

Effects of CA Antagonists on Ethanol-Induced Excitation in Habituated and Nonhabituated Mice: Interaction With Stress Factors?

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KOECHLING, U. M. AND Z. AMIT. *Effects of CA antagonists on ethanol-induced excitation in habituated and nonhabituated mice: Interaction with stress factors?* PHARMACOL BIOCHEM BEHAV 44(4) 791-796, 1993.—The effects of CA antagonists on ethanol induced locomotion in habituated (H) and nonhabituated (NH) mice was examined. H-mice were exposed to the testing apparatus for 4 days before testing. Mice were pretreated with pimozide (D₂ antagonist), Schering 23390 (D₁ antagonist), phenoxybenzamine (α_1 antagonist), or yohimbine (α_2 antagonist). Mice were then treated with ethanol. H mice had lower activity scores compared to NH mice. Ethanol produced an increase in activity for both groups. In NH animals, pimozide attenuated excitation in inverse relation to the ethanol dosage. In H mice, pimozide attenuated excitation only at doses that in themselves produced a decrease in activity. Schering 23390 reduced excitation only at doses that affected activity per se in both groups. Phenoxybenzamine reduced excitation dose-dependently in both groups. Yohimbine decreased excitation in both groups. Results suggest that stress emanating from a novel environment may affect not only activity per se but also the interaction between CA antagonists and ethanol.

Ethanol	Locomotion	Catecholamines	Novelty stress	Dopamine	Norepinephrine
Drug antagonists	Pimozide	Schering 23390	Phenoxybenzamine	Yohimbine	

PREVIOUS research (4,10) has suggested that ethanol can induce increases and decreases in motor activity and that both are dose-dependent (8,14,15,28,29).

Investigations of the neural substrate for ethanol-induced motor excitation suggested that both norepinephrine (NE) and dopamine (DA) may play a role in the mediation of this phenomenon (4, 11, 20, 21). In an attempt to delineate the relative contribution of DA and NE to ethanol-induced motor excitation we (18) previously assessed the effect of several catecholamine (CA) receptor antagonists on this behavior. More specifically, this study was designed to explore the relative contributions of the D₁ and D₂ DA receptors and the α_1 - and α_2 -NE receptors to ethanol-induced motor activation. The results of this study suggested that ethanol-induced excitation may be mediated by both DA, via the D₂ receptor, and by NE, via the α_1 receptor (18).

In addition to studies investigating the possible neural substrate of ethanol-induced excitation, there have also been investigators (6,22) who have addressed the possible effects of environmental variables, particularly stress and anxiety, on ethanol-induced activity. In this respect, it has been reported (22) that the magnitude of motor stimulation produced by ethanol was greater under conditions of bright rather than

dim lighting. Others (6) have also obtained similar results with Fast and Slow mice. They found that for these two genetic lines of mice, bred for differential response to the stimulatory properties of ethanol, the magnitude of response to ethanol was significantly greater under bright as opposed to dim illumination.

In contrast to the relatively few studies that have suggested a specific role for environmental variables in ethanol-induced activity, there have been a large number of investigations (1,16,27,31), which have assessed a more general interaction of CAs with environmental factors. Results from these studies have suggested that novelty-elicited changes in behavior involved, at least in part, the DA system. In particular, lesions of the mesolimbic DA system have been reported to disrupt increases in locomotion, rearing, and approach behaviors elicited by novel stimuli (12,13,26). On the other hand, systemic administration of the D₂ DA antagonist haloperidol has been shown to decrease novelty-induced grooming behavior (17). It has also been demonstrated that amphetamine depressed exploratory behaviors in a novel environment (19,25). A systematic examination (30) of the contribution of specific DA receptor sub-types in the modulation of novelty-induced grooming behaviors, suggested that the DA D₁ rather than D₂

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receptors played an important role in the mediation of this behavior. Although there have been a vast number of studies that have assessed the effects of DA on behaviors in novel and habituated conditions, most of these studies were conducted using rats, and relatively few studies have examined these effects in mice (23,25). Results of these studies (23,25) have suggested that, in mice, DA agonists, such as apomorphine and methamphetamine, decreased exploration in a novel environment. This decrease in exploration, however, was found to be significantly lower for mice previously exposed to the novel environment (24). Furthermore, it was found (25) that this effect was antagonized by neuroleptics such as benzamides tiapride and sulpiride, but not by thioridazine. These findings suggest that CA drugs acting on differential receptors may not only be mediating exploratory behavior, but may also be involved in the modulation of factors related to the exposure to a novel environment.

In similar fashion, a variety of studies have examined the involvement of DA in the mediation of exploratory behaviors induced by a novel environment, and other studies have assessed the contribution of NE to these effects (2,3,7,16,27). These studies (2,3) have suggested that NE may also play a role in the mediation of exploratory behavior measured in a novel environment. More specifically, it was found (3) that the α_2 receptor antagonist, idazoxan, decreased exploration in mice in a novel testing situation.

The data obtained by studies on the effects of both DA and NE on activity in a novel environment, enabled other researchers to examine the interaction between CAs, environmental variables and ethanol-induced motor excitation. The present investigation represents a further examination of the effects of different CA antagonists on ethanol-induced motor excitation in mice exposed to specific environmental manipulations. More specifically, it was the purpose of this study to investigate the possible interaction of the various DA and NE receptor subtypes, with the habituation to novelty and its related stress of ethanol-induced locomotion in mice. Schering 23390, a selective D_1 antagonist and pimozone, a D_2 antagonist, were utilized to examine the role of DA in ethanol excitation. Phenoxybenzamine, an α_1 antagonist, and yohimbine, an α_2 antagonist, were used to investigate the contribution of NE to ethanol induced motor activation. The effects of the latter antagonists were assessed in animals that were either naive, or that had been habituated to the testing apparatus.

EXPERIMENT 1: NOVEL ENVIRONMENT

METHOD

Male Swiss-Webster mice, weighing approximately 26–28 g at the time of testing were used in the present experiment. Mice were housed four to a cage in the animal facility, which was controlled for temperature and humidity with a 12L : 12D cycle, and with ad lib access to standard lab chow and water.

A 20% (v/v) ethanol solution was prepared by diluting 95% ethanol with tap water. Mice were injected with volumes of 5, 7.5, and 10 ml/kg to yield ethanol doses of 0.8, 1.2, or 1.6 g/kg. Pimozone was dissolved in 0.3% tartaric acid, and Schering 23390 was dissolved in 0.9% saline. Phenoxybenzamine was dissolved in glacial acetic acid, and the final solution made up with 5.5% glucose. Yohimbine was dissolved in 2N HCL and made up to volume with 0.9% saline. All injections were made intraperitoneally (IP) in a volume of 10 ml/kg. Mice were treated 30 min prior to testing with each of the

following: pimozone (0.0, 0.0321, 0.0625, 0.125, 0.25, and 0.5 mg/kg); Schering 23390 (0.0, 0.0125, 0.025, 0.5, and 0.1 mg/kg); phenoxybenzamine (0.0, 1.0, 2.0, 5.0, 10.0, and 15.0 mg/kg); yohimbine (0.0, 0.0125, 0.025, 1.0, 4.0, and 8.0 mg/kg); and, then injected with ethanol (0.0, 0.8, 1.2, and 1.6 g/kg). Doses of all compounds used in this experiment were determined on the basis of previous studies (3,7,9,10,18,20) concerning their CNS effects. Each mouse was pretreated with only one dose of each of the antagonists, and treated with only one dose of ethanol. Following the second set of injections, each animal was placed in an open-field apparatus for a 7-min period. The open-field consisted of a glass cylinder 22 cm in diameter and 25 cm high. The floor of the cylinder was divided into four equal quadrants. A locomotion score was assigned each time an animal crossed one of the lines with all four legs. Animals ($n = 6$ per group) were tested, in random order, between 8:00 a.m. and 3:00 p.m.

Data Analysis

Results were analyzed using a two-way independent analysis of variance (ANOVA). Post-hoc mean differences between groups were determined using Tukey's Honestly Significant Difference (HSD) test. Since our *a priori* assumptions, as derived from our hypotheses, focused on a comparison between habituated and nonhabituated animals as affected by each antagonist, carrying out separate statistical analyses did not violate our *a priori* assumptions.

EXPERIMENT 2: HABITUATED ENVIRONMENT

In Experiment 1 we assessed the effects of pimozone and Schering 23390, and the effects of phenoxybenzamine and yohimbine on ethanol-induced locomotion in animals that had not been previously habituated to the testing apparatus. In Experiment 2 all animals were habituated to the open-field for a period of 30 min on four consecutive days before testing, prior to receiving the same drug regimens as in Experiment 1. Testing took place on the day subsequent to habituation. Mice ($n = 6$ per group) were pretreated 30 min prior to testing, with either of the following: pimozone (0.0, 0.125, 0.25, and 0.5 mg/kg); Schering 23390 (0.0, 0.00625, 0.0125, 0.025, and 0.05 mg/kg); phenoxybenzamine (0.0, 0.5, and 1.0 mg/kg); yohimbine (0.0, 0.025, 0.5, and 1.0 mg/kg); and then injected with ethanol (0.0, 0.8, 1.2, and 1.6 g/kg). All other procedures were the same as in the first experiment.

Data Analysis

Statistical analyses of the effects of CA antagonists for animals that had been habituated to the testing apparatus prior to testing was carried out using separate two-way independent ANOVAS. Post-hoc differences were analyzed using Tukey's HSD tests.

EXPERIMENT 1

RESULTS

The results obtained via the ANOVA, revealed a significant main effect for both ethanol [$F(3, 99) = 24.63, p < 0.001$] and pimozone [$F(5, 99) = 6.174, p < 0.001$], and a significant interaction [$F(15, 99) = 3.76, p < 0.001$].

As can be seen from Fig. 1, ethanol produced a significant increase in motor activity for the 0.8 g/kg ($p < 0.01$) and 1.2 g/kg ($p < 0.05$) doses. The highest ethanol dose (1.6 g/kg)

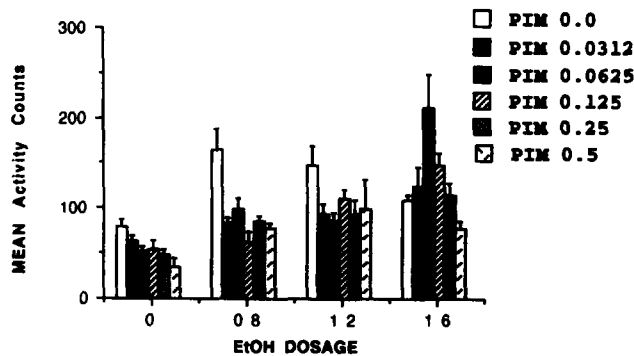


FIG. 1. Mean activity scores for nonhabituated animals pretreated with pimozide (mg/kg) at each ethanol dose (g/kg).

did not significantly increase activity compared to saline treated animals. Pretreatment with pimozide at all doses, produced no significant effect on motor activity by itself. At the 0.8 g/kg ethanol dose, pimozide at all doses produced a significant ($p < 0.05$) decrease in ethanol excitation. At the 1.2 g/kg ethanol dose, only the 0.0625 mg/kg pimozide dose produced a decrease ($p < 0.05$) in ethanol excitation. All other doses of pimozide did not significantly reduce ethanol-induced locomotion at the 1.2 g/kg ethanol dose. Also ethanol resulted in a significant increase ($p < 0.01$) in motor activity at the 1.6 g/kg ethanol dose. At the highest dose (1.6 g/kg) of ethanol only the 0.5 mg/kg pimozide dose reduced ($p < 0.05$) ethanol excitation (see Fig. 1).

A separate statistical analysis was carried out for animals pretreated with Schering 23390. A two-way ANOVA indicated a significant main effect for ethanol [$F(3, 82) = 69.62, p < 0.001$] and Schering 23390 [$F(4, 82) = 30.07, p < 0.001$], and a significant interaction [$F(12, 82) = 3.43, p < 0.001$].

Ethanol alone produced a significant increase ($p < 0.01$) in motor activity at all doses (see Fig. 2), compared to saline-pretreated controls. Schering 23390 by itself reduced motor activity at the 0.05 and 0.1 mg/kg doses ($p < 0.01$). These two doses also reduced ($p < 0.01$) ethanol induced motor activity at the 0.8 g/kg ethanol doses. All other doses of Schering 23390 neither effected motor activity per se, nor motor activity induced by ethanol.

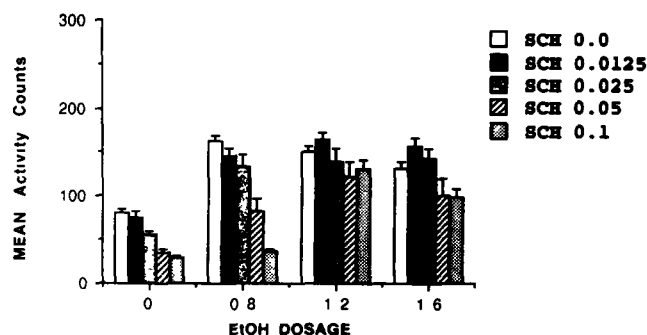


FIG. 2. Mean activity scores for nonhabituated animals pretreated with Schering 23390 (mg/kg) at each ethanol dose (g/kg).

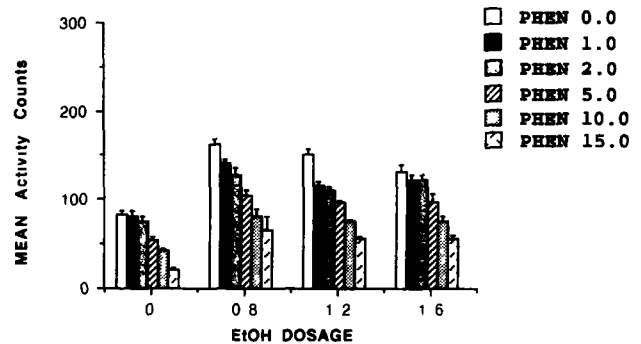


FIG. 3. Mean activity scores for nonhabituated animals pretreated with phenoxybenzamine (mg/kg) at each ethanol dose (g/kg).

A separate statistical analysis was computed for mice pretreated with phenoxybenzamine. Statistical analysis revealed significant main effects for ethanol [$F(5, 103) = 81.84, p < 0.001$] and phenoxybenzamine [$F(5, 103) = 95.33, p < 0.001$], and a significant interaction [$F(15, 103) = 2.84, p < 0.001$].

As can be seen from Fig. 3, significant increases ($p < 0.01$) in motor activity were produced by all three ethanol doses. Pretreatment with phenoxybenzamine alone attenuated motor activity at the 5.0, 10.0, and 15.0 mg/kg ($p < 0.01$) doses. These three doses also attenuated motor activity induced by all three ethanol doses. The 1.0 and 2.0 doses of phenoxybenzamine had no effect on motor activity per se. Of these two doses, the 2.0 mg/kg dose of phenoxybenzamine significantly reduced ethanol excitation at the 0.8 and 1.2 ethanol doses ($p < 0.01$). The lowest dose (1.0 mg/kg) of phenoxybenzamine significantly reduced ethanol excitation at the 1.2 g/kg ethanol dose ($p < 0.01$).

Significant main effects were obtained for ethanol [$F(3, 103) = 115.54, p < 0.001$] and yohimbine [$F(5, 103) = 77.51, p < 0.001$]. The interaction between these two factors was also significant [$F(15, 103) = 8.89, p < 0.001$].

Only the highest dose of yohimbine (8.0 mg/kg) significantly ($p < 0.001$) reduced motor activity per se (see Fig. 4). This latter dose also reduced ethanol excitation for all three

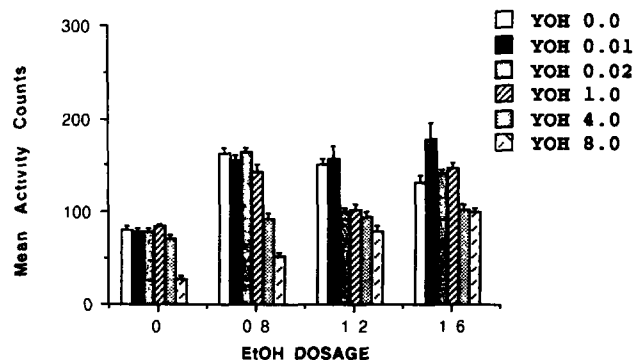


FIG. 4. Mean activity scores for nonhabituated animals pretreated with yohimbine (mg/kg) at each ethanol dose (g/kg).

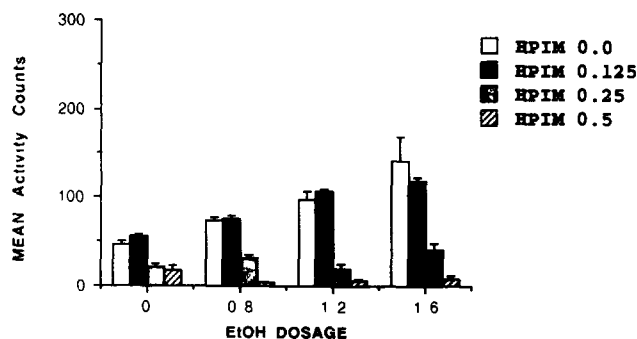


FIG. 5. Mean activity scores for habituated animals pretreated with pimozide (mg/kg) at each ethanol dose (g/kg).

doses of ethanol ($p < 0.01$). Yohimbine at the 4.0 mg/kg dose had no effect on motor activity per se, but reduced ethanol excitation at all ethanol doses ($p < 0.01$). The lowest dose (0.01) of yohimbine however, produced a significant ($p < 0.01$) increase in motor activity induced by the 1.6 g/kg ethanol dose.

EXPERIMENT 2

The results of the ANOVA revealed significant main effects for pimozide [$F(3, 80) = 497.19, p < 0.001$] and ethanol [$F(3, 80) = 94.16, p < 0.001$]; and, a significant interaction [$F(9, 80) = 29.79, p < 0.001$].

While all doses of ethanol significantly ($p < 0.01$) increased motor activity, the highest dose (1.6 g/kg) produced the greatest increase in activity (see Fig. 5). Only the lowest (0.125 mg/kg) dose of pimozide had no effect on motor activity when administered alone, the two higher pimozide doses (0.25 and 0.5 mg/kg) significantly ($p < 0.01$) reduced motor activity. This dose (0.125 mg/kg) had no effect on ethanol induced motor activation.

The results of the ANOVA indicated significant main effects for Schering 23390 [$F(4, 100) = 53.07, p < 0.001$] and for ethanol [$F(3, 100) = 123.11, p < 0.001$]; and, a significant interaction [$F(12, 100) = 18.29, p < 0.001$].

Ethanol alone significantly ($p < 0.01$) increased motor activity at all doses. Only the lowest dose (0.00625 mg/kg) of Schering 23390 had no effect on motor activity per se (see

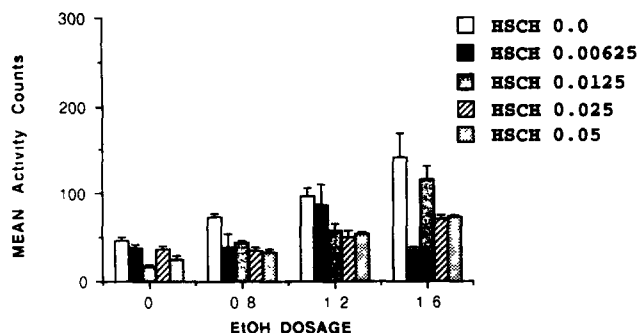


FIG. 6. Mean activity scores for habituated animals pretreated with Schering 23390 (mg/kg) at each ethanol dose (g/kg).

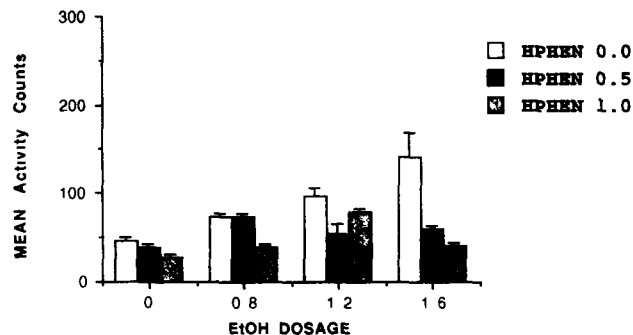


FIG. 7. Mean activity scores for habituated animals pretreated with phenoxybenzamine (mg/kg) at each ethanol dose (g/kg).

Fig. 6). This dose (0.00625 mg/kg) significantly ($p < 0.01$) attenuated ethanol induced activity at the 0.8 and 1.6 g/kg ethanol doses.

The results from a two-way independent ANOVA revealed significant main effects for phenoxybenzamine [$F(1, 40) = 187.54, p < 0.001$] and for ethanol [$F(3, 40) = 40.94, p < 0.001$]. The interaction between these two factors was also significant [$F(3, 40) = 29.75, p < 0.001$].

As can be seen from Fig. 7, phenoxybenzamine at all doses (0.5 and 1.0 mg/kg) had no effect on motor activity per se. Only the lowest dose (0.5 mg/kg) of phenoxybenzamine did not reduce ethanol induced excitation, while the 1.0 mg/kg dose significantly ($p < 0.01$) attenuated ethanol induced motor activity at all doses of ethanol.

The results from a two-way independent ANOVA indicated significant main effects, for yohimbine [$F(3, 80) = 167.76, p < 0.001$], and for ethanol [$F(3, 80) = 53.25, p < 0.001$]; and, a significant interaction [$F(9, 80) = 20.75, p < 0.001$].

The lowest dose of yohimbine (0.025 mg/kg) had no effect on motor activity per se, while this dose also significantly ($p < 0.01$) reduced ethanol induced excitation at all ethanol doses. All other doses of yohimbine (see Fig. 8) alone significantly ($p < 0.01$) reduced motor activity.

DISCUSSION

Ethanol, for all test doses, was observed to produce an increase in locomotion, in both nonhabituated and habituated

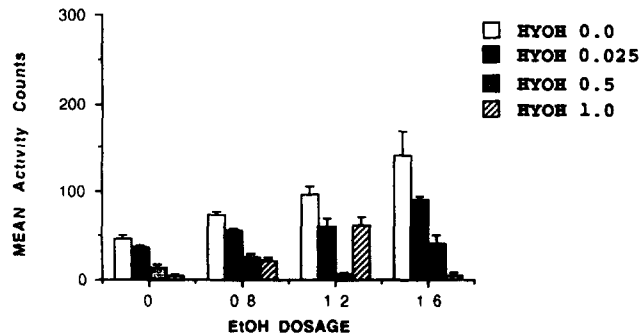


FIG. 8. Mean activity scores for habituated animals pretreated with yohimbine (mg/kg) at each ethanol dose (g/kg).

animals. These findings were consistent with previous reports (8,11,14,20,28,29) in the literature, that the administration of low doses of ethanol will induce an increase in motor activity in mice.

Although ethanol increased locomotion in both NH and H animals, some differences of the relative effects of ethanol in the two latter conditions were observed. Comparison between NH and H animals suggested that overall scores of ethanol induced activity were generally lower for the H animals. However, in contrast to the NH animals, H animals exhibited the greatest increase in locomotion following the administration of the highest dose of ethanol. In addition, the variability in scores was generally lower in H as opposed to NH animals.

The results of the present study also supported previous findings suggesting that the CAs play a role in the mediation of the stimulatory properties of ethanol (11,14,20,21,29).

Previous results (18) suggested a role for the DA, D_2 receptor and the NE, α_1 receptor in the mediation of ethanol induced motor excitation in NH animals. Specifically, it was observed that pimozide and phenoxybenzamine, in doses that in themselves did not interfere with motor activity, produced the greatest attenuation of ethanol induced activation.

For the H condition, only the lowest dose of the D_2 receptor antagonist, pimozide, produced a small but significant decrease in ethanol induced activation, without having an effect on motor activity per se. This suggested that pimozide produced a differential effect on ethanol excitation when animals have been previously habituated to the testing apparatus. It is noteworthy that the effect of pimozide for the H condition was restricted to its lowest dose. More specifically, pimozide attenuated ethanol excitation over a wider range of doses, primarily, when animals were naive to the testing environment.

Similarly, we previously reported that in NH animals, the D_1 receptor antagonist, Schering 23390 had a nonspecific effect, since it attenuated ethanol induced locomotion only at doses which also reduced motor activity per se. In the present study with H animals, only the lowest dose of Schering 23390 attenuated ethanol induced motor activity at the 0.8 and 1.6 g/kg ethanol doses. This suggested that Schering 23390 had differential effects for animals in the H as opposed to NH condition. Further, it suggested that Schering 23390 may produce specific effects in terms of attenuating ethanol-induced excitation when environmental factors related to novelty are controlled for.

With regards to phenoxybenzamine, previous results (18) showed that this α_1 antagonist produced a dose-dependent reduction in ethanol-induced motor activation in NH animals. Furthermore, similar results were obtained in the H animals. Phenoxybenzamine, in these animals, produced a reduction in ethanol-induced activation at doses which had no effect on motor activity per se.

The results of the present investigation suggested that, unlike the results obtained for the involvement of the two subpopulations of DA receptors, the NE α_2 receptors played a role in ethanol-induced excitation for H and NH animals. More specifically, the medium dose (4.0 mg/kg) of yohimbine reduced ethanol excitation. Note that, at this (4.0 mg/kg) and lower doses, yohimbine had no effect on motor activity per se for NH animals. Similarly, in H animals the lowest dose of yohimbine attenuated ethanol excitation, but had no effect when administered alone. Despite the present data, the involvement of the α_2 receptor in ethanol-induced excita-

tion remains somewhat unclear, because it has been suggested that yohimbine lacks specificity for the NE α_2 receptor (5, 9). Therefore, the mechanism of the effect of yohimbine on ethanol-induced excitation still awaits more precise clarification.

Overall, our results suggested that exposure to the novelty of the open-field affected motor activity and changed the pattern as well as magnitude of the effects of CA antagonists on locomotion induced by stimulatory doses of ethanol. This change in activity was found to be specific to some antagonists but not to others. Furthermore, in both H and NH groups of mice, the effects of the different antagonists were evident only with certain doses of ethanol, but not with others. We previously (18) reported that NH mice pretreated with either pimozide, Schering 23390 or yohimbine, and subsequently treated with the highest dose of ethanol (1.6 g/kg), were observed to exhibit an augmentation of locomotor activity which was significantly higher than activity scores in animals treated with ethanol alone. This was not the case for groups of animals that had been pretreated with phenoxybenzamine. More specifically, for groups of mice treated with phenoxybenzamine, no increase in locomotion was seen at the highest dose of ethanol (1.6 g/kg). In addition, all groups of animals in the H condition, regardless of which pretreatment condition, did not display this increase in activity. The results of the present study therefore suggested that the open-field activity of animals not habituated to this apparatus may be confounded by stress due to novelty of the testing situation. Therefore, the data from H animals seem to be more amenable to interpretation than data of NH animals. The present results further suggest that research that makes use of paradigms in which environmental factors, such as novelty to the testing apparatus were not controlled by the experimental design itself, may in fact lead to spurious results. This appears to be true in general, and in particular, seems to apply to studies where ethanol is also exerting its effects on behavior.

In conclusion, our results suggest that CAs play a role in ethanol-induced motor excitation for both NH and H animals. If we accept the notion that NH and H groups can be placed on a gradient of stress, then, the current results suggested that DA and NE contribute differentially to ethanol induced motor excitation. More specifically, it was observed that the D_2 receptor played a role in the mediation of ethanol excitation in a novel testing situation, but that this effect was ameliorated when factors due to novelty were controlled for. The involvement of the D_1 receptor in ethanol excitation also seems to be modulated by novelty specific to the testing apparatus. Current results suggest that the involvement of D_1 receptor in this behavior is restricted to H conditions and not NH conditions. Overall, these results suggest that the contribution of DA to ethanol induced excitation is modulated by stress due to a novel testing situation. The involvement of NE in ethanol induced motor activation does not seem to be related to the novelty stress. The present results suggest that, for the α_1 receptor specifically, factors related to novelty stress did not contribute significantly to the magnitude of its effects in terms of mediating ethanol induced motor activity.

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