Pharmacology Biochemistry and Behavior, Vol. 41, pp. 663-664, 1992

0091-3057/92 $5.00 + .00

BRIEF COMMUNICATION

Ethanol's Antiseizure Efficacy Is Reduced by Stress

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Received 20 November 1990

MASTROPAOLO, J., M. R. NOVITZKI AND S. I. DEUTSCH. *Ethanol's antiseizure efficacy is reduced by stress.* PHARMACOL BIOCHEM BEHAV 41(3) 663-664, 1992.—The ability of ethanol to antagonize the electrical precipitation of seizures in an incremental electroconvulsive shock paradigm was examined in groups of stressed and control mice. In stressed mice, the dose-response curve for ethanol's antiseizure efficacy was down-shifted and right-shifted relative to controls. These data may have clinical implications with respect to the interaction between stress, ethanol, and proneness to seizures.

Seizure Stress Ethanol Electroconvulsive shock

USING a novel outcome measure [i.e., incremental electroconvulsive shock (IECS)], previous work demonstrated that stress reduced the antiseizure efficacy of flurazepam (1). Those data are consistent with work showing a reduction in in vivo benzodiazepine receptor binding following stress in the intact animal (4).

Ethanol has been reported to potentiate GABA-stimulated chloride ion uptake into a cell-free vesicular preparation, containing pre- and postsynaptic elements, at concentrations relevant to acute intoxication in the nontolerant human (3). This effect of ethanol results from a selective interaction with the benzodiazepine binding site on the $GABA_A$ receptor complex (2).

In view of the ability of stress to reduce the antiseizure efficacy of flurazepam and the "cross-tolerance" between benzodiazepines and ethanol, it would be expected that stress would alter the antiseizure efficacy of ethanol in the IECS paradigm. Therefore, we examined the effect of cold water swim stress on the ability of ethanol to alter the threshold voltage for seizure production in the IECS paradigm.

METHOD

Animals

Experimentally naive, male NIH Swiss mice weighing approximately 25-30 g were used throughout.

Drugs

Absolute ethanol (UPS 200 proof) was obtained from the Florida Distillers Company (Alfred, FL). Absolute ethanol was dissolved in distilled, deionized water. Drug and vehicle were prepared freshly on the day of each experiment; they were injected IP in a volume of 0.01 ml/g of body weight.

Stress Procedure

Mice were forced to swim in cold (6°C) water for 10 min 24 h prior to testing in the IECS paradigm.

IECS Procedure

In the IECS procedure, a Hittman electroconvulsive shock generator (Medcraft model B24-III) was utilized to administer 0.3 s of voltage via earclip electrodes. The procedure began with 70 V and increased every 2 s in 10-V increments until a full seizure (maximal tonic hindlimb extension) occurred or 170 V was reached. The antiseizure efficacy of ethanol was assessed in groups that received injections of either vehicle or increasing doses of ethanol (i.e., 0.56, 0.75, 1.0, 1.34, and 1.8 g/kg) 20 min prior to the IECS procedure. Groups of 12 mice were tested in each of the experimental conditions.

Data were analyzed with a two-way analysis of variance (ANOVA). All reports of statistical significance were based on a p value of <0.05.

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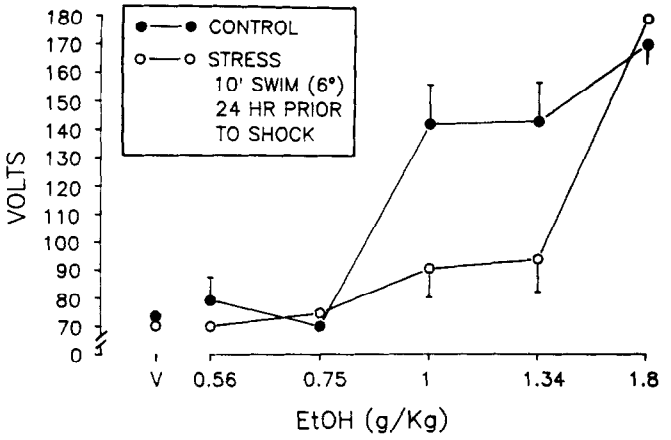

FIG. 1. Mean seizure voltage for control mice (closed circles) and mice stressed (open circles) 24 h prior to being injected with either the distilled water vehicle (unconnected points above V) or one of five doses of ethanol. The vertical lines through the points represent the SEM.

RESULTS AND DISCUSSION

The analysis revealed a significant main effect for ethanol, indicating that in both stressed and control mice ethanol increased the threshold voltage for electrically precipitated seizures. In addition, there was a significant main effect for stress, indicating that ethanol's antiseizure efficacy was significantly reduced in stressed animals (see. Fig. 1).

The current finding is consistent with previous work demonstrating a stress-induced reduction in benzodiazepine receptor sensitivity (1,4). The mechanism accounting for this stress-induced reduction in the antiseizure efficacy of ethanol is unknown. Conceivably, ethanol's diminished antiseizure efficacy is mediated by the stress-induced reduction in available benzodiazepine receptors with which ethanol interacts (4). The present finding may be relevant to clinical situations involving stress, ethanol, and proneness to seizures.

The data may be relevant to ethanol consumption and acute intoxication immediately following a severely stressful event. If ethanol's acute antiseizure effect is related to its anxiolytic properties, the data suggest that the nontolerant human may require a much greater amount of ethanol to experience the subjective anxiolytic effects compared with the prestressed state. Moreover, the area of the brain mediating the antiseizure and anxiolytic properties may differ from those regions responsible for its ataxic effects (e.g., cerebellum). Thus, a stressed individual who drinks to experience the anxiolytic effects of acute intoxication may be at greater risk to experience other properties associated with ethanol, namely, sedative and ataxic ones.

ACKNOWLEDGEMENTS

This work was supported by a grant from the Department of Veterans Affairs to S.I.D. and Inter-Agency Agreement No. RA-ND-90-10 between the National Institute on Drug Abuse and the Department of Veterans Affairs Medical Center, Washington, DC. The authors extend especial thanks to Laura Probla for graphics and Norman Booker for technical assistance.

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