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Effect of 3-Amino-1,2,4-Triazole on Ethanol-Induced Narcosis, Lethality and Hypothermia in Rats

C. M. G. ARAGON, K. SPIVAK AND Z. AMIT

Concordia University, Center for Studies in Behavioral Neurobiology
1455 de Maisonneuve Blvd. West, Montreal, Quebec, Canada H3G 1M8

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ARAGON, C. M. G., K. SPIVAK AND Z. AMIT. *Effect of 3-amino-1,2,4-triazole on ethanol-induced narcosis, lethality and hypothermia in rats.* PHARMACOL BIOCHEM BEHAV **39**(1) 55–59, 1991.—It has been proposed that ethanol can be oxidized in brain via the peroxidatic activity of catalase and that centrally formed acetaldehyde may mediate several of the psychopharmacological actions of ethanol. The present study was designed to investigate the role of brain catalase in the mediation of ethanol-induced narcosis, hypothermia and lethality in rats. Rats were pretreated with the catalase inhibitor 3-amino-1,2,4-triazole (AT) or saline. Five hours later, animals in each pretreatment group received IP injections of ethanol (3 or 4 g/kg). Ethanol-induced narcosis was significantly attenuated in AT-pretreated rats compared to the saline control group. As well, AT pretreatments reduced significantly the lethal effect of these ethanol doses. However, AT-pretreated ethanol-injected animals significantly reduce their body temperature as compared to the saline-ethanol animals. Blood ethanol determinations revealed that AT did interfere with ethanol metabolism. AT inhibits significantly brain catalase activity at all doses used in this study. The results indicate a role for brain catalase in ethanol effects. Furthermore, they suggest that catalase may be involved in the oxidation of ethanol in brain and that centrally formed acetaldehyde may play a role in ethanol-induced narcosis and lethality, but not hypothermia.

Ethanol Narcosis Lethality Hypothermia Acetaldehyde 3-Amino-1,2,4-triazole Catalase

ETHANOL, through its action in the central nervous system, is known to produce a variety of behavioral effects in rats. These include, among others, positive reinforcement (15,25), conditioned taste aversion (CTA) (3, 9, 19), narcosis (18), motor incoordination (16), locomotor depression (6,27) and hypothermia (17). Acetaldehyde, the first metabolite of ethanol, has initially been implicated in both the reinforcing (1) and aversive (3) properties of ethanol. More recently, several other ethanol-induced effects were also reported to be mediated through the possible activity of central acetaldehyde, e.g., CTA (5,26) and locomotor activity (6,27).

The presence or absence of acetaldehyde in the brain has been an issue of considerable controversy. This lack of consensus is linked to the fact that numerous attempts to measure or detect the presence of acetaldehyde in brain following exposure to ethanol have been inconclusive (13,31). However, the identification and presence of ethanol-metabolizing enzymes in cerebral tissue provides some indirect evidence of the possible presence of acetaldehyde in brain. For example, it has been reported that brain catalase, in conjunction with endogenous hydrogen peroxide, may, in fact, oxidize ethanol in vivo (10). We have also recently reported the results of several studies which support the notion that at least some of the behavioral effects of ethanol may be mediated through the activity of acetaldehyde, centrally formed via the peroxidatic activity of brain catalase. We demonstrated that brain (and not liver) catalase was positively correlated with voluntary ethanol consumption in rats (7). Furthermore, inhibition of brain catalase by 3-amino-1,2,4-triazole (AT), a H_2O_2-dependent catalase inhibitor, blocked ethanol-induced locomotor depression (6) and ethanol-induced CTA (5).

Given these findings, it seemed logical to extend our investigation and examine the role of the enzyme catalase in the mediation of the psychopharmacological effects of narcotic doses of ethanol. Specifically, the present study investigated the role of brain catalase and by implication, centrally formed acetaldehyde, in the mediation of ethanol-induced sleep time (narcosis), lethality and hypothermia. Brain catalase activity was manipulated through the administration of the catalase inhibitor 3-amino-1,2,4-triazole (AT).

METHOD

Subjects

Subjects were male Long-Evans rats (Charles River Breeding Farms, Canada) weighing 260–300 grams. Animals were housed individually in stainless steel cages in a room regulated for humidity, temperature and a day/night cycle of 12 hours lights on (8 a.m. to 8 p.m.) and 12 hours lights off (8 p.m. to 8 a.m.). Food and water were available ad lib.

Drugs

3-Amino-1,2,4-triazole (AT) (Sigma Co., St. Louis) was dissolved in saline (1 g/2 ml). Ethanol was diluted to 25% v/v with

saline from a 95% stock solution. All injections were administered intraperitoneally (IP).

Narcosis Time

After 7 days adaptation to laboratory housing conditions, animals were randomly assigned to four pretreatment groups. One group of subjects received an injection of saline (2 ml/kg) and the other three groups received an injection of one of three doses of AT (0.250, 0.5 or 1 g/kg). Five hours later, narcosis was induced in each pretreatment group by an acute administration of ethanol (3 or 4 g/kg) (N = 12 per pretreatment and ethanol dose). The time interval between AT pretreatment and ethanol treatment was chosen because AT produces maximum inhibition of brain catalase 5 h after AT administration (4). The duration of narcosis or sleep time was defined as the time from loss of righting reflex to the time the righting reflex was regained. Recovery of the righting reflex was determined when subjects could right themselves three times within 60 s after being placed on their backs. Immediately following recovery of the righting reflex, animals were sacrificed by decapitation. Trunk blood of each animal was collected for blood ethanol determination. These assays were included to determine a possible relationship between blood levels of ethanol and duration of sleep time.

Lethality

Lethality was expressed as the number of rats dead 24 hours after ethanol injections relative to the total number of animals tested. Lethality was observed under the same experimental conditions as narcosis. In order to study the effect of different ethanol concentrations on lethality, rats were injected with ethanol solutions of 10, 17 and 25% of v/v at doses of 3 and 4 g/kg (n = 6 per ethanol solution and dose).

Hypothermia

This experiment was conducted in the animal colony where the ambient temperature was verified to be 24°C at all times. Animals were first habituated to the insertion of a rectal thermal probe during six consecutive daily sessions. The habituation sessions and the subsequent experimental sessions were carried out at the same point in the day/night cycle. Following habituation sessions the animals were divided into four equal groups (N = 8). Five hours before the beginning of the experimental session two of the four groups received injections of AT (1 g/kg). The two remaining groups received injections of saline (2 ml/kg). Rectal temperature was measured in all animals at the beginning of the session and used as baseline. Immediately following baseline temperature measurement, animals received injections as follows: Of the two AT-pretreated groups one received saline injections and the other ethanol (3 g/kg). Of the two saline-pretreated groups one received saline injections and the other ethanol (3 g/kg). Rectal temperature was then measured in all animals at 30, 60, 90 and 120 minutes following baseline measures.

Blood Ethanol Determinations

Additional animals were used to determine whether AT influenced the overall metabolism of ethanol at the doses and times tested in the behavioral studies. Animals were pretreated with AT (1 g/kg) or saline as previously described. Five hours later they received IP injections of ethanol (3 or 4 g/kg). Animals were sacrificed by decapitation at 15, 30, 60, 120 and 240 minutes postinjection. Trunk blood was collected and assayed for ethanol levels by head-space gas chromatography with a flame ionization detector (31).

TABLE 1

EFFECT OF PRETREATMENT WITH 3-AMINO-1,2,4-TRIAZOLE ON NARCOSIS TIME INDUCED BY DIFFERENT DOSES OF ETHANOL

	Ethanol Dose	
Pretreatment	3 g/kg IP	4 g/kg IP
Saline	147 ± 11	350 ± 21
AT 0.250 g/kg IP	134 ± 9	323 ± 15
AT 0.500 g/kg IP	118 ± 10	259 ± 16
AT 1.000 g/kg IP	97 ± 12	254 ± 8

Data represents mean ± S.E.M. in minutes.

Catalase Activity Determinations

Five hours after IP administration of AT (0.25, 0.5 or 1 g/kg) or saline, another group of rats were killed by exsanguination under ether anesthesia. Organs were perfused in vitro by whole body perfusion using 300–500 ml of heparinized (1000 units/l) iostonic saline. The saline solution was infused into the left ventricle, and a small incision was made in the right ventricle for the effluent. Perfusion was continued until the kidneys were visibly cleared of erythrocytes. Brains were removed and 10% homogenates were prepared with 0.1% Triton X-100 in 10 mM potassium phosphate buffer, pH 7.0. Brain catalase activity was measured using a Yellow Springs oxygen monitor equipped with a Clark style oxygen electrode (11). The reaction cell was temperature controlled and maintained at 25°C. A 0.01 mM potassium phosphate buffer, pH 7.0 (1.7 ml), was deoxygenated with a stream of N_2. Hydrogen peroxide (7.6 μmol in 10 μl) was added to the deoxygenated buffer at zero time, and the baseline O_2 formation rate was recorded. Then at 1 min a 25-μl aliquot of brain homogenate was added. The difference between the rate of O_2 formation before and after the addition of tissue homogenate was taken as the actual reaction time. Brain catalase activity is expressed in nmol of O_2 formed per min per μg of protein. Protein was determined using the Lowry method with bovine serum albumin as the standard.

RESULTS

Ethanol-Induced Narcosis

Results of the experiment on ethanol-induced narcosis are shown in Table 1. A two-way analysis of variance (ANOVA) (pretreatment × treatment) completely randomized design revealed a significant pretreatment effect, $F(3,88) = 24.29$, $p<0.01$, a significant treatment effect, $F(1,88) = 617.66$, $p<0.01$, and a significant pretreatment × treatment interaction, $F(3,88) = 4.24$, $p<0.01$. Pairwise comparisons using Tukey tests revealed significant differences between AT (1 g/kg)- and saline-pretreated animals independently of the ethanol dose, $q(8,88) = 43.60$, $p<0.05$. AT (0.5 g/kg)-pretreated animals were also significantly different from saline-pretreated rats when tested with 4 g/kg of ethanol. Finally, animals pretreated with AT (0.5 and 1.0 g/kg) demonstrated a significant shorter narcosis time than those pretreated with AT (0.25 g/kg) and injected with 4 g/kg of ethanol. All the animals recovered the righting reflex.

TABLE 2

EFFECT OF 3-AMINO-1,2,4-TRIAZOLE (AT) PRETREATMENT ON LETHALITY INDUCED BY ETHANOL*

Pretreatment	Ethanol Dose 3 g/kg IP	4 g/kg IP
Saline	4/12	8/12
AT 0.250 g/kg IP	3/12	6/12
AT 0.500 g/kg IP	0/12	6/12
AT 1.000 g/kg IP	1/12	3/12

*Number of rats dead at 24 hours over total tested.

The duration of the ethanol-induced narcosis did not last longer than 6 h.

There were no significant correlations between individual narcosis time and levels of blood ethanol of rats ($r = .21$, $p<0.05$ for the ethanol dose of 3 g/kg; $r = .02$, $p>0.05$ for the 4 g/kg dose). Trunk blood was collected from the tested rats immediately following recovery of the righting reflex.

Ethanol-Induced Lethality

The effect of AT administration on ethanol-induced lethality is summarized in Table 2. Prior administration of AT to rats reduced significantly the lethal effects of a dose of 3 g/kg (chi-square = 6, $p<0.05$, contingency coefficient $C = 0.333$) and 4 g/kg of ethanol (chi-square = 6, $p<0.05$, $C = 0.285$). No differences on lethality were observed between animals injected with ethanol solutions of 10, 17 and 25% at the ethanol doses tested ($p>0.05$).

Ethanol-Induced Hypothermia

As can be seen in Fig. 1, there were no significant changes in rectal temperature throughout the sequence of temperature readings within the saline/saline (S-S) and aminotriazole/saline (AT-S) groups ($p>0.05$). Furthermore, there were also no differences in rectal temperature between the S-S and AT-S groups throughout the sequence of temperature readings ($p>0.05$). A two-way analysis of variance (ANOVA) (pretreatment × treatment) with repeated measures yielded a significant pretreatment × treatment interaction, $F(1,28) = 7.21$, $p<0.01$. The saline/ethanol (S-E) group revealed a significant drop in rectal temperature at all temperature readings. The aminotriazole/ethanol (AT-E) group displayed a further drop in rectal temperature which was significantly lower than that of the S-E group at all temperature readings. Pretreatment with AT does not affect the baseline temperature at any reading time.

Blood Ethanol Levels

The effect of AT on the metabolism of ethanol is presented in Fig. 2. A three-way analysis of variance (ANOVA) (Pretreatment × Dose × Time) revealed a significant effect of AT pretreatment (1 g/kg), $F(1,140) = 6.68$, $p<0.01$. However, no significant pretreatment × dose or pretreatment × dose × time interactions ($p>0.05$) were found in this study.

Catalase Activity

Mean catalatic activity of brain catalase in animals treated with saline or AT are shown in Table 3. A one-way analysis of variance (ANOVA) yielded a significant interaction, $F(3,23) = 1061.33$, $p<0.01$. An independent t-test was performed on the catalatic activity of the brains of the four groups of rats. These analyses revealed a significant difference between the activities

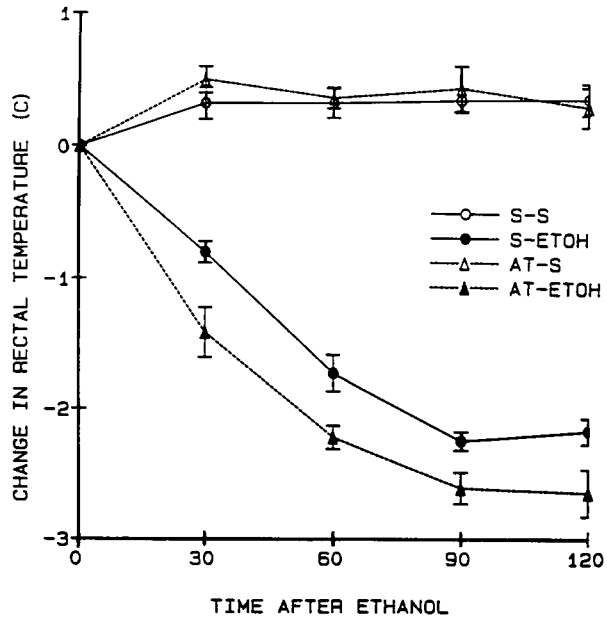

FIG. 1. Change in rectal temperature of saline- and 3-amino-1,2,4-triazole (1 g/kg, 5 hours before ethanol)-pretreated rats following injections of ethanol (3 g/kg). Data represent mean ± S.E.M. temperature change, °C.

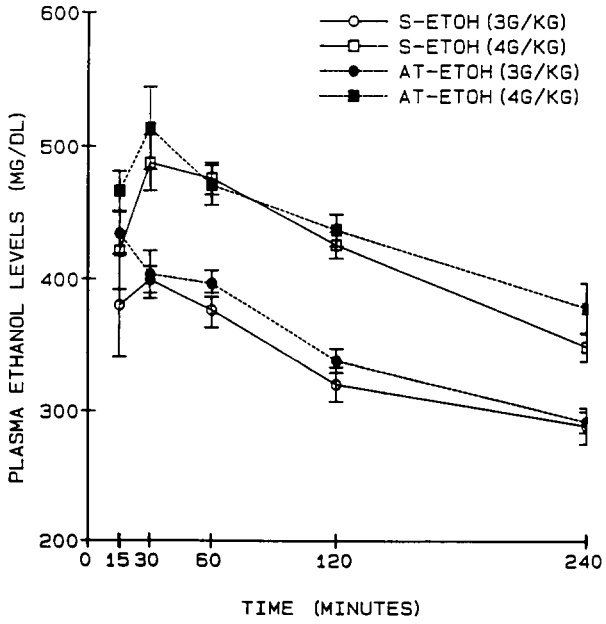

FIG. 2. Effect of 3-amino-1,2,4-triazole pretreatment (1 g/kg, 5 hours before ethanol) on the course of ethanol blood level of rats receiving 3 or 4 g/kg ethanol, compared with that of saline-pretreated controls. Each data point represents mean ± S.E.M. of N = 8.

TABLE 3

BRAIN CATALASE ACTIVITY LEVELS OF RATS FIVE HOURS FOLLOWING ADMINISTRATION OF 3-AMINO-1,2,3-TRIAZOLE (N = 6)

Treatment	nmol O_2/min/μg Protein
Saline	0.610 ± 0.009
AT 0.25 g/kg IP	0.173 ± 0.010*
AT 0.50 g/kg IP	0.139 ± 0.003*
AT 1.00 g/kg IP	0.105 ± 0.005*

*$p<0.01$, compared from saline values. Experimental details were as described under the Method section.

of all treatment groups ($t=2.845$, $p<0.01$). In other words, saline ≠ AT 0.25 g/kg ≠ AT 0.5 g/kg ≠ AT 1.00 g/kg.

DISCUSSION

The data obtained in the present study revealed a bidirectional effect of AT on several psychopharmacological effects such as narcosis, hypothermia and lethality induced by hypnotic doses of ethanol. While AT antagonized the narcotic and lethal effects of ethanol, it seemed to have a synergistic effect with ethanol in inducing hypothermia (EIH). These observations confirm, in part, previous findings where an antagonistic interaction between AT and ethanol subhypnotic doses has been demonstrated (2, 5, 6). For example, we have reported that when ethanol-treated rats pretreated with AT were compared with untreated controls, the former displayed less motor depression (6), less ethanol-induced corticosterone release (2), and a complete blockade of ethanol-induced conditioned taste aversion (5). These AT effects appear to be specific to ethanol, since AT did not attenuate the behavioral effects induced by other drugs such as morphine or lithium chloride (5). AT did not affect plasma levels of ethanol measured at different times following IP injections of moderate doses of ethanol (up to 2 g/kg) (5,6). We have suggested, therefore, that the alterations in these ethanol-induced behaviors by AT must be due to some direct effect at a central level, possibly by the manipulation of brain catalase activity (5,6).

An effect of AT pretreatment on blood ethanol levels after intraperitoneal administration of hypnotic doses of ethanol was, however, demonstrated in this study. Animals pretreated with AT showed, in general, higher levels of blood ethanol independent of the dose or time tested. This finding supports a previous study by Tampier and Mardones (29) where AT (1 g/kg) pretreatment resulted in higher ethanol blood levels during the first hour following IP ethanol administration in rats of doses higher than 3 g/kg. Since AT inhibits liver catalase in vivo (22,29), these findings lent support to the notion that liver catalase may play a moderate role in the disposal of ethanol, following the administration of high narcotic doses.

While the observed small differences in blood ethanol levels could be the cause of the interaction between AT and ethanol obtained in this study, a more plausible explanation must be considered since it is more in line with the results of previous studies. The finding that AT antagonized the effects of ethanol in such diverse behaviors as motor activity (6), conditioned taste aversion (5), corticosterone release (2), narcosis and lethality in various strains of rats and mice and across several ethanol doses suggested that the interaction of AT and ethanol must occur at a fundamental physiological juncture necessary for the expression of some of ethanol's induced behaviors. Furthermore, brain AT levels decline very sharply after 2 hours postadministration and are undetectable after 5 hours (manuscript in preparation). Therefore, it is suggested that ethanol must act on some biochemical or cellular structure that has been previously altered by AT. This AT-modified element appears to be central for the expression of some of ethanol's psychopharmacological effects.

The protective effect that AT exerts on narcosis and lethality may be due to the effect of AT on brain catalase. Brain catalase determinations revealed a dose-dependent decrease from control values 5 hours after AT administration. One must bear in mind, however, that the dose of 0.25 g/kg of AT which significantly decreased brain catalase did not result in significant changes in both narcosis and lethality. Clearly, this finding may argue against the contention stated above. However, since little if anything is known about the minimal levels of catalase necessary to show behavioral effects, one cannot, despite this finding, rule out the argument presented in this paper. In support of this line of reasoning, we wish to point to the well-known facts that significant depletions of catecholamines (at a level of 70% of whole brain) do not result in behavioral deficits (32). Only massive depletions (e.g., 90% of whole brain) revealed such behavioral deficits. When ethanol was administered, the inhibition of catalase by AT could be the factor altering some of ethanol's induced behaviors. It was, therefore, our contention that brain catalase may play an important role in mediating ethanol's central effects. Furthermore, we also reported a relationship between brain catalase and voluntary ethanol consumption in rats (7), suggesting a role for brain catalase activity in determining the level of ethanol intake in individual animals. Inhibition of brain catalase does not, however, completely block the expression of such effects as narcosis or lethality. It follows that ethanol metabolism, through the brain catalase system, is a contributing but not an exclusive factor for narcosis and lethality induced by these high doses of ethanol.

AT inhibits irreversibly both the catalatic and peroxidatic activities of catalase. It has been demonstrated that prior administration of ethanol prevented the inhibition of brain catalase by AT in studies in vivo (10). We have suggested that ethanol's protection of catalase from inhibition by AT provided indirect evidence supporting the notion that ethanol is oxidized in the brain in vivo via the peroxidatic activity of catalase. We have also suggested that the role of catalase in some of ethanol's psychopharmacological effects occurs through its ability to oxidize ethanol in the brain. The presence and distribution of catalase in brain has been verified by both biochemical (8,14) and histochemical methods (21). The presence of hydrogen peroxide, necessary for oxidation of ethanol by catalase, has been demonstrated in the brain (11, 23, 24) and acetaldehyde, the first metabolite of this oxidation, has been implicated in ethanol's effects (1,20). Therefore, when all these findings are taken together, one could suggest that AT alters some of the behavioral effects of ethanol through its inhibition of brain catalase and subsequent reduction in the formation of central acetaldehyde. It is important to point out that catalase may not be homogenously distributed in rat brain (8,21), therefore, acetaldehyde produced in a specific central environment might be of great consequence in that environment.

While the above findings may provide a role for central acetaldehyde in some of ethanol's behavioral effects, a different mechanism must be proposed for ethanol-induced hypothermia. Pretreatment with AT significantly increased the hypothermic effect observed in the S-E group. It was further demonstrated that the increase in hypothermia observed in the AT-E group was not an artifact of AT administration, since the AT-S group did not differ from the S-S group in rectal temperature. These findings seem to preclude the possibility that ethanol-induced hypothermia (EIH) is mediated by brain acetaldehyde and raises the pos-

sibility that it is mediated directly by ethanol. The logic of this argument stems from the notion that if AT inhibits the formation of brain acetaldehyde then one would expect an attenuation of EIH following treatment with AT if brain acetaldehyde was in fact the mediator. The fact that we found moderately higher levels of blood ethanol in AT-pretreated rats allows us to draw a conclusion suggesting a role for ethanol in facilitating EIH following treatment with AT. This differential effect of AT in narcosis and EIH seems to be supported by several lines of research reported in the literature. Thus it has been reported that the degree of ethanol-mediated hypothermia in individual mice of a genetically heterogenous line was negatively and significantly correlated to the period of time the animals were void of the righting reflex (12). In other words, narcosis and EIH are mediated by separate mechanisms. Other studies have reported also that hypothermia induced by ethanol on one hand, and ethanol's effects on locomotion on the other, are mediated through different mechanisms (19).

In summary, the catalase inhibitor 3-amino-1,2,4-triazole attenuated narcosis and lethality produced by ethanol in rats. These findings seem to support the notion that acetaldehyde formation in brain via the peroxidatic activity of catalase may mediate some of the psychopharmacological effects of ethanol. The present findings that EIH is not mediated via the action of acetaldehyde but is probably mediated directly by ethanol leads to the conclusion that the psychopharmacological actions of ethanol are controlled by several distinct mechanisms. This finding is in agreement with several lines of research within the alcohol field (12,19), as well as with other studies investigating multiple mechanisms mediating the psychopharmacological effects of drugs such as morphine (30).

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