased and increased the ethanol-induced sleeping time by about 60% and 90%, respectively; the lower dose of 0.3 mg/kg failed to affect this parameter (Fig. 1B). Since the effects of ifenprodil were more pronounced when it was administered 5 min after ethanol, drugs under study were routinely injected at this sequence in all subsequent experiments.

The sleeping time was not changed by the 5-HT_3 receptor antagonist ondansetron 0.03 mg/kg, by the non-competitive NMDA receptor antagonist MK-801 0.01 mg/kg or by combination of both (Fig. 2A). As shown in Fig. 2B, the α_1-adrenoceptor antagonist prazosin 1 mg/kg mimicked the effect of ifenprodil 10 mg/kg in that it prolonged the duration of the sedative effect of ethanol by about 90%. The prolongation of the hypnotic effect induced by either of these substances was not potentiated when they were combined with each other. None of the compounds had behavioral actions in mice by themselves.

3.1.2. Brain and blood ethanol concentrations

As shown in Table 1, the brain and blood ethanol levels 5 min after its i.p. injection at a dose of 4 g/kg (i.e., about 3 min after the loss of the righting reflex, corresponding to the moment of administration of ifenprodil or water as its

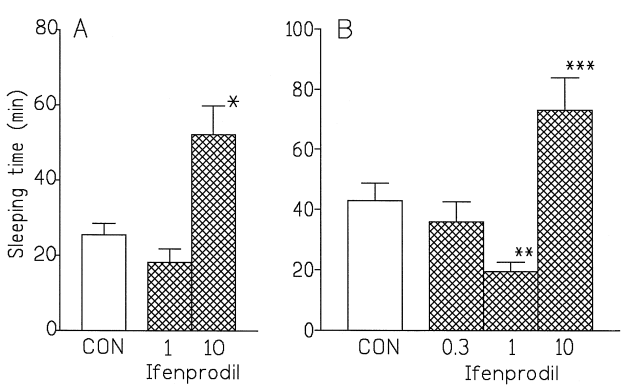

Fig. 1. Influence of ifenprodil on the ethanol-induced sleeping time in mice. Animals received ethanol (4 g/kg i.p.) 5 min after (A) or before (B) H_2O (CON; control group) or ifenprodil. Doses are given in mg/kg. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ compared to the control. Means ± S.E.M. of 5–32 animals.

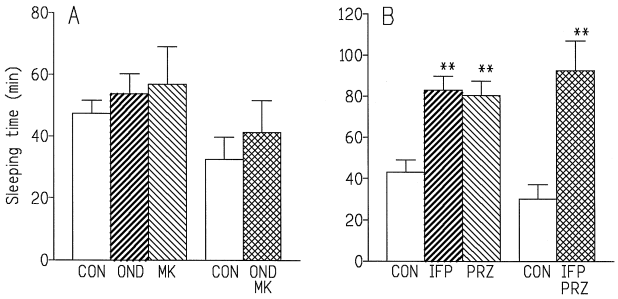

Fig. 2. Influence (A) of ondansetron (OND; 0.03 mg/kg), MK-801 (MK; 0.01 mg/kg) or a combination of OND plus MK and (B) of ifenprodil (IFP; 10 mg/kg), prazosin (PRZ; 1 mg/kg) or a combination of both on the ethanol-induced sleeping time in mice. Animals received ethanol (4 g/kg i.p.) and 5 min later H_2O (CON; control groups) or antagonists of particular receptors. Doses are given in mg/kg. $^{**}P < 0.01$ compared to the respective control. Means ± S.E.M. of 8–14 animals.

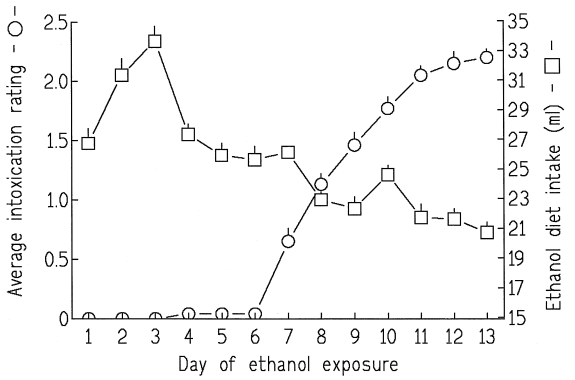

Fig. 3. Mean intoxicating ratings and ethanol diet intake during the ethanol exposure period. Mice received a liquid diet containing 2.3% ethanol for the first 3 days (1–3), then 4.6% ethanol for the next 3 days (4–6) and 7% for a further 7 days (7–13). Mean ± S.E.M. of 26 mice. See Section 2 for explanation of intoxication ratings.

solvent) amounted to 117 μmol/g and 120 μmol/ml, respectively. Thirty minutes later, i.e., at the moment of the recovery of the righting reflex (see Section 3.1.1), both the blood and the brain levels were diminished by about 30%. Ifenprodil 1 mg/kg failed to affect the ethanol concentration.

3.2. Chronic experiments

The average intoxication score and ethanol liquid diet intake during the chronic ethanol exposure were dependent on the ethanol concentration in the diet (Fig. 3). Thus, during the first 3 days when mice were offered the liquid diet containing 2.3% ethanol, they consumed an increasing amount of diet. Then, when the ethanol concentration in the diet was increased to 4.7% and 7% during the next 3 and 7 days, respectively, the ethanol diet intake decreased. The first ethanol intoxication signs were noticed on the 7th day of ethanol exposure only and, subsequently, they increased gradually (Fig. 3). On the 13th day (i.e., just before removal of ethanol) mice exhibited pronounced decrease in activity and loss of the righting reflex was also observed (intoxication ratings 2 and 3). Consumption of ethanol diet caused a significant drop in body weight (from 28.2 ± 0.4 g on the 1st day to 21.8 ± 0.4 g on the 13th day; $n = 26$; $P < 0.001$).

In mice fed with pure liquid control diet (the same volume as ethanol-exposed animals had consumed the previous day), we observed no changes in their behaviour or in body weight (30.3 ± 1.2 on the first day and 29.7 ± 0.5 g on the 13th day, $n = 11$).

After withdrawal from ethanol a rapid increase in seizure severity within the first 2 h was noticed in control mice (Fig. 4A). The most severe seizures occurred from 2 to 6 h after ethanol withdrawal. Twenty four hours after replacing ethanol-containing by ethanol-free diet, we did no longer observe any signs of withdrawal reaction. Treatment with ifenprodil 1 and 10 mg/kg (i.p. injection) decreased the severity of ethanol withdrawal seizure scores at 3–4 and 2–4 h after withdrawal, respectively (Fig. 4A). As shown in Fig. 4B ifenprodil 10 mg/kg markedly decreased the area under the 11-h seizure severity curve (seizures were monitored at 1- or 2-h intervals during this first 11-h period after withdrawal).

The mice fed with the control diet were divided into three groups and i.p. injections of water (the solvent of ifenprodil; control; $n = 3$) or ifenprodil [1 ($n = 4$) or 10 mg/kg ($n = 4$)] were administered 0, 3 and 7 h after withdrawal of the control diet (the same regimen as in the ethanol dependent mice described above). Withdrawal of the control diet did not induce seizures. Behavioral ratings, taken over the course of 24 h, were not changed in

Table 1
Influence of ifenprodil on ethanol levels in the brain tissue and blood.

Time after administration of ethanol (min)	Ethanol levels in the brain (μmol/g) after administration of		Ethanol levels in the blood (μmol/ml) after administration of	
	Water	Ifenprodil	Water	Ifenprodil
5	117 ± 8		120 ± 4	
20	91 ± 1	93 ± 3	99 ± 5	97 ± 8
35	80 ± 3	79 ± 3	89 ± 3	96 ± 3

Ethanol (4 g/kg) was administered intraperitoneally. Ifenprodil (1 mg/kg) or water was injected i.p. 5 min later. Whole brain tissue and blood (venous/arterial flow) were obtained after decapitation of mice. Means ± S.E.M. of 5–6 animals.

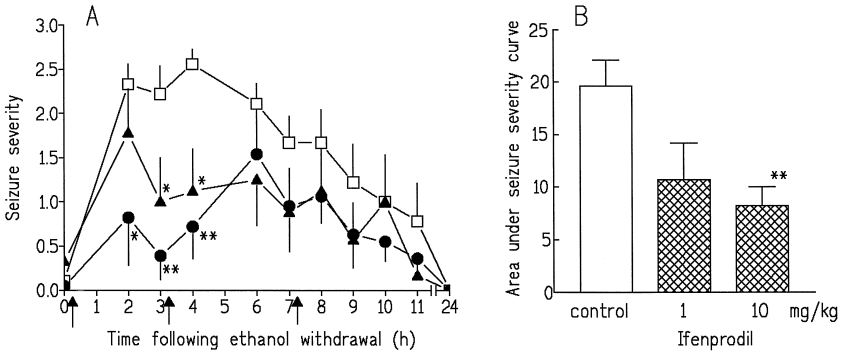

Fig. 4. Influence of ifenprodil on the severity of ethanol withdrawal symptoms in mice at various time points over the first 24 h of withdrawal. Doses of ifenprodil, i.e., 1 (●) or 10 mg/kg (▲) or water (control; □) were administered three times (i.p.; at 0, 3 and 7 h after ethanol removal, indicated by arrows). The results are expressed as seizure severity scores (A) and area under the 11-h seizure severity scores (B). See Section 2 for explanation of seizure severity scores. Means ± S.E.M. of 8–9 animals. $^{*}P < 0.05$, $^{**}P < 0.01$ compared to the control.

ifenprodil treated mice compared to the controls injected with water.

4. Discussion

The main aim of our study was to examine the influence of ifenprodil on the ethanol-induced behaviour in mice since, for many reasons, ifenprodil was considered to be suitable for the treatment of acute alcohol intoxication, chronic alcoholism and/or its complications. Firstly, it possesses antagonistic properties not only at NMDA but also at 5-HT_3 receptors, two ligand-gated cation channels which have been shown to be targets for an action of ethanol (for references, Section 1). Secondly, ifenprodil has a high affinity for NMDA receptors containing NMDAR-2B subunits, a component of an NMDA isoreceptor sensitive to acute and chronic ethanol exposure (for references, see Introduction). Thirdly, ifenprodil and eliprodil (a closely related drug), which act at the polyamine site of the NMDA receptor (Carter et al., 1989), do not induce substantial behavioral effects by themselves (Danysz et al., 1992; Murata and Kawasaki, 1993; Ginski and Witkin, 1994); they offer several advantages compared to other non-competitive NMDA receptor antagonists, such as MK-801, phencyclidine, ketamine and dextrorphan, since they appear to be devoid of severe memory disrupting and behavioral side effects of the latter drugs (head weaving, body rolling, rotations, ataxia, salivation; Danysz et al., 1992; Murata and Kawasaki, 1993; Ginski and Witkin, 1994).

In particular, the influence of ifenprodil on the ethanol-induced sleeping time and withdrawal reaction after its chronic administration was studied here since these parameters, which are modified by antagonists of both NMDA and 5-HT_3 receptors (for literature, see below) represent models of acute ethanol intoxication and ethanol withdrawal reaction in humans, respectively. Furthermore, the ethanol-induced inhibition of NMDA-evoked current in rat neocortical neurones (Lovinger, 1995) and of NMDA-stimulated release of various neurotransmitters in slices of rat cerebral cortex and corpus striatum (Fink and Göthert) has been shown to be counteracted by ifenprodil, suggesting that ifenprodil might diminish the acute effects of ethanol in vivo.

In our experiments, we did not also observe any changes in the behaviour of mice after administration of ifenprodil alone at doses of 0.3–10 mg/kg what is in agreement with publications mentioned above. Yet, ifenprodil caused various changes in the behaviour of mice induced by acute and chronic ethanol administration.

Only at a dose of 1 mg/kg, ifenprodil shortened, whereas at a dose of 10 mg/kg (given before or after ethanol) it considerably prolonged, the hypnotic response to an acute injection of a high dose of ethanol. Thus, we confirmed and extended findings of Daniell (1992) who demonstrated that ifenprodil, given before ethanol at very high dose of 100 mg/kg (which produced moderate sedation by itself), markedly prolonged the ethanol-induced sleeping time in mice. What is the mechanism underlying the modulatory action of ifenprodil on the ethanol-induced sleeping time? The effect of ifenprodil is not caused by a change in the pharmacokinetics of ethanol, since under the same conditions as in the determinations of the sleeping time the blood and brain ethanol concentrations in the absence and presence of ifenprodil did not differ from each other. Rather, an interaction at one of the relevant receptor systems has to be considered.

It has been shown that the hypnotic effect of ethanol in rats was diminished by the 5-HT_3 receptor antagonists tropisetron and ondansetron in the dose range of 0.001–0.25 mg/kg (Kostowski, 1996). On the other hand, not only ifenprodil but also other non-competitive NMDA receptor antagonists such as MK-801 and memantine at rather high doses prolonged the ethanol-induced sleeping time in rats (Danysz et al., 1992; Beleslin et al., 1997). On the basis of these results, it was conceivable that the shortening and prolongation of ethanol-induced sleeping

time by ifenprodil 1 and 10 mg/kg, respectively, which we found in mice, might be related to the predominance of the weak 5-HT_3 receptor-blocking property of the low dose and to the predominance of the very strong NMDA receptor blockade of the high dose of ifenprodil, respectively. In view of these possibilities, we performed additional experiments with the 5-HT_3 receptor antagonist ondansetron at the dose of 0.03 mg/kg and with the very potent non-competitive NMDA receptor antagonist MK-801 at the dose of 0.01 mg/kg (which failed to induce any behavioral changes in mice by itself; Buczko et al., 1998); the aim was to check whether these drugs might mimic the effects of ifenprodil. However, the ethanol-induced sleeping time was not modified by ondansetron or MK-801 nor by combination of both.

In contrast, the prolongation of the ethanol-induced sleeping time by the highest dose of ifenprodil was qualitatively and quantitatively mimicked by the α_1-adrenoceptor antagonist prazosin. Combined administration of both drugs did not produce a more pronounced response than either of them alone. The lack of additivity is compatible with the assumption that both drugs produce their effects by the same site and mechanism of action, i.e., the blockade of α_1-adrenoceptors. So far, the participation of α_1-adrenoceptors in the mechanism of the behavioral effects of the higher doses of ifenprodil had been postulated without any experimental evidence (e.g., Daniell, 1992).

Physical ethanol dependence is characterized by the development of withdrawal symptoms upon termination of ethanol intake after chronic ingestion. One of the most severe symptoms is the occurrence of seizures. In our study, ifenprodil 1 and 10 mg/kg attenuated the ethanol withdrawal seizures. It is consistent with the data of Kotlinska and Liljequist (1996). They demonstrated that eliprodil caused a dose-dependent (2 and 5 mg/kg) inhibition of audiogenic seizure activity induced by ethanol withdrawal in rats. Kotlinska and Liljequist (1996) suggested that the antagonists acting at the NMDA receptor polyamine site (ifenprodil and eliprodil) which do not produce psychotomimetic and/or sedative effects may represent a new class of therapeutically useful pharmacological agents for the treatment of ethanol withdrawal seizures. Our results are also compatible with the findings that ifenprodil exhibited protective action against seizures induced by pentylenetetrazole (Tsuda et al., 1997) or by the inverse benzodiazepine agonist DMCM (methyl-6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate) administered during diazepam withdrawal in mice (Tsuda et al., 1998).

It is well documented that NMDA receptors play a key role in the expression of ethanol withdrawal seizures. Thus, it has been demonstrated in vivo and in vitro that chronic ethanol exposure increases the number and function of NMDA receptors. Furthermore, several studies have shown that competitive and non-competitive antagonists of NMDA receptors attenuate ethanol withdrawal seizures in mice and rats (for references, see Introduction). In agreement with this, NMDA at doses that had little or no effect in control animals caused an exacerbation of withdrawal seizures in ethanol-dependent mice (Grant et al., 1990). In contrast, inconsistent results have been obtained in studies in which the involvement of 5-HT_3 receptors in ethanol withdrawal hyperexcitability has been examined. Thus, 5-HT_3 receptor antagonists have been demonstrated to exacerbate (MDL 7222; Grant et al., 1994), to alleviate (ondansetron, ICS 205930; Costall et al., 1990; Kostowski et al., 1993) or not to affect (ondansetron, ICS 205-930, MDL 72222, zacopride; Mehta and Ticku, 1993) ethanol withdrawal seizures. Taken together the antagonistic properties of ifenprodil against NMDA rather than 5-HT_3 receptors seem to be responsible for its antiseizure effect in ethanol withdrawal in mice.

In conclusion, the present study revealed that ifenprodil, which did not cause any behavioral effects by itself, influenced changes in mice behaviour induced by both acute and chronic ethanol administration. At moderate dose (1 mg/kg) it reduces the acute hypnotic effect of ethanol by an as yet unknown mechanism, whereas at the dose of 10 mg/kg it prolongs the sleeping time, by blocking α_1-adrenoceptors. Thus, the α_1-adrenolytic activity of ifenprodil may be important component in the mechanism of action of the high doses of this substance. The inhibitory influence of ifenprodil at both doses on the intensity of withdrawal seizures after chronic ethanol administration seems to be related to the NMDA receptor blocking property; the alleviation of ethanol withdrawal symptoms by modulators of the polyamine site is the most promising effect with respect to a putative application of such drugs in the treatment of alcoholism and/or its complications.

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