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Aspirin Pretreatment Reduces Ethanol Withdrawal Severity in a Mouse Model of Binge Drinking

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HALE, R. L., C. L. RANDALL, H. C. BECKER AND K. P. TURNER. *Aspirin pretreatment reduces ethanol withdrawal severity in a mouse model of binge drinking.* PHARMACOL BIOCHEM BEHAV 43(4) 1169–1173, 1992.—Nonsteroidal antiinflammatory drugs (NSAIDs) such as aspirin, ibuprofen, and indomethacin, which inhibit prostaglandin (PG) synthesis, have a pronounced effect on a broad range of ethanol (EtOH) actions. Given this, it is somewhat surprising that NSAID treatment has not been found to alter major signs of ethanol withdrawal. To date, the only effect found has been indirect, that is, NSAID treatment reduces the efficacy of PG precursor administration in the treatment of ethanol withdrawal via the inhibition of PG formation. However, in those studies reporting negative results NSAID administration was delayed until EtOH withdrawal. Studies demonstrating NSAID-related attenuation of other actions of EtOH have typically employed a pretreatment paradigm in which NSAIDs are administered prior to, not after, ethanol exposure. Thus, it may be that the point in the ethanol exposure/withdrawal episode at which NSAIDs are administered could be crucial in determining their effects of the ethanol withdrawal syndrome. To address this issue, we employed a multiple-exposure "binge drinking" model. On each of 6 treatment days, male BALB/c mice were injected subcutaneously with either acetylsalicylic acid (ASA, 150 mg/kg) or the buffer vehicle, followed 1 h later by either ethanol (4.0 g/kg) or saline (0.9%) by gavage. Ethanol withdrawal severity, as measured by handling-induced convulsions, was determined 2, 4, 6, 8, 10, 12, and 24 h after EtOH gavage. ASA pretreatment was found to significantly reduce handling-induced convulsions in ethanol-intubated animals. In fact, the attenuation was of such a magnitude that the ASA-pretreated ethanol group did not significantly differ in withdrawal severity from non-ethanol-exposed controls. This effect was not likely due to ASA-related alterations in ethanol pharmacokinetics. These findings have relevance for the understanding of the basic mechanisms underlying ethanol dependence, as well as the potential role of PGs in this phenomenon.

Nonsteroidal antiinflammatory drugs Acetylsalicylic acid Ethanol withdrawal Prostaglandins

THE present study was undertaken to investigate the effects of nonsteroidal antiinflammatory drugs (NSAIDs) on the ethanol (EtOH) withdrawal syndrome (EWS). NSAIDs such as aspirin, ibuprofen, and indomethacin have a pronounced attenuating effect on a broad range of EtOH's actions [for review, see (29)], including EtOH-induced locomotor stimulation (15,27), motor impairment (13,14), hypothermia (10,13), lethality (8), hypnosis (4,7,9,12,13) and teratogenicity (24–26), as well as operant response rate depression (11). Further, the degree to which these drugs antagonize EtOH's actions has been found to be positively correlated with the degree to which they inhibit prostaglandin (PG) synthesis (7,26), suggesting their effect is via this mechanism. In addition, their antagonistic action has been shown to be associated with a decreased neurosensitivity to EtOH rather than being due to a change in ethanol pharmacokinetics (7).

In studies to date, NSAIDs have not been found to significantly affect the EWS (30), except to reduce the ameliorative effects of PG precursors [but not of PGs themselves; (28)] and to reduce hangover-associated headache (18,22,23). However, in those studies failing to demonstrate an effect NSAID administration was delayed until after EtOH exposure (i.e., during the period of abstinence). It is interesting to note that studies demonstrating NSAID-related antagonism of the actions of EtOH typically employed a pretreatment paradigm in which NSAIDs are administered *prior* to, not after, ethanol exposure (18,22,23). In fact, with regard to ethanol-induced hypnosis it has been reported that while NSAID (indomethacin) pretreatment significantly reduces EtOH sleep time, treatment after ethanol exposure has either no effect (9) or a diminishing effect the longer the delay (4). Thus, the timing of NSAID treatment may be a critical factor in determining

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NSAIDs' ability to mitigate several of ethanol's effects, including the EWS.

The purpose of the present study, then, was to examine the effect of NSAID pretreatment (administration prior to the ethanol exposure period) on the severity of the subsequent EWS. As a first attempt to address this issue, we incorporated the "binge-drinking" model of Kosobud and Crabbe (20), which produces acute withdrawal in mice, into a multiple-exposure paradigm. A multiple-exposure paradigm was selected to access potential changes in efficacy of NSAID treatment over time. It may be, for example, that while acute, initial NSAID treatment reduces the severity of withdrawal more chronic, repeated NSAID treatment may actually exacerbate withdrawal symptomatology [for a theoretical basis for such a pattern, see (16,17)]. Such concerns can only be assessed in a multiple-exposure paradigm. Using this modified paradigm, we administered the NSAID aspirin [acetylsalicylic acid (ASA)] to male BALB/c mice prior to EtOH exposure across several repeated acute exposure/withdrawal episodes.

METHOD

Subjects

Male BALB/c mice (Charles River, Raleigh, NC) were used. Animals were approximately 120 days old at the time of testing, with a mean body weight of 31.7 g. Throughout the study, mice were singly housed, with food and laboratory chow available ad lib. The colony facility is AAALAC accredited.

Procedure

A multiple-exposure binge-drinking model of EtOH withdrawal was employed. On the first (baseline) exposure day, all mice were pretreated with vehicle (1% sodium bicarbonate buffer, 0.02 ml/g, SC), followed by EtOH (4.0 g/kg, 0.03 ml/g, IG). Experimental groups were assessed for withdrawal severity as described below and matched on initial withdrawal severity. On the 6 treatment days that followed, one group of animals was injected with ASA (150 mg/kg, SC) and another with the buffer vehicle. One hour later, half of each group received ethanol (4.0 g/kg) and the other half received saline (0.9%) by gavage (*n*s = 5-7/group). Thus, the study represented a two (ASA treatment) × two (ethanol treatment) repeated-measures design. Experimental treatments occurred on a Monday-Wednesday-Friday schedule, beginning with the baseline withdrawal assessment on a Friday. Thus, following baseline assessment animals were treated with ethanol (or saline) a total of six times, resulting in six acute exposure/withdrawal episodes.

Withdrawal Testing

Withdrawal severity, as measured by handling-induced convulsions (HICs), was determined 2, 4, 6, 8, 10, 12, and 24 h after each EtOH gavage by examiners blind to subjects' treatment condition. HIC values (see Table 1 for scoring) were converted to areas under the 24-h withdrawal curve (AUC) for purposes of statistical analysis. Blood ethanol concentrations (BECs) were determined by spectrophotometric assay of retro-orbital blood samples collected 1 h after gavage on the baseline day and on 3 of the 6 experimental treatment days (i.e., treatment days 1, 4, and 6).

TABLE 1

HANDLING-INDUCED CONVULSIONS SCORING SCALE*

0	= no activity on tail lift or after a gentle 360° spin
1	= no activity on tail lift, but facial grimace after 360° spin
1.5	= facial grimace on tail lift
2	= tonic convulsion after 360° spin
3	= tonic/clonic convulsion after 360° spin
4	= tonic convulsion on tail lift
5	= tonic/clonic on tail lift, often delayed by 1-2 sec
6	= severe tonic/clonic on tail lift, no delay
7	= severe tonic/clonic in holding pan, prior to tail lift

*Modified after Crabbe and Kosobud (3).

Data Analysis

Baseline assessments of AUC, BEC, and body weights were conducted with analyses of variance (ANOVAs). Analyses of AUC, BEC, and body weights across the six experimental sessions were carried out with two (ASA or vehicle pretreatment) × two (ethanol or saline gavage) × 6 (sessions) repeated-measures ANOVAs. Probability levels for effects involving repeated measures were adjusted using the Greenhouse-Geisser correction. Posthoc pairwise comparisons were conducted using Fisher's protected least significant difference (PLSD) test, with chance controlled at the 0.05 level.

RESULTS

Baseline Measures

Initial withdrawal AUCs did not differ among the treatment groups, $F(1, 20) = 0.00$–0.13, $p = 0.72$–0.96 (experimental treatment main effects and their interaction). Thus, prior to experimental manipulations all groups had equivalent baseline AUCs. In addition, no differences existed between groups in terms of 1-h post gavage BECs on the baseline day, $F(1, 20) = 0.01$–0.60, $p = 0.45$–0.89. Groups also did not differ on initial body weight, $F(1, 20) = 0.13$–2.05, $p = 0.17$–0.73.

Body Weight

A marginal reduction in body weights was evident across the six acute exposure/withdrawal episodes, $F(5, 100) = 4.15$, $p = 0.06$. This effect was evident to an equal extent in ASA and vehicle control groups, that is, neither ASA or EtOH exposure, nor their combination, resulted in significant body weight differences, $F(1, 20) = 0.57$–0.79, $p = 0.38$–0.46, nor did these drug treatments or their combination modify the marginal reduction in body weight noted across episodes, $F(5, 100) = 0.32$–3.21, $p = 0.18$–0.72.

Ethanol Withdrawal AUC

The major study findings are illustrated in Fig. 1. Analysis of withdrawal AUC values revealed the expected difference in withdrawal severity between ethanol-treated and control-gavaged animals, $F(1, 20) = 9.40$, $p = 0.01$. In addition, a significant decrease in EtOH withdrawal severity was evident across withdrawal episodes, $F(5, 100) = 3.07$, $p = 0.04$. As-

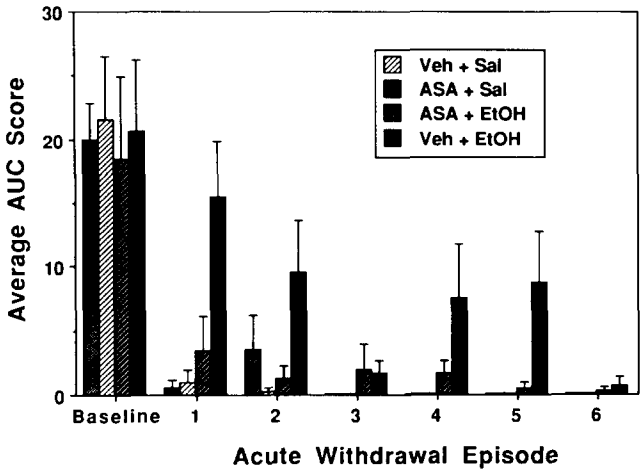

FIG. 1. Ethanol withdrawal severity across binge exposure days as measured by area under the handling-induced convulsion curve. Withdrawal is expressed as a function of aspirin pretreatment and ethanol exposure conditions.

pirin (ASA), per se, had only a marginal effect on withdrawal severity, $F(1, 20) = 4.09$, $p = 0.06$. This marginal effect must be further qualified, however, by the interactive effects of ASA with ethanol, that is, when administered prior to EtOH exposure ASA significantly reduced the severity of withdrawal, $F(1, 20) = 5.76$, $p = 0.03$. ASA's prophylactic action fluctuated only marginally across withdrawal episodes, $F(5, 100) = 2.66$, $p = 0.06$. Posthoc comparisons revealed that ASA pretreatment significantly reduced handling-induced convulsions in ethanol-intubated animals (see Figs. 2A and 2B). The prophylactic efficacy of ASA was such that ASA-pretreated, EtOH-gavaged animals did not significantly differ in withdrawal signs from non-ethanol-exposed controls (Fisher's PLSD $p = 0.45$–0.79), although all three groups' withdrawal scores were significantly below that of the vehicle-pretreated, ethanol-gavaged group's score (Fisher's PLSD $p = 0.001$–0.005).

BEC's

BECs of ethanol-gavaged animals (saline, non-ethanol-gavaged mice excluded; see Table 2) decreased significantly across treatment days 1, 4, and 6, $F(2, 20) = 4.09$, $p = 0.05$. Aspirin pretreatment had no effect on BEC [main effect, $F(1, 10) = 2.71$, $p = 0.13$, interaction, $F(2, 20) = 0.18$, $p = 0.77$]. Further, within the BEC ranges of each session (again excluding saline, non-ethanol-gavaged animals) no significant correlations were detected between BEC and withdrawal AUC ($r = 0.19$–0.40, $p = 0.20$–0.56).

DISCUSSION

These results provide the first information on the effect of pretreatment with nonsteroidal antiinflammatory drugs on subsequent major ethanol withdrawal episodes, as measured by convulsive behavior. We can report that pretreatment with the NSAID ASA (150 mg/kg, SC) prior to binge-like exposure to EtOH (4 g/kg, IG) significantly reduces the severity of handling-induced convulsions during the subsequent ethanol abstinence period. It remains to be seen whether this attenuation in EWS by ASA generalizes to other model systems of ethanol dependence (e.g., 2,5).

The reduction in EWS severity produced by aspirin pretreatment in the present study was robust. When AUC scores for each session were expressed as a percent of the vehicle-pretreated ethanol-gavaged group's withdrawal on that session, ASA pretreatment was found to reduce EtOH withdrawal an average of 64%. Non-ethanol-exposed controls, as would be expected, had even lower response levels, although not significantly lower than the aspirin-pretreated ethanol-gavaged group.

The attenuation of EtOH withdrawal signs due to ASA pretreatment was not likely due to ASA-related alterations in ethanol pharmacokinetics. One-hour postgavage blood alcohol levels did not vary as a function of ASA pretreatment on

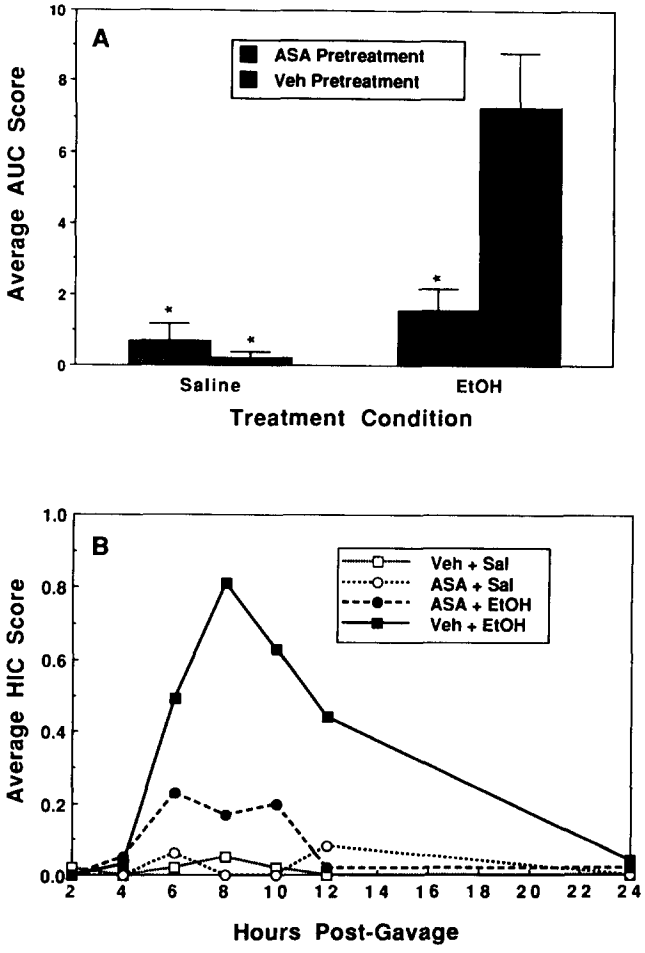

FIG. 2. Ethanol (EtOH) withdrawal severity averaged across binge exposure days as expressed as mean area under the handling-induced convulsion curve (A) or in the form of the average handling-induced convulsion curve from which the AUC values were derived (B). In each panel, withdrawal severity is expressed as a function of aspirin pretreatment and ethanol exposure conditions. In each, the acetylsalicylic acid (ASA) + EtOH group's withdrawal severity score is significantly less than that of the vehicle (Veh) + EtOH group, $^*p < 0.05$, and is not significantly different from that of the two non-ethanol-treated groups.

TABLE 2

BLOOD ETHANOL CONCENTRATIONS (mg/dl)

Withdrawal Episode	Mean (±SE) BEC (*n*)			
	ASA + Sal (5)	Veh + Sal (7)	ASA + EtOH (6)	Veh + EtOH (6)
Baseline	354 (19)	362 (14)	350 (15)	356 (7)
Day 1	–	–	311 (23)	339 (10)
Day 4	–	–	303 (18)	324 (12)
Day 6	–	–	267 (23)	290 (20)

One-hour postgavage blood ethanol concentration (BEC) as a function of experimental treatment condition. BEC was not significantly altered by aspirin pretreatment, $p > .05$. However, BECs in ethanol-gavaged animals (whether aspirin or vehicle pretreated) were progressively reduced with repeated ethanol exposure, $p < 0.05$. ASA + Sal = aspirin pretreated, saline-gavaged group. Veh + Sal = vehicle-pretreated, saline-gavaged group. ASA + EtOH = aspirin-pretreated, ethanol-gavaged group. Veh + EtOH = vehicle-pretreated, ethanol-gavaged group.

the 3 treatment days examined. (However, whether differences in BECs due to ASA might be found at other postethanol time points warrants further investigation.) In addition, on none of the 3 days was there a significant correlation between the BECs of EtOH-intubated animals and their AUC withdrawal scores ($rs = 0.19$–0.40, $p = 0.20$–0.56). This was likely due to the limited range of BEC values produced in the present paradigm.

A high dosage of ASA, as in the present study, can produce significant adverse side effects, such as gastrointestinal distress. Such adverse effects might alter subsequent ethanol withdrawal severity. This possibility does not appear tenable in the present case. First, ASAs prophylactic action was evident on the first administration and, if anything, became marginally reduced with repeated ASA treatments. Accounting for this pattern of prophylaxis in terms of ASA's adverse effects, which would be expected to be cumulative, would be difficult. Further, ASA had no modifying effect on body weight, suggesting, at least as indexed by body weight, that the present dose of ASA, in the present murine strain, did not significantly compromise health. Thus, it does not appear that the present prophylactic effect of ASA can be readily explained in terms of possible high-dose ASA-related side effects.

While ASA pretreatment was found to greatly attenuate the severity of EWS, as measured by HIC, several caveats must be expressed. It should be noted that the present study was marked by a significant reduction in withdrawal responses across repeated testing so that, on average, withdrawal signs were relatively mild. This reduction was particularly evident on the last testing day of each week (see Fig. 1). Thus, it might be argued that the present prophylactic effect of ASA might be limited to cases of relatively mild withdrawal. However, exploratory analysis of the present data allows that concern to be largely ruled out. When only the first treatment day's data is analyzed (a time point involving major convulsive signs of withdrawal), ASA's prophylactic effect is still evident [interaction, $F(1, 20) = 4.70$, $p = 0.04$]. A further concern is that significant metabolic tolerance to ethanol developed in the course of the study. However, at no time did ASA pretreatment significantly alter 1-h post-EtOH gavage BECs. In addition, because all animals were assigned to groups based upon initial withdrawal scores the impact of aspirin pretreatment on ethanol withdrawal in previously ethanol-naive animals is not known. Finally, only one sign of ethanol withdrawal (handling-induced convulsions), and only one NSAID (aspirin), at only one dose, was used. Previous work reporting null findings when aspirin was administered during abstinence employed lower doses [15–30 mg/kg, but IP; (28,30)] and different model systems. We know that the dose employed in the present study (150 mg/kg, SC) reduces PGE levels in mouse reproductive tissue by about 80% (26). It remains to be determined whether the present reduction in withdrawal intensity is a function of the dose employed or of the temporal pattern of administration. Clearly, additional work is necessary to address these important issues.

Aspirin's action as a prostaglandin synthesis inhibitor may provide an important clue regarding at least one mechanism by which ASA (and possibly other NSAIDs) pretreatment may attenuate ethanol withdrawal signs. Increased formation of the major vasocontrictive prostanoid thromboxane A_2 (TXA_2), as measured by its stable metabolite TXB_2, has been reported in hospitalized alcoholics at admission and during early alcohol withdrawal (1, but cf. 21). This pattern also may be present during drinking in nonalcoholics (19). By virtue of their ability to inhibit cyclooxygenase, the critical enzyme responsible for prostanoid synthesis, NSAIDs such as aspirin would prevent such increases in TXA_2. The picture regarding the critical PG changes that may be related to ethanol consumption and abstinence is, however, by no means clear [for a brief discussion, see (6,19)]. Much more work will be required before the specific prostanoid changes influencing the EWS are elucidated. Work examining the effects of specific TXA_2 inhibition on the EWS should be a promising first step in that direction.

In conclusion, the present findings provide the first clear evidence that the NSAID aspirin can significantly reduce major signs of ethanol withdrawal. Further research based upon these findings may lead to important insights into the mechanism(s) underlying aspirin's prophylactic effect on ethanol withdrawal and thus into the process of ethanol dependence itself.

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