Pharmacology Biochemistry and Behavior, Vol. 58, No. 4, pp. 1159–1165, 1997
© 1997 Elsevier Science Inc.
Printed in the USA. All rights reserved
0091-3057/97 $17.00 + .00

ELSEVIER

PII S0091-3057(97)00317-1

Interactions of Ethanol with Nicotine, Dizocilpine, CGP 40116, and 1-(m-Chlorophenyl)-biguanide in Rats

PRZEMYSLAW BIENKOWSKI,*† ELIZA KOROS,* JERZY PIASECKI* AND WOJCIECH KOSTOWSKI*†

*Department of Pharmacology and Physiology of the Nervous System, Institute of Psychiatry and Neurology, Al. Sobieskiego 1/9, PL-02957, Warsaw, Poland
†Department of Experimental and Clinical Pharmacology, Warsaw Medical Academy, PL-02927, Warsaw, Poland

Received 6 February 1997; Revised 10 May 1997; Accepted 10 May 1997

BIENKOWSKI, P., E. KOROS, J. PIASECKI AND W. KOSTOWSKI. *Interactions of ethanol with nicotine, dizocilpine, CGP 40116, and 1-(m-chlorophenyl)-biguanide in rats.* PHARMACOL BIOCHEM BEHAV **58**(4) 1159–1165, 1997.—The present study examined the effect of ethanol (0.25–1.0 g/kg, IP) alone and in combination with drugs affecting different ligand-gated ion channels on a horizontal locomotor activity of male Wistar rats. None of the drugs given alone affected the locomotor activity. Similarly, combining ethanol either with nicotine (0.1 or 0.6 mg/kg, SC) or the competitive NMDA receptor antagonist, CGP 40116 (0.5 mg/kg, IP) did not result in any significant changes in ambulation. On the other hand, a significant hyperadditive interaction between ethanol (0.5 or 1.0 g/kg) and the uncompetitive NMDA receptor antagonist, dizocilpine (0.1 mg/kg, IP) was found. Thus, a combined administration of ethanol and dizocilpine produced a marked stimulation of the locomotor activity. Combining 1.0 g/kg ethanol with the 5-HT_3 receptor agonist, 1-(m-chlorophenyl)-biguanide (5.0 mg/kg, IP) tended to produce locomotor stimulation. Our results suggest the existence of interaction between ethanol and the NMDA receptor complex in mediation of locomotor stimulation. Alternatively, a common neurotransmitter system (other than glutamatergic) mediate central stimulatory effects of ethanol and dizocilpine. A possible role of dopamine in this interaction is being discussed. © 1997 Elsevier Science Inc.

Ethanol Nicotine Dizocilpine CGP 40116 1-(m-Chlorophenyl)-biguanide Locomotion Rat

ALTHOUGH ethanol is usually classified as a sedative/hypnotic drug, its effect on locomotor activity in rats is complex. Depending on the dose, ethanol produces locomotor stimulation (5,11,35,39,43,61), depression of locomotor activity (47,48, 52,54,61), or biphasic effects (51,61). Notably, the locomotor stimulant properties of ethanol are more consistently reported for mice than for rats (5,39,40). Locomotor stimulant effects of many abused drugs, including ethanol, have been attributed to their excitatory action on a CNS dopamine (DA) neurotransmission (30,36,37,63). Like opioids, psychostimulants, or nicotine, ethanol stimulates the DA release in the nucleus accumbens septi (NAS) (30,37,62,66). The increase in the DA release within the NAS is currently considered as the main neurochemical substrate of locomotor stimulation and positive reinforceing effects of drugs (36,37,62). Importantly, ethanol has been reported to enhance the ambulation-increasing effects of morphine (41), mazindol (25), and caffeine (42), and the stimulation of the DA neurotransmission has been shown to be involved in these interactions.

The exact mechanism of the ethanol-induced dopamine release remains unknown. Several reports suggested an important contribution of central serotonergic 5-HT_3 receptors and nicotinic acetylcholine receptors (nAChRs) in this phenomenon (4,6,7,27,44,58,64). Both 5-HT_3 receptors and nAChRs receptors belong to the superfamily of the so-called "ligand gated ion channels" (or ionotropic receptors), and are involved in the regulation of the limbic DA neurotransmission (2,7,28,44,58,65). In agreement with the above, both 5-HT_3

Requests for reprints should be addressed to Wojciech Kostowski, Department of Pharmacology and Physiology of the Nervous System, Institute of Psychiatry and Neurology, Al. Sobieskiego 1/9, PL-02957, Warsaw, Poland.

receptor agonists [e.g., 1-(phenyl)-biguanide] and nAChR agonists (e.g., nicotine) have been found to increase the DA release in the striatum and in the NAS (2,10,33,37).

These and other ionotropic receptors, i.e., the $GABA_A$ and the NMDA receptor complex, seem to be particularly sensitive to low ethanol concentrations in several in vitro preparations [(1,13,20,23,44,45); for review see (6,26,28)] and are considered as important targets for receptor-specific actions of ethanol within the brain (6,17,26,28,29,38,53,59,60). Ethanol has been consistently reported to enhance serotonin action at the $5\text{-}HT_3$ receptor (44,46). In accordance with the above, the enhancement of dopamine release caused by ethanol was reversed by $5\text{-}HT_3$ receptor antagonists (7,64). Recent studies on the ethanol interaction with the central nAChRs have generated conflicting results. Ethanol enhanced excitatory responses to nicotine in the majority of cells in the rat substantia nigra reticulata and ventral pallidum (13). In contrast, a modest inhibition of excitatory responses to nicotine has been found for the rat locus coeruleus neurones (23). In line with the former finding, the noncompetitive nAChR receptor antagonist, mecamylamine (2) has been shown to diminish the ethanol-induced dopamine release in the NAS (4) and to reduce the ethanol-induced rise in the DOPAC/DA quotient (5,58). At the behavioral level, the locomotor stimulant effect of ethanol was decreased by either the $5\text{-}HT_3$ receptor antagonist, ondansetron or mecamylamine (39,58).

Ethanol has been found to antagonize the *N*-methyl-D-aspartate (NMDA) receptor-mediated biochemical and electrophysiological responses, leading to the hypothesis that at least certain central effects of ethanol may result from the interaction with the NMDA receptor complex (26,28,45). In line with this hypothesis are the data showing that NMDA receptors may contribute to ethanol-induced discriminative stimulus effects, intoxication and withdrawal symptoms (3,17,29,29,53). Besides, the pattern of behavioral responses induced by ethanol is similar in many aspects (anxiolysis, ataxia, miorelaxation, sedation, analgesia) to the behavioral effects observed after both competitive and uncompetitive NMDA receptor antagonists (26,28,50). Little is known, however, about the role of NMDA receptors in the locomotor stimulant effect of ethanol. Notably, uncompetitive NMDA receptor antagonists, like phencyclidine (PCP) and other PCP-like drugs (e.g., dizocilpine), produce strong locomotor stimulant effects in laboratory animals (40,52). In contrast, competitive NMDA receptor antagonists tend to decrease ambulation (15,65). Both classes of drugs, however, may enhance the DA transmission in the brain (15,16,21,22).

The aim of the present study was to examine the interaction of ethanol with drugs acting on nAChRs, $5\text{-}HT_3$ and NMDA receptors in the test of spontaneous locomotor activity in the rat. To this purpose, low, nonsedative doses of ethanol were combined with the nAChR agonist (nicotine), the $5\text{-}HT_3$ receptor agonist [1-(m-chlorophenyl)-biguanide] (49), and the uncompetitive or the competitive NMDA receptor antagonist (dizocilpine or CGP 40116, respectively) (21,55,57). The doses of ethanol and the other drugs have been shown [(50); Bienkowski et al., unpublished] to be the highest ones not affecting the locomotor activity of our rats.

METHOD

Subjects

Male Wistar rats (280–330 g at the beginning of each experiment) were housed in a group of four in a standard plastic cage with free access to food (Bacutil, Poland) and tap water. The animals were allowed at least 2 weeks of acclimation upon arrival at our laboratory. The subjects were kept in standard laboratory conditions at 22 ± 1°C, 60% humidity, and 12-h light–dark cycle (lights on at 0700 h). All experiments were conducted between 0900–1400 h, and each rat was used only once. The experimental procedures were reviewed and approved by our institutional ethical committee.

Locomotor Activity—General Procedure

All experiments took place in an air-conditioned enclosure with background white noise of 50 dB. The apparatus (COTM, Bialystok, Poland) consisted of four identical "open-field" cages (60 × 60 × 40 cm, W × L × H). The cages had clear Plexiglas walls and removable, smooth, black metal floors. Each cage was transected by two perpendicular coplanar arrays of 16 infrared photobeams and was dimly lit by a separate source of light mounted 50 cm above the floor. Beam interruptions were recorded and analyzed by means of an IBM-compatible PC equipped with software and interface (COTM, Bialystok, Poland).

To reduce stress associated with the procedure, the animals were handled several times during the acclimation period. In addition, the day before the test session all animals were transported to the test enclosure, briefly handled and left in the cages for 20 min to get habituated to the new environment. On the next day the subjects received an appropriate treatment and their locomotor activities were recorded for 20 min. The data used for analysis were expressed as the mean (±SEM) distance (in inches) travelled during the 20-min test session.

Locomotor Activity—Detailed Procedure

The experiments were conducted in the order described below.

Experiment 1—Ethanol/Dizocilpine Interaction

The animals were randomly assigned to six experimental groups (n = 8 rats) differing in treatment received before the test session: the saline-saline (S-S), the 0.1 mg/kg dizocilpine-saline (D-S), the saline-0.25 g/kg ethanol (S-E.25), the saline-0.5 g/kg ethanol (S-E.5), the 0.1 mg/kg dizocilpine-0.25 g/kg ethanol (D-E.25), and the 0.1 mg/kg dizocilpine-0.5 g/kg ethanol (D-E.5) group. Dizocilpine was administered 20 min before the ethanol injection. Immediately after the latter injection the rat was placed in the cage and the recording started.

Due to certain technical reasons, the combination of 1.0 g/kg ethanol and 0.1 mg/kg dizocilpine was tested in a separate experiment. Four experimental groups (n = 8 rats) were randomly formed: the S-S, the D-S, the saline-1.0 g/kg ethanol (S-E1), and the D-E1 group.

Experiment 2—Ethanol/Nicotine Interaction

The subjects were randomly divided into eight experimental groups (n = 8 rats): the S-S, the 0.6 mg/kg nicotine-saline (N.6-S), the S-E.25, the S-E.5, the S-E1, the N.6-E.25, the N.6-E.5, and the N.6-E1 group. Nicotine was given 20 min before ethanol. Immediately after the ethanol injection the rat was placed in the test cage. Because neither in Experiments 1–2 (see Results) nor in our preliminary studies (Bienkowski et al., unpublished) ethanol given alone had any impact on the locomotor activity, the groups receiving ethanol alone were not included in subsequent experiments.

In a separate experiment a lower nicotine dose (0.1 mg/kg) was combined with ethanol. The animals were randomly as-

signed to five experimental groups (n = 8 rats): the S-S, the 0.1 mg/kg nicotine-saline (N.1-S), the N.1-E.25, the N.1-E.5, and the N.1-E1 group.

Experiment 3—Ethanol/CGP 40116 Interaction

Five experimental groups (n = 8 rats) were randomly formed: the S-S, the 0.5 mg/kg CGP 40116-saline (CGP-S), the CGP-E.25, the CGP-E.5, and the CGP-E1 group. CGP 40116 was injected 60 min before ethanol.

Experiment 4—Ethanol/1-(m-Chlorophenyl)-biguanide (mCPBG) Interaction

Four experimental groups (n = 8 rats) were randomly formed: the S-S, the 5.0 mg/kg mCPBG-saline (BIG-S), the BIG-E.5, and the BIG-E1 group. mCPBG was injected 20 min before ethanol.

Drugs

Ethanol solution (10% v/v) was prepared from the 95% stock solution and 0.9% NaCl, and administered IP in appropriate volumes to obtain a desired dose. (−)-Nicotine di-d-tartrate, dizocilpine (formerly: (+)MK-801 hydrochloride), 1-(m-chlorophenyl)-biguanide hydrochloride (RBI, Natick, MA), and CGP 40116 (D-(E)-2-amino-4-methyl-5-phosphono-3-pentenoic acid; Ciba-Geigy, Basel, Switzerland) were dissolved in 0.9% NaCl and administered in the volume of 1.0 ml/kg. The pH of nicotine solutions was adjusted to 7.0 with dilute NaOH. All solutions were prepared immediately prior to use. The doses of dizocilpine, nicotine and 1-(m-chlorophenyl)-biguanide refer to salt forms. All drugs were injected IP except nicotine, which was administered SC.

Statistics

The data were compared with a one-way ANOVA with the Newman–Keuls test (with the Bonferroni's correction) for post hoc comparisons. Probability levels (p) less than 0.05 were considered significant.

RESULTS

Experiment 1–Ethanol/Dizocilpine Interaction

The ANOVA indicated a significant effect of treatment, $F(5, 42) = 3.54$, $p < 0.01$, for the experiment with lower ethanol doses (0.25–0.5 g/kg) and dizocilpine (Fig. 1, upper panel). The group treated with 0.5 g/kg ethanol and dizocilpine (E.5-D group) showed a marked stimulation of the locomotor activity, which was significantly different ($p < 0.05$) from either the saline treated control group, either the S-E.5 group or the D-S group. Similarly, the ANOVA showed a significant effect of treatment, $F(3, 30) = 4.52$, $p < 0.01$, for the second experiment with ethanol (1.0 g/kg) and dizocilpine (Fig. 1, lower panel). A post hoc analysis revealed that the locomotor activity of the E1-D group was significantly higher than the activity of S-S group, the S-E1 group ($p < 0.05$) and the D-S group ($p < 0.01$). Importantly, ethanol (0.25–1.0 g/kg) in combination with saline did not affect the locomotor activity of the subjects.

Experiment 2—Ethanol/Nicotine Interaction

The ANOVA did not show any significant effect of treatment, $F(7, 72) = 0.42$, $p = 0.85$, for the experiment with ethanol (0.25–1.0 g/kg) and 0.6 mg/kg nicotine (Fig. 2, upper panel). Again, ethanol given alone (i.e., in combination with saline) did not change the locomotor activity of the rats and thus the ethanol-treated control groups were not included in the other experiments. Similarly, there was no significant effect of treatment, $F(4, 51) = 2.07$, $p = 0.097$, for the experiment with the combinations of ethanol and 0.1 mg/kg nicotine (Fig. 2, lower panel).

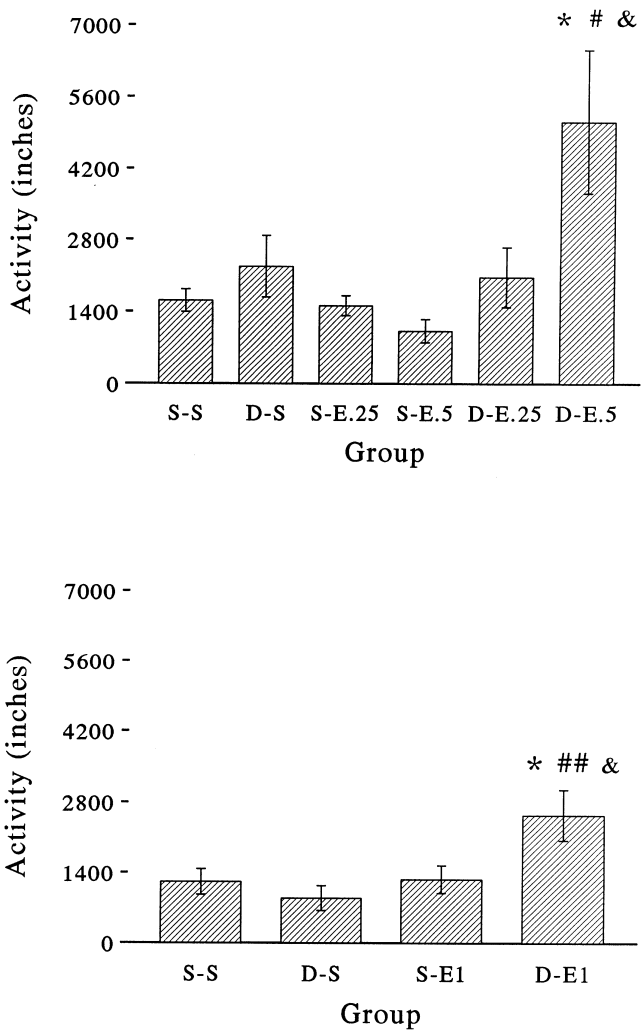

FIG. 1. Locomotor activity induced by combined administration of 0.1 mg/kg dizocilpine and different doses of ethanol (0.25, 0.5 g/kg—higher panel; 1.0 g/kg—lower panel). S = saline, D = dizocilpine, E = ethanol. $^{*}p < 0.05$ vs. the S-S group; $^{\&}p < 0.05$ vs. the S-E.5 or the S-E1 group; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ vs. the D-S group.

Experiment 3—Ethanol/CGP 40116 Interaction

Although the ANOVA showed a significant effect of treatment, $F(4, 35) = 2.86$, $p = 0.037$, the only significant difference ($p < 0.05$) found referred to the CGP-S and the CGP-E.25 group (Fig. 3). Thus, ethanol given in combination with CGP 40116 did not alter the locomotor activity significantly compared with the saline-treated control group (the S-S group).

Experiment 4—Ethanol/mCPBG Interaction

The ANOVA did not reveal any significant effect of treatment, although a trend towards significance was observed,

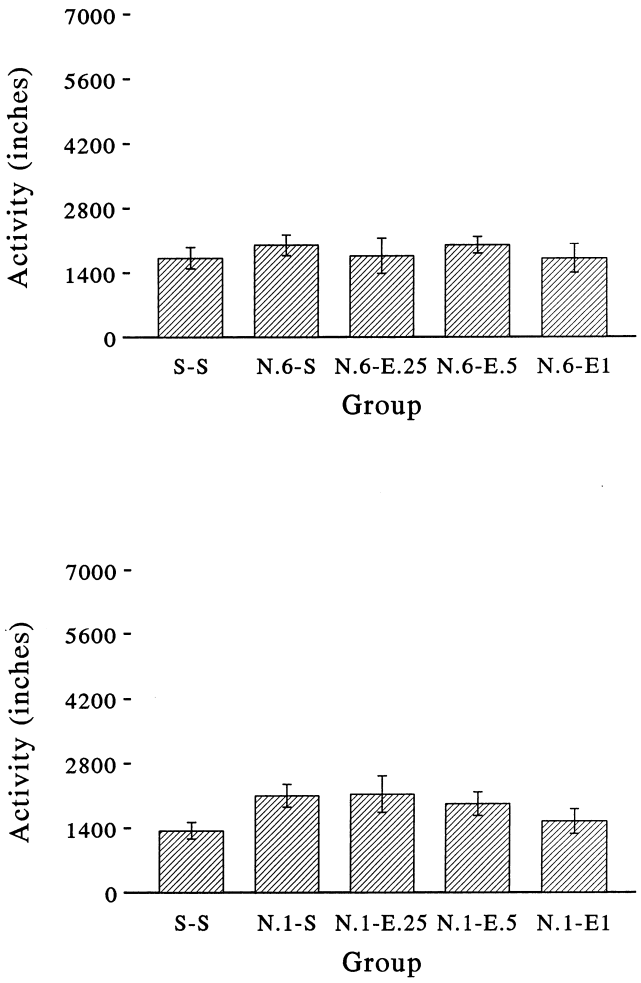

FIG. 2. Locomotor activity induced by combined administration of nicotine (0.6 mg/kg—higher panel; 0.1 mg/kg—lower panel) and different doses of ethanol. S = saline, N = nicotine, E = ethanol.

$F(3, 28) = 2.84$, $p = 0.055$. The group treated with the combination of 1.0 g/kg ethanol and 5.0 mg/kg mCPBG showed a higher locomotor activity ($p < 0.05$) than the saline treated control group (the S-S group). However, it did not differ ($p > 0.4$) from the group receiving mCPBG alone (the BIG-S group) (Fig. 4).

DISCUSSION

The results of Experiment 1 show that ethanol, in the range of doses not affecting the spontaneous locomotor activity, enhances the locomotor stimulant effect of dizocilpine. Our results are in agreement with the previous report (40) indicating that a combination of ethanol and dizocilpine (0.1 mg/kg) produced a prominent increase in the ambulatory activity of mice. However, the stimulatory effect of a higher dose of dizocilpine was significantly diminished by ethanol possibly due to a marked ataxia resulting from the combined administration of the drugs (40). In agreement with the above, ethanol attenuated dizocilpine-induced hyperlocomotion in mice (43) and rats (52). This latter result (52) seems to be at variance with our findings but several obvious differences between the two studies might explain the disagreement. First, in the previous report, the relatively low dose of ethanol (0.75 g/kg)

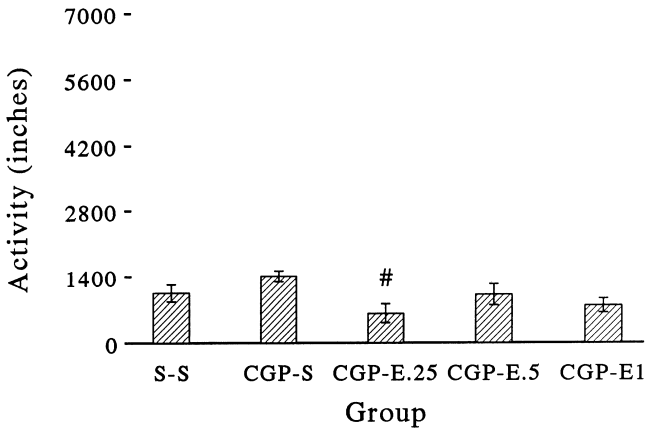

FIG. 3. Locomotor activity induced by combined administration of 0.5 mg/kg CGP 40116 and different doses of ethanol. S = saline, CGP = CGP 40116, E = ethanol. $^{\#}p < 0.05$ vs. the CGP-S.

produced a significant depression of the locomotor activity, which, as the authors hypothesized (52), could be associated with a higher susceptibility of rats to the central depressant properties of ethanol during the dark phase of the day/night cycle (The present study was performed in the light phase.) Second, the 0.1 mg/kg dose of dizocilpine produced a marked stimulation of the locomotor activity in the study of Robledo et al. (52), and the lack of a further intensification of this effect by ethanol could be attributed to the "ceiling effect." Alternatively, ethanol might mainly increase the sedative/ataxic effects of dizocilpine. Probably, in the present study (Experiment 1) ethanol mainly enhanced the stimulant component of dizocilpine action, as we selected these doses of both drugs that do not affect the animal's locomotor behavior (see the introductory paragraphs and Results). In addition, in the previous study (52) the locomotor activity was recorded for 12 h, in 2-h intervals. Thus, a more subtle, time-limited interactions between the drugs might have been overlooked. Taken together, the results from this report and the previous one suggest that both the excitation and the depression of the locomotor activity may result from a combined ethanol/

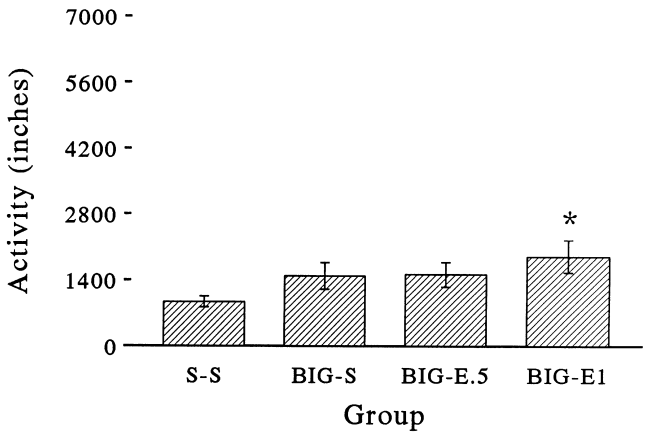

FIG. 4. Locomotor activity induced by combined administration of 5.0 mg/kg 1-(m-chlorophenyl)-biguanide and different doses of ethanol. S = saline, BIG = 1-(m-chlorophenyl)-biguanide, E = ethanol. $^{*}p < 0.05$ vs. the S-S group.

dizocilpine administration, depending on the balance between the stimulatory and the sedative effects produced by a given combination of the drugs.

It has been proposed that the psychomotor stimulant properties of certain uncompetitive NMDA receptor antagonists, including dizocilpine, result from an enhancement of the CNS DA transmission at the level of the NAS and/or the ventral tegmental area (VTA) (21,22,31,37). As mentioned above (see the introductory paragraphs), ethanol also stimulates DA release, and both the NAS and the VTA have been proposed as possible neuroanatomical substrates for this effect (24,30,37,66). It is, therefore, probable that the ethanol/dizocilpine interaction observed in the present study depended at least in part on a hyperadditivity within the central DA pathways. However, this hypothesis should be treated with caution because both ethanol and NMDA receptor antagonists, including dizocilpine, given in combination with other drugs may intensify the locomotor activity even in monoamine-depleted mice (8,9).

On the basis of the results from Experiment 1, one could speculate that across the carefully selected dose range, ethanol may intensify central stimulatory effects of other uncompetitive NMDA receptor antagonists, including PCP. Such an interaction could explain, at least in part, the well-known phenomenon of ethanol/PCP coabuse in humans (12).

In contrast to the results of Experiment 1, there was a lack of any significant locomotor interaction between ethanol and the competitive NMDA receptor antagonist, CGP 40116 observed (Experiment 3). However, dizocilpine and CGP 40116 antagonise the NMDA receptor complex acting at different receptor/modulatory sites (22,28,55,65). In addition, competitive NMDA receptor antagonists (in contrast to uncompetitive antagonists) did not enhance the electrophysiological activity of the VTA dopaminergic neurones (21,22). Given the data (21,22,24) that ethanol and dizocilpine increase the burst firing of the VTA dopaminergic neurons, one could hypothesize that the difference between dizocilpine and CGP 40116 observed in our study is due to their different action within the VTA.

The dose of CGP 40116 (0.5 mg/kg) was selected on the basis of our previous studies showing that higher doses of the drug (>1.0 mg/kg) decreased the ambulatory activity of rats. Besides, 0.5 mg/kg dose of CGP 40116 partially substituted for the discriminative stimulus effects of ethanol (3) and enhanced the ethanol discrimination (i.e., shifted the dose–response curve to the left) in our recent drug discrimination study (Bienkowski and Kostowski, unpublished).

As mentioned before (see introductory paragraphs), nAChRs have been suggested to be involved in the dopaminergic and the locomotor stimulatory effects of ethanol in rodents (4,5,58). Besides, several human studies have demonstrated that there is a high correlation between ethanol consumption and tobacco smoking (14,19,32,34). The use of one substance increases the risk of developing dependence on the other one (19,32,34). Thus, we predicted that an ethanol/nicotine combination could enhance the locomotor activity. The results of Experiment 2 do not support such an assumption. In contrast, ethanol (0.3 g/kg) has been previously found to increase the locomotor stimulant effects of 0.17 mg/kg nicotine (54). However, the effect was rather modest and observed only for one combination of doses. There are two major differences between the study of Schaefer and Michael (54) and our present investigation. First, a different rat line (Sprague–Dawley) was used in the study mentioned above (54). The role of genotype in the locomotor response to ethanol or nicotine has been indicated in many reports (18,27). For example, both nicotine and ethanol have been reported to increase the ambulatory activity of an alcohol-preferring P line of rats and to decrease the activity of an alcohol nonpreferring NP line of rats (27,61). Second, in the study of Schaefer and Michael, ethanol and nicotine were administered simultaneously (54), and there was a 20-min interval between nicotine and ethanol injection in the present study. Because nAChRs are known to desensitize rapidly and ethanol has been suggested to enhance the rate of the nAChR desensitization (1,2,18,20), the schedule of drugs administration is another factor that could explain our negative findings. Interestingly, using the same schedule of administration we have recently found that nicotine enhances the ethanol discrimination [Bienkowski and Kostowski, unpublished; see also (56)]. On the basis of the present results, one could speculate that the locomotor interactions are not of major importance in this latter finding.

In the present study the subjects were habituated to the cages for 20 min the day before the test session. Therefore, their locomotion were likely to be disturbed by the exploratory locomotor activity that might overshadow more subtle interactions between ethanol and nicotine. Thus, further studies using more extensive habituation seem to be warranted.

Although the overall statistical analysis of the data from Experiment 4 did not reveal any significant effect of treatment, a clear tendency towards it was noted ($p = 0.055$). The combination of ethanol and mCPBG almost doubled the locomotor activity of rats (compared with the activity of the S-S control group). As mentioned before (see the introductory paragraphs), 5-HT_3 receptors have been implicated to be involved in several central effects of ethanol in rodents (6,7, 38,44). Notably, a significant attenuation of the ethanol-induced locomotor stimulant effects by 5-HT_3 receptor antagonists have been found in our laboratory, using mice as subjects (39). Thus, the results of Experiment 4, though preliminary in nature, are in line with the previous reports. Certainly, further studies are needed to confirm a possible role of 5-HT_3 receptors in the locomotor stimulant effect of ethanol in rodents.

ACKNOWLEDGEMENTS

This work was supported by Institute of Psychiatry and Neurology (Grant No. 12/97) and The State Committee for Scientific Research (KBN) (Grant No. G.P. 20701907).

REFERENCES

1. Aracava, Y.; Fróes-Ferrao, M. M.; Perrier, E. F. R.; Albuquerque, E. X.: Sensitivity of *N*-methyl-D-aspartate (NMDA) and nicotinic acetylcholine receptors to ethanol and pyrazole. Ann. NY Acad. Sci. 625:451–472; 1991.
2. Arneric, S. P.; Sullivan J. P.; Williams, M.: Neuronal nicotinic acetylcholine receptors: Novel targets for central nervous system therapeutics. In: Bloom, F. E.; Kupfer, D. J., eds. Psychopharmacology: The fourth generation of progress. New York: Raven Press, Ltd.; 1995:95–110.
3. Bienkowski, P.; Stefanski, R.; Kostowski, W.: Competitive NMDA receptor antagonist, CGP 40116 substitutes for the discriminative stimulus effects of ethanol. Eur. J. Pharmacol. 314: 277–280; 1996.
4. Blomqvist, O.; Engel, J. A.; Nissbrandt, H.; Söderpalm, B.: The

mesolimbic dopamine-activating properties of ethanol are antagonised by mecamylamine. Eur. J. Pharmacol. 249:207–213; 1993.
5. Blomqvist, O.; Söderpalm, B.; Engel, J. A.: Ethanol-induced locomotor activity: Involvement of central nicotinic acetylcholine receptors? Brain Res. Bull. 29:173–178; 1992.
6. Breese, G. R.; Morrow, A. L.; Simson, P. E.; Criswell, H. E.; McCown, T. J.; Duncan, G. E.; Keir, W. J.: The neuroanatomical specificity of ethanol action on ligand-gated ion channels: A hypothesis. Alcohol Alcohol. Suppl. 2:309–313; 1993.
7. Carboni E.; Acquas F.; Frau R.; Di Chiara, G.: Differential inhibitory effects of 5-HT_3 antagonists on drug-induced dopamine release. Eur. J. Pharmacol. 164:515–519;1989.
8. Carlsson, M. L.; Engberg, G.: Ethanol behaves as an NMDA antagonist with respect to locomotor stimulation in monoamine-depleted mice. J. Neural Trasm. [Gen Sect] 87:155–160; 1992.
9. Carlsson, M. L.; Svensson, A.; Carlsson, A.: Synergistic interactions between muscarinic antagonists, adrenergic agonists and NMDA antagonists with respect to locomotor stimulatory effects in monoamine-depleted mice. Naunyn Schmiedebergs Arch. Pharmacol. 343:568–573; 1991.
10. Chen, J.; van Praag, H. M.; Gardner, E. L.: Activation of 5-HT_3 receptor by 1-phenylbiguanide increases dopamine release in the rat nucleus accumbens. Brain Res. 543:354–357; 1991.
11. Cott, J. M.; Carlsson, J. E.; Lindqvist, M.: Suppression of ethanol-induced locomotor stimulation by GABA-like drugs. Naunyn Schmiedebergs Arch. Pharmacol. 295:203–209; 1976.
12. Crider, R.: Phencyclidine: Changing abuse pattern. NIDA Res. Monogr. 64:163–173; 1986.
13. Criswell, H. E.; Simson, P. E.; Duncan, G. E.; McCown, T. J.; Herbert, J. S.; Morrow, L. A.; Breese, G. R.: Molecular basis for regionally specific action of ethanol on $GABA_A$ receptors: Generalisation to other ligand-gated ion channels. J. Pharmacol. Exp. Ther. 267:522–537; 1993.
14. Cummings, R. O.; Shaper, A. G.; Walker, M.; Wale, C. J.: Smoking and drinking by middle-aged British men: Effects of class and town of residence. Br. Med. J. 282:1497–1502; 1981.
15. Dall'Olio, R.; Rimondini, R.; Gandolfi, O.: The competitive NMDA antagonists CGP 43487 and APV potentiate dopaminergic function. Psychopharmacology (Berlin) 118:310–315; 1995.
16. Dall'Olio, R.; Rimondini, R.; Gandolfi, O.: Effect of NMDA receptor antagonists on D_1, D_2 and D_1/D_2 mediated behaviors in intact rats. Psychopharmacology (Berlin) 123:187–190; 1996.
17. Danysz, W.; Dyr, W.; Jankowska, E.; Glazewski, S.; Kostowski, W.: The involvement of NMDA receptors in acute and chronic effects of ethanol. Alcohol. Clin. Exp. Res. 16:499–504; 1992.
18. de Fiebre, C. M.; Medhurst, L. J.; Collins, A. C.: Nicotine response and nicotinic receptors in long-sleep and short-sleep mice. Alcohol 4:493–501; 1987.
19. Dyers, A. R.; Stamler, J.; Paul, O.; Berkson, D. M.; Lepper, M. H.; McKean, M. H.; Shekelle, R. B.; Lindberg, H. A.; Garside, D.: Alcohol consumption, cardiovascular risk factors, and mortality in two Chicago epidemiological studies. Circulation 56:1067–1074; 1977.
20. El-Fakahany, E. F.; Roxanne Miller, F.; Abbassy, M. A.; Eldefrawi, A. T.; Eldefrawi, M. E.: Alcohol modulation of drug binding to the channel sites of the nicotinic acetylcholine receptor. J. Pharmacol. Exp. Ther. 224:289–296; 1983.
21. French, E. D.; Vantini, G.: Noncompetitive *N*-methyl-D-aspartate antagonists are potent activators of ventral tegmental A10 dopamine neurons. Neurosci. Lett. 119:159–162; 1990.
22. French, E. D.; Mura, A.; Wang, T.: MK 801, phecyclidine (PCP) and PCP-like drugs increase burst firing in rat A10 dopamine neurons: Comparison to competitive NMDA antagonists. Synapse 13:108–116; 1993.
23. Fröhlich, R.; Patzelt, C.; Illes, P.: Inhibition by ethanol of excitatory amino acid receptors and nicotinic acetylcholine receptors at rat locus coeruleus neurons. Naunyn Schmiedebergs Arch. Pharmacol. 350:626–631; 1994.
24. Gessa, G. L.; Muntoni, G.; Collu, M.; Vargiu, L.; Mereu, G. L.: Low doses of ethanol activate dopaminergic neurons in the ventral tegmental area. Brain Res. 348:201–203; 1985.
25. Gevaerd, M. S.; Takahashi, R. N.: Interaction of mazindol with alcohol in mice. Addict. Biol. 1:303–307; 1996.
26. Gonzales, R. A.: NMDA receptors excite alcohol research. Trends Pharmacol. Sci. 11:137–139; 1990.
27. Gordon, T. L.; Meehan, S. M.; Schechter, M. D.: Differential effects of nicotine but not cathinone on motor activity of P and NP rats. Pharmacol. Biochem. Behav. 44:657–659; 1993.
28. Grant, K. A.: Emerging neurochemical concepts in the actions of ethanol at ligand-gated ion channels. Behav. Pharmacol. 5:383–404; 1994.
29. Grant, K. A.; Colombo, G.: Discriminative stimulus effects of ethanol: Effect of training dose on the substitution of *N*-methyl-D-aspartate antagonists. J. Pharmacol. Exp. Ther. 264:1241–1247; 1993.
30. Imperato, A.; Di Chiara, G.: Preferential stimulation of dopamine release in the nucleus accumbens of freely moving rats by ethanol. J. Pharmacol. Exp. Ther. 239:219–228; 1986.
31. Imperato, A.; Scrocco, M. G.; Bacchi, S.; Angelucci, L.: NMDA receptors and in vivo dopamine release in the nucleus accumbens and caudatus. Eur. J. Pharmacol. 187:555–556; 1990.
32. Istvan, J.; Matarazzo, J. D.: Tobacco, alcohol, and caffeine use: A review of their interrelationships. Psychol. Bull. 95:301–326; 1984.
33. Jiang, L. H.; Ashby, C. R.; Kasser, R. J.; Wang, R. Y.: The effect of intraventricular administration of the 5-HT_3 receptor agonist 2-methylserotonin on the release of dopamine in the nucleus accumbens: An in vivo chronocoulometric study. Brain Res. 513: 156–160; 1990.
34. Keenan, R. M.; Hatsukami, D. K.; Pickens, R. W.; Gust S. W.; Strelow, L. J.: The relationship between chronic ethanol exposure and cigarette smoking in the laboratory and the natural environment. Psychopharmacology (Berlin) 100:77–83; 1990.
35. Kocchar, A.; Erickson, C. K.: Central cholinergic correlates of low dose ethanol-induced locomotor stimulation. Alcohol. Clin. Exp. Res. 10:595–601; 1986.
36. Koob, G. F.: Neurobiological sites of drug dependence. Biol. Psychiatry 2:36–39; 1991.
37. Koob, G. F.: Drugs of abuse: Anatomy, pharmacology and function of reward pathways. Trends Pharmacol. Sci. 13:177–193; 1992.
38. Kostowski, W.; Dyr, W.; Krzascik, P.: The abilities of 5-HT_3 receptor antagonist ICS 205-930 to inhibit alcohol preference and withdrawal seizures in rats. Alcohol 10:369–373; 1993.
39. Kostowski, W.; Sikora, J.; Bisaga, A.; Rosnowska, E.: Effects of 5-HT_3 receptor antagonists on ethanol-induced locomotor activity in mice. Pol. J. Pharmacol. 47:293–297; 1995.
40. Kuribara, H.: Potentiation of the ambulation-increasing effect induced by combined administration of MK-801 with ethanol in mice. Psychopharmacology (Berlin) 113:453–456; 1994.
41. Kuribara, H.; Asahi, T.; Tadokoro, S.: Enhancement of the ambulation-increasing effect of opioid analgesics by ethanol in mice. Jpn. J. Pharmacol. 56:457–463; 1991.
42. Kuribara, H.; Asahi, T.; Tadokoro, S.: Ethanol enhances but diazepam and pentobarbital reduces the ambulation-increasing effect of caffeine in mice. Jpn. J. Alcohol. Drug Depend. 27:528–539; 1991.
43. Liljequist, S.: NMDA receptor antagonists inhibit ethanol-produced locomotor stimulation in NMRI mice. Alcohol 8:309–312; 1991.
44. Lovinger, D. M.: Ethanol potentiates on current mediated by 5-HT_3 receptors in NCB-20 cells. Alcohol. Clin. Exp. Res. 14:303–314; 1990.
45. Lovinger, D. M.; White, G.; Weight, F.: Ethanol inhibits NMDA-activated ion current in hippocampal neurons. Science 243:1721–1724; 1989.
46. Machu, T. K.; Harris, R. A.: Alcohols and anesthetics enhance the function of 5-hydroxytryptamine(3) receptors expressed in *Xenopus laevis* oocytes. J. Pharmacol. Exp. Ther. 271:898–905; 1994.
47. Martz, A.; Deitrich, R. A.; Harris, A.: Behavioral evidence for the involvement of γ-aminobutyric acid in the actions of ethanol. Eur. J. Pharmacol. 89:53–62; 1983.
48. Mason, S. T.; Corcoran, M. E.; Fibiger, H. C.: Noradrenergic processes involved in the actions of ethanol. Eur. J. Pharmacol. 54:383–387; 1979.
49. Middlemiss, D. N.; Tricklebank, M. D.: Centrally active 5-HT receptor agonists and antagonists. Neurosci. Biobehav. Rev. 16: 75–82; 1992.

50. Plaznik, A.; Palejko, W.; Nazar, M.; Jessa, M.: Effects of antagonists at the NMDA receptor complex in two models of anxiety. Eur. Neuropsychopharmacol. 4:503–512; 1994.
51. Pohorecky, L. A.: Biphasic actions of ethanol. Biobehav. Rev. 1:231–240; 1977.
52. Robledo, P.; Kaneko, W.; Ehlers, C. L.: Combined effects of ethanol and MK 801 on locomotor activity in the rat. Pharmacol. Biochem. Behav. 39:513–516; 1991.
53. Sanna, E.; Serra, M.; Cossu, A.; Colombo, G.; Follesa, P.; Cuccheddu, T.; Concas, A.; Biggio, G.: Chronic ethanol intoxication induces differential effects on $GABA_A$ and NMDA receptor function in the rat. Alcohol. Clin. Exp. Res. 17:115–123; 1993.
54. Schaefer, G. J.; Michael, R. P.: Interactions between alcohol and nicotine on intracranial self-stimulation and locomotor activity in rats. Drug Alcohol Depend. 30:37–47; 1992.
55. Schmutz, M.; Portet, C.; Jeker, A.; Klebs, K.; Vassout, A.; Allgeier, H.; Heckendorn, R.; Fagg, G. E.; Olpe, H. R.; van Riesen, H.: The competitive NMDA receptor antagonists CGP 37849/CGP 39551 are potent, orally active anticonvulsants in rodents. Naunyn Schmiedebergs Arch. Pharmacol. 342:61–66, 1990.
56. Signs, S.; Schechter, M. D.: Nicotine-induced potentiation of ethanol discrimination. Pharmacol. Biochem. Behav. 24:769–771; 1986.
57. Snell, L. D.; Yi, S.-J.; Johnson, K. M.: Comparison of the effects of MK-801 and phencyclidine on catecholamine uptake and NMDA-induced norepinephrine release. Eur. J. Pharmacol. 145:223–226; 1988.
58. Söderpalm, B.; Blomqvist, O.; Johnson, D.; Engel, J. A.: Involvement of central nicotinic acetylcholine receptors in the mesolimbic DA-activating and reinforcing properties of ethanol. Soc. Neurosci. Abstr. 19:610; 1993.
59. Stefanski, R.; Bienkowski, P.; Kostowski, W.: Studies on the role of $5\text{-}HT_3$ receptors in the mediation of the ethanol interoceptive cue. Eur. J. Pharmacol. 309:141–147; 1996.
60. Tomkins, D. M.; Le, A.; Sellers, D. M.: Effects of the $5\text{-}HT_3$ receptor antagonist ondansetron on voluntary ethanol intake in rats and mice maintained on a limited access procedure. Psychopharmacology (Berlin) 117:479–485; 1995.
61. Waller, M. B.; Murphy, J. M.; McBride, W. J.; Lumeng, L.; Li, T.-K.: Effect of low dose of ethanol on spontaneous motor activity in alcohol-preferring and -nonpreferring lines of rats. Pharmacol. Biochem. Behav. 24:617–623; 1986.
62. Weiss, F.; Lorang, M. T.; Bloom, F. E.; Koob, G. F.: Alcohol self-administration stimulates dopamine release in the rat nucleus accumbens: Genetic and motivational determinants. J. Pharmacol. Exp. Ther. 267:250–258; 1993.
63. Wise, R. A.; Bozarth, M. A.: Actions of drugs of abuse on brain reward systems: An update with specific attention to opiates. Pharmacol. Biochem. Behav. 17:469–492; 1982.
64. Wozniak, K. M.; Pert, A.; Mele, A.; Linnoila, M.: Antagonism of $5\text{-}HT_3$ receptor attenuates the effect of ethanol on extracellular dopamine. Eur. J. Pharmacol. 187:287–290; 1990.
65. Wroblewski, J. T.; Danysz, W.: Modulation of glutamate receptors: Molecular mechanisms and functional implications. Annu. Rev. Pharmacol. Toxicol. 29:441–447; 1989.
66. Yoshimoto, K.; McBride, W. J.; Lumeng, L.; Li, T.-K.: Alcohol stimulates the release of dopamine and serotonin in the nucleus accumbens. Alcohol 9:17–22; 1992.