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Ethanol-Induced Depression of Aggression in Mice Antagonized by Hyperbaric Exposure

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ALKANA, R. L., J. F. DEBOLD, D. A. FINN, M. BABBINI AND P. J. SYAPIN. *Ethanol-induced depression of aggression in mice antagonized by hyperbaric exposure.* PHARMACOL BIOCHEM BEHAV **38**(3) 639–644, 1991.—The present study investigated the effect of hyperbaric exposure on ethanol-induced depression of aggressive behavior measured by resident-intruder confrontations. Adult male CFW mice (residents) were paired with females and housed together for 26 days. Then, resident mice were intubated with either ethanol (2 g/kg) or water (20 ml/kg) and were exposed to 1 atmosphere absolute (ATA) air, 1 ATA helium oxygen (heliox) or 12 ATA heliox using a within-subjects counterbalanced design. Thirty minutes after intubation an intruder was introduced. Ethanol significantly decreased aggressive behaviors (attack latency, attack bites, sideways threats, tail rattles and pursuit) in 1 ATA-treated animals. Pressure completely antagonized the depression of aggression induced by ethanol. Ethanol alone and pressure alone did not significantly affect nonaggressive behaviors. There were no statistically significant differences between groups in blood ethanol concentrations 50 minutes after intubation. These results suggest that ethanol's effects on aggressive behavior result from the same membrane actions leading to loss of righting reflex, depression of locomotor activity, tolerance and dependence.

Atmospheric pressure Hyperbaric Alcohol-ethyl Ethanol Behavior Aggression
Mechanisms of anesthesia Mechanisms of intoxication Mice

THE general anesthetic effects of ethanol and other intoxicant-anesthetics can be reversed in a wide variety of species (tadpoles, newts, mice and rats) by exposure to atmospheric or hydrostatic pressures of 100 to 300 atmospheres absolute (ATA) (17, 18, 20, 22). In rodents, the acute and chronic behavioral effects of ethanol can be antagonized by exposure to smaller increases in pressure. Here, exposure to 12 ATA of helium-oxygen (heliox) gas mixtures reduced the duration of ethanol-induced loss of righting reflex (4,5) and increased the blood and brain ethanol concentrations at return of the righting reflex (23) in mice. In addition, hyperbaric exposure precipitated and exacerbated withdrawal symptoms in mice previously made physically dependent on ethanol (3), and attenuated the development of chronic functional ethanol tolerance and physical dependence when exposure occurred during the acquisition period (7).

Mechanistic studies indicate that the antagonism does not reflect pressure- or helium-induced changes in body temperature (23), oxygen partial pressure (5), general excitability of the brain (38) or ethanol pharmacokinetics (5, 6, 23). Further, the pharmacological and biophysical characteristics (dose-response; pressure-response; temperature-pressure interaction) of these low-level hyperbaric studies closely match or parallel those of high-pressure reversal of anesthesia (17, 28, 29, 36, 42). Collectively, these findings support the hypothesis that low-level hyperbaric exposure directly blocks or reverses the membrane actions of ethanol leading to acute intoxication, tolerance and physical dependence.

If hyperbaric exposure blocks or reverses the initial actions of ethanol leading to intoxication, then the antagonist effects of pressure should extend to all intoxicating effects of ethanol mediated by the same pressure-sensitive mechanism(s). However, the ability of hyperbaric exposure to antagonize a broad spectrum of ethanol's behavioral effects has not been explored. Most investigations have focused on the ability of hyperbaric exposure to antagonize the anesthetic and hypnotic effects of ethanol. Recent findings demonstrating that hyperbaric exposure antagonizes the

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depressant effects of ethanol on locomotor activity (14,37) support the hypothesis that a common mechanism underlies ethanol's anesthetic and behavioral effects at subhypnotic doses, but the effects of pressure on other aspects of intoxication have not been investigated.

To further test this hypothesis, the present study investigated the ability of hyperbaric exposure to antagonize the inhibitory effect of a moderate, subhypnotic dose of ethanol on aggressive behavior in mice. We selected aggressive behavior because it provides a sensitive behavioral assay of ethanol's action on the central nervous system. A number of investigators have reported that ethanol can inhibit aggression in mice at doses which do not significantly suppress other social or nonaggressive behaviors (11, 21, 26, 43).

METHOD

Animals and Housing

Adult male and female CFW mice (Charles River Laboratories) were individually housed in male-female (resident) pairs in polycarbonate cages ($17 \times 28 \times 12$ cm) for 26 days before the beginning of the experiment. Male CFW mice of the same age (intruder mice) were housed in groups of 10 or 20 in larger polypropylene cages ($36 \times 56 \times 18$ cm) for the same period. The floors of the cages were covered with pinewood bedding. All animals were maintained at 22 ± 1°C and had free access to Wayne Rodent Blox and tap water. They were exposed to a 12-hour light:dark cycle (0700 on). The animals were 61 days old and weighed 26.3 ± 0.5 g at the start of the experiment.

Overall Protocol and Experimental Design

Animals were brought to the laboratory 30 minutes prior to the initiation of testing each day. Food, but not water was removed from resident and intruder cages at this time. The female and any pups in the resident cage were removed to a new cage immediately prior to administering ethanol or water.

The experiment was performed according to a within-subjects balanced cross-over design. Animals were tested between 0900 and 1300 hours. The resident male was administered either 2.0 g/kg ethanol (20% w/v in water) or 20 ml/kg water by gastric gavage in its first session and received the alternative treatment in its second session one week later. Following intubation, the resident was marked for easy identification and returned to its home cage. At 9.5 minutes postintubation, a randomly selected intruder male was placed into the delivery system in the lid of the cage. Ten minutes postintubation, the cage with both animals in separate compartments was placed into a stainless steel hyperbaric chamber with transparent Plexiglas end pieces. The atmospheric conditions within the chambers were adjusted to 1 ATA air, 1 ATA heliox or 12 ATA heliox. All three atmospheric conditions were tested simultaneously each day to eliminate bias from order effects or day to day variability. Thirty minutes following intubation, the intruder was introduced into the resident's cage through a motorized door in the cage lid. The resident animal's behavior within the chamber was recorded on video tape for 5 minutes immediately prior to introduction of the intruder, and for up to 10 minutes afterwards. Aggressive and nonaggressive behaviors were later scored from the video tape recordings, as specified below, by a trained observer blind to the treatment conditions. Resident mice that received ethanol on their second day of testing were rapidly decompressed 48 minutes after intubation. At 50 minutes postintubation, a 20 μl blood sample was taken from the retro-orbital sinus (33) of this subset of mice, prepared and frozen for determination of ethanol concentrations by gas chromatography using a previously described head space method (23).

Experimental Procedures

Assessment of aggressive behavior. During the two-week period prior to initiating experimentation, resident males were tested for aggressive behaviors in their home cage three times. For each of these trial sessions, the resident was briefly exposed to a lightly restrained male intruder. Only resident animals that exhibited attack bites in at least one of these screening sessions continued in the experiment (5 of 25 mice were excluded). Subsequently, resident mice which exhibited aggressive behaviors were given water by gavage twice during the week prior to experimentation in order to familiarize them with this procedure.

The methodology for the quantification of aggression has been previously described (11,25). Each behavioral item was encoded by the depression of a designated key on a hand-held console when the behavior started and the release of the key when it ended. The console was interfaced with a PDP 11/73 computer (Digital Equipment Corporation, Maynard, MA). The frequency (total number of occurrences in five minutes) and duration of aggressive behaviors (attack bites, sideways threat postures, tail rattles, pursuit) and nonaggressive behaviors (autogrooming, rearing and climbing, walking, ano-genital investigation of intruder) as well as attack latency were determined by evaluating the videorecords of resident-intruder confrontations. Scoring began with the introduction of the intruder, 30 minutes after intubation, and ended 5 minutes after the first attack bite. Scoring was terminated 5 minutes after introduction of the intruder if no attack had occurred. Resident mice that did not attack during this period were assigned an attack latency of 300 seconds.

Atmospheric conditions. The separated resident-intruder pair was placed into an 18-liter, cylindrical hyperbaric chamber. The atmospheric pressure and gas conditions within the hyperbaric chambers were brought to 1 ATA air or to 1 or 12 ATA heliox using premixed certified compressed gases (MG Industries, Los Angeles). The 12 ATA mice were pressurized at a rate of 2 ATA per minute using previously described procedures which provided adequate oxygenation and avoided oxygen toxicity during compression (3,37). The final oxygen partial pressure in all conditions was 0.2 ATA. Following compression, gas flow through the chambers was set at 1.2 liters/minute. For water-treated animals, the internal chamber temperatures were adjusted as follows: 25°C for 1 ATA air, and 30°C for 1 and 12 ATA heliox. For ethanol-treated animals the temperatures were: 33.5°C for 1 ATA air and 34.5°C for 1 and 12 ATA heliox. Previous studies demonstrated that these ambient temperatures offset the hypothermic effects of helium and ethanol (23). The purpose of preventing hypothermia in the animals was two-fold. The first was to eliminate differences in body temperature between ethanol treatment groups since body temperature has been shown to strongly influence brain sensitivity to ethanol's depressant effects on other behaviors (1,2). The second was to focus the experiment on the direct effects of ethanol on aggressive behavior by eliminating effects which might be secondary to ethanol- (or heliox) induced hypothermia. The ambient temperature within the chambers was maintained within ± 0.5°C of the designated temperatures by an automated system described elsewhere (37).

Data Analysis

Separate two-way Analyses of Variance (ANOVA) were used to determine if there were significant main effects of and interactions between ethanol dose and atmospheric treatment condition on the frequency and/or duration of aggressive and nonaggressive behaviors. These were followed by simple main effect analyses when warranted. The Newman-Keuls test was utilized for post hoc comparisons between groups (41). Fisher's Exact Test was used to compare the proportions of animals that attacked. The

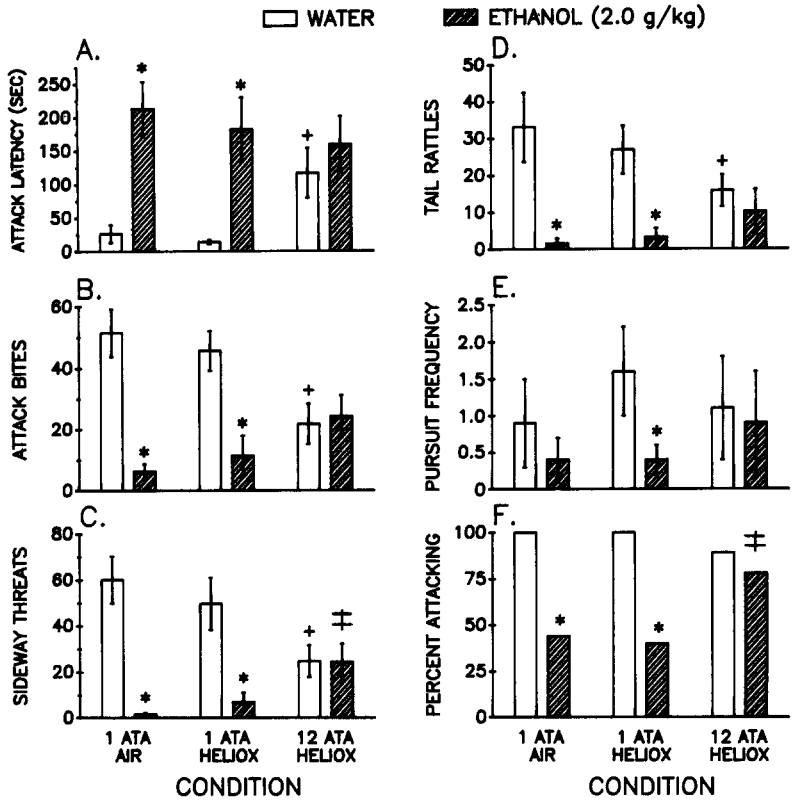

FIG. 1. The effects of ethanol and atmospheric treatment on aggressive behavior measured by (A) attack latencies, (B) attack bites, (C) sideways threats, (D) tail rattles, (E) pursuit, and (F) percent animals attacking. Ethanol significantly decreased aggressive behaviors in the 1 ATA control conditions, but not in the 12 ATA condition for all measures of aggression tested. The number of sideways threats and percent attacking for mice given ethanol was significantly higher in the 12 ATA than in the 1 ATA conditions. In animals given water, exposure to 12 ATA heliox significantly reduced attack latencies, attack bites, sideways threats and tail rattles, but did not significantly alter pursuit or the percent of animals attacking. Values shown represent the mean ± SE for 8–10 animals per group for the behavior during the 5-minute rating period. See results for ANOVAs. [*$p<0.05$, ethanol versus respective 1 ATA water control; †$p<0.05$, 12 ATA water vs. 1 ATA water controls, Newman-Keuls (A–E) or Fisher's (F) tests; ‡$p<0.05$, 12 ATA ethanol versus collapsed 1 ATA ethanol controls, Newman-Keuls (C) or Fisher's (F) tests].

sequence of occurrence of aggressive behaviors was subjected to a lag sequential analysis (40). A p level of <0.05 was considered statistically significant.

RESULTS

The effects of ethanol and atmospheric treatment on aggressive behaviors are illustrated in Fig. 1. Two-way ANOVA indicated that administration of 2.0 g/kg ethanol significantly altered measures of aggressive behavior including attack latencies, $F(1,25)=20.19$, $p<0.01$ (Fig. 1A), frequency of attack bites, $F(1,25)=36.87$, $p<0.01$ (Fig. 1B), sideways threat postures, $F(1,25)=40.32$, $p<0.01$ (Fig. 1C), tail-rattles, $F(1,25)=31.34$, $p<0.01$ (Fig. 1D) and pursuit, $F(1,25)=4.73$, $p<0.05$ (Fig. 1E). The interaction between ethanol and atmospheric conditions was significant for attack bites, $F(2,25)=10.16$, $p<0.01$, sideways threat postures, $F(2,25)=9.38$, $p<0.01$ and tail rattles, $F(2,25)=4.51$, $p<0.05$.

Further analyses indicated that ethanol significantly increased attack latencies (Fig. 1A) and decreased attack bites (Fig. 1B), sideways threats (Fig. 1C), tail rattles (Fig. 1D), and pursuit frequency (Fig. 1E) in the 1 ATA-exposed animals compared to their respective water controls. In contrast, the level of aggression measured by these behaviors in the 12 ATA-exposed mice given ethanol was not significantly different from that seen when the same animals were tested at 12 ATA after receiving water (Fig. 1A–E). In addition, Fisher's tests indicated that ethanol did not significantly reduce the percent of mice that attacked intruders in the hyperbaric group, whereas the proportion of mice attacking was significantly reduced following ethanol in both 1 ATA control groups ($p=0.03$, 1 ATA air; $p=0.01$, 1 ATA heliox) (Fig. 1F). Moreover, the level of aggressive activity under ethanol measured by sideways threats and the percent of animals attacking was significantly higher in mice exposed to 12 ATA heliox than in mice exposed to the 1 ATA conditions (Fig. 1C and F). Collectively, these results indicate that hyperbaric exposure antagonized the depressant effect of ethanol on the aggressive behaviors measured.

Although the mice tested under 12 atmospheres did not show any suppressive effects of ethanol, there did appear to be an effect of the hyperbaric testing condition on baseline levels of some

TABLE 1

NONAGGRESSIVE BEHAVIORS OF MALE MICE TREATED WITH ETHANOL OR WATER (PO) UNDER DIFFERENT ATMOSPHERIC CONDITIONS

	Atmospheric Condition and Treatment					
	1 ATA Air (n=9)		1 ATA Heliox (n=10)		12 ATA Heliox (n=9)	
Behavior	Water	Ethanol	Water	Ethanol	Water	Ethanol
Autogroom (frequency)	2.0 ± 0.7	3.6 ± 0.9	3.8 ± 1.1	5.3 ± 2.6	4.1 ± 1.0	5.0 ± 1.2
Rear/Climb (s)	2.5 ± 1.0	8.0 ± 2.6	3.1 ± 1.9	2.9 ± 1.4	10.1 ± 3.5	5.7 ± 1.8
Walk Duration (s)	56.7 ± 5.7	66.9 ± 5.9	57.6 ± 4.9	45.2 ± 7.4	42.5 ± 5.3	69.4 ± 12.5*
Investigation of Intruder (s)	16.7 ± 4.0	14.1 ± 4.1	30.5 ± 15.5	7.5 ± 2.6	5.9 ± 2.0	12.2 ± 3.4

*$p<0.05$ vs. respective water control (Newman-Keuls test).

The values represent the mean ± SE for the frequency (total occurrences in 5 minutes) or duration in seconds for the behavior during the 5-minute rating period for the mice depicted in Fig. 1. See the Method section for details and the Results section for ANOVAs.

aspects of aggression seen after water administration. An analysis of the simple main effects of atmospheric condition followed by post hoc testing indicated that mice given water and exposed to 12 ATA heliox had significantly fewer attack bites, $F(2,25) = 6.37$, $p<0.01$ (Fig. 1B), sideways threat postures, $F(2,25) = 5.42$, $p<0.05$ (Fig. 1C) and tail rattles, $F(2,25) = 5.64$, $p<0.01$ (Fig. 1D) and had longer attack latencies, $F(2,25) = 4.64$, $p<0.05$ (Fig. 1A) than mice given water and exposed to 1 ATA conditions. Importantly, hyperbaric exposure per se did not significantly affect the percent of resident animals that attacked the intruders (Fig. 1F).

Sideways threats by the resident generally precede and follow bouts of attack bites directed toward the intruder. Pursuit of the intruder, although infrequent, usually occurs between bouts of attack bites (26). Lag sequential analysis indicated that this sequence or patterning of aggressive behavior was not altered by either ethanol or pressure. If the behaviors occurred at all, they occurred in the normal sequence.

In the overall statistical analysis of behavior in the animal's home cage there were no systematic effects of ethanol on nonaggressive behaviors by the resident (Table 1). Specifically, autogrooming, ano-genital investigation of the intruder and rearing and climbing the walls were not significantly altered by ethanol. The only behavior for which there was an overall effect of ethanol was time spent walking during the test, $F(1,24) = 5.29$, $p<0.05$. This measure was significantly increased by ethanol in the 12 ATA condition.

There were no statistically significant differences between groups in the blood ethanol concentrations taken 50 minutes after ethanol administration, $F(2,11) = 1.43$, $p>0.25$. The mean ± SE blood ethanol concentrations were 2.54 ± 0.07, 2.26 ± 0.21 and 2.07 ± 0.22 mg/ml for the 1 ATA air (N=4), 1 ATA heliox (N=5) and 12 ATA heliox (N=5) mice, respectively.

DISCUSSION

Exposure to 12 ATA heliox completely antagonized the statistically significant depressant effect of ethanol on aggressive behaviors in male CFW mice. These results agree with and extend previous findings in C57 and BALB mice which demonstrated that hyperbaric exposure antagonizes acute ethanol-induced loss of righting reflex (4, 5, 23) and depression of locomotor activity (37) and attenuates the development of tolerance and physical dependence (7). Taken together, these findings support the hypothesis that a common, pressure-sensitive mechanism, which may act at one or more molecular sites, underlies a broad spectrum of ethanol's acute and chronic behavioral effects.

Exposure to 12 ATA decreased some measures of baseline aggressive behaviors in animals given water compared to similarly treated 1 ATA air and heliox controls. Although the reason for the decrease is unknown, pressure may have altered the auditory and olfactory cues by which the resident identifies or finds the intruder. Resident animals may use auditory cues to localize intruders (30). These cues could have been altered by the increased pressure or masked in part by the sounds of the gas flowing through the chamber. Similarly, olfactory cues represent the critical stimulus which elicits the resident to attack the intruder (10). The physical effects of increased atmospheric pressure may have altered the strength or other aspects of this stimulus. In previous investigations, exposure to 12 ATA heliox depressed spontaneous locomotor activity, measured by an automated array of light-sensitive sensors, in saline-treated C57 mice (37). Although not evident in the activity measures utilized in the present experiment, which used visual inspection, the previous study suggests that hyperbaric-induced reductions in activity may have contributed to the decrease in baseline aggression in the present study.

The significant depressant effect of 12 ATA heliox on some aggressive behaviors in the water controls makes the effect of hyperbaric exposure on ethanol more difficult to interpret than if no effect of pressure on control animals occurred since a shift in baseline can influence interactions (34). However, this shift cannot explain the findings of the present experiment for the following reasons. First, within-subject comparisons indicated that there were no statistically significant differences between ethanol and water treatments in mice exposed to 12 ATA heliox for any of the measures of aggressive behavior employed suggesting that exposure to 12 ATA heliox completely offset ethanol's depressant effect on aggression. Second, the extent of aggressive behavior was notably higher in the mice given water and exposed to 12 ATA heliox than in animals given ethanol and tested at 1 ATA air or

heliox indicating that the failure of ethanol to depress aggression in 12 ATA-exposed mice cannot be attributed to a floor effect. Third, the number of sideways threats and percent of animals attacking under ethanol was significantly higher in the 12 ATA heliox versus 1 ATA conditions indicating that antagonism could be demonstrated despite the baseline shift. Collectively, these results provide solid evidence that hyperbaric exposure antagonized ethanol-induced depression of aggressive behavior.

Although the mechanism by which pressure antagonizes ethanol's behavioral effects is uncertain, hyperbaric exposure did not significantly alter blood ethanol concentrations taken 50 minutes after intubation. This finding agrees with previous work indicating that hyperbaric exposure antagonizes ethanol by reducing brain sensitivity to ethanol, not by changing the pharmacokinetics of ethanol (5, 6, 23).

The antagonistic effect of pressure on ethanol-induced depression of aggressive behavior could reflect a pressure-induced increase in baseline aggressive behavior or an increase in general excitability of the central nervous system. However, hyperbaric exposure decreased aggressive behavior in water-treated mice in the present study. In addition, recent evidence indicates that exposure to 12 ATA heliox does not significantly change the seizure threshold for picrotoxin, isoniazid and other convulsant drugs (38). Therefore, it is unlikely that the present results reflect pressure-induced increases in aggressive behavior or CNS excitability. Previous work has also eliminated changes in oxygen partial pressure (5) or body temperature (23) as factors mediating the antagonism.

Further research is necessary to establish the mechanism by which pressure antagonizes ethanol's behavioral effects. Nonetheless, the available evidence from high-pressure studies of intoxicant-anesthetics indicates that pressure acts by affecting their initial perturbing action on membranes (9, 17, 18, 24, 31, 35, 39), their effects on neurochemical function (8, 15, 16, 19, 32, 44) or by forcing the drugs out of critical sites (12,13). Taken with the present and previous results showing that pressure antagonizes a broad spectrum of ethanol's acute and chronic effects, these mechanistic studies indicate that hyperbaric exposure can be used as a tool for investigating the neurochemical mechanisms which cause acute intoxication, tolerance and physical dependence.

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