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Effects of In Utero Administration of Alcohol on Alcohol Sensitivity in Adult Rats

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REYES, E., E. DURAN AND S. H. SWITZER. *Effects of in utero administration of alcohol on alcohol sensitivity in adult rats.* PHARMACOL BIOCHEM BEHAV **44**(2) 307–312, 1993.—In utero exposure to alcohol has been associated with many physical deficits and behavioral abnormalities. The purpose of these studies was to determine the effects of in utero administration of alcohol on behaviors related to tolerance and sensitivity to alcohol in adult rats. Pregnant rats were maintained on a liquid diet containing alcohol [35% ethanol-derived calories (EDC)] throughout pregnancy. Offspring manifested physical characteristics of Fetal Alcohol Syndrome. The 35% EDC group was able to stay on a wooden dowel longer and at higher blood alcohol concentrations than were pair-fed controls. Following a hypnotic dose of alcohol, rats in the 35% EDC group slept longer than pair-fed controls. A greater alcohol-induced hypothermic effect was seen in females in the 35% EDC group than in controls. Treatment did not affect rate of metabolism of alcohol. These studies suggest that in utero administration of alcohol may be a factor in determining an individual's sensitivity and tolerance to alcohol and possibly their preference for alcohol.

Alcohol Fetal Alcohol Syndrome Tolerance Sensitivity Alcohol-induced hypothermia Elimination rates

THAT in utero exposure to alcohol is detrimental to the fetus has been recognized for centuries (3,17,41); however, it was not until recently that the term Fetal Alcohol Syndrome (FAS) was applied to children born to alcoholic mothers (19). The syndrome has been described by Smith and Jones and includes physical as well as behavioral abnormalities. To be classified as FAS, a child must have characteristics in each of three categories: a) prenatal or postnatal growth retardation; b) characteristic facial dysmorphology; c) CNS involvement (43). The morphological effects include low birth weight, small head circumference, and facial abnormalities (9,11,19,25). Hyperactivity, mental retardation, and irritability in infancy have also been associated with in utero exposure to alcohol (2,5,18,25,35,40).

Animal rodent models have been used to study the effects of prenatal exposure to alcohol (24,28,30). Although the term FAS may not technically apply to the effects seen in animal models, many of the same morphological and behavioral effects have been reported (15,28,30,33). Neurochemical changes have been described associated with the in utero exposure to alcohol (10,16,27,42). Like their human counterparts, these rats also have learning impairments and are slower learners than their controls (1,13,26). Rats born to mothers that received alcohol during gestation have a greater preference for alcohol than do their appropriate controls. In early studies, this effect may have been partially due to a taste preference for the wine or other alcoholic beverage given to mothers (26); however, the use of liquid diets has produced similar results (7,28). In utero exposure to alcohol increases the preference for alcohol in adults. Open-field behavior has produced conflicting results: One study shows an increase (8) and another a decrease (7) in activity. These effects appear to be age dependent, which may account for the conflicting results. The effects on stress have also been studied and the results here are also ambiguous (29,37,39). It appears that rats born to alcohol-treated mothers have a decreased response to some forms of stress as adults. Not all stress-producing stimuli, however, result in a decreased responsiveness of the hypothalamic-pituitary-adrenal system. Cardiac puncture, for example, produces an enhanced responses (37).

Several studies have been conducted dealing with the effects of alcohol on tolerance or sensitivity-related behaviors. The use of inbred strains of mice and inbred lines of rats have shown that tolerance and sensitivity to alcohol may be related (4,23,36). The more sensitive animals become tolerant to alcohol the fastest (36). The effects of in utero exposure to alcohol on tolerance and related behaviors in adults has been studied but the results are not conclusive (36,38). Some investigators found that the in utero administration of alcohol enhances alcohol sensitivity (38) while others reported a reduced sensitivity (34). It was the intent of the studies presented here to investigate the effects of in utero exposure of alcohol on tolerance and sensitivity to alcohol in young adult rats when mothers have been maintained on alcohol throughout gestation.

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METHOD

Sprague-Dawley rats (Harlan Labs, Indianapolis, IN) were maintained on a 12 L : 12 D cycle with the lights on between 0700 and 1900 h. The room was maintained at 27°C and the lighting at 50 candle power. Mature, female rats were placed with mature males overnight. Vaginal smears were taken each morning to establish evidence of copulation (6). When spermatozoa were identified on the vaginal smear, the female was placed in an individual polypropylene translucent cage.

On the first day of gestation, pregnant rats were placed on either an alcohol or a pair-fed liquid diet as described by Reyes et al. (28) or maintained on an ad lib lab chow and water diet (LC) throughout the pregnancy. The liquid diets were purchased from BioServ Inc. (Frenchtown, NJ). The alcohol diet contained 6.7% v/v ethanol [35% ethanol-derived calories (EDC)] and the pair-fed diet contained 0% v/v ethanol (0% EDC) and was made isocaloric by the addition of maltrose dextrin. Mothers in the 35% EDC group were given 100 ml food daily and the amount consumed determined by what was left in the feeding tube the next day. Mothers in the 0% EDC group were pair-fed against mothers in the 35% EDC group. Following parturition, litters were culled to six and pups were placed with non-alcohol-treated surrogate mothers until weaned at 30 days of age and maintained on ad lib lab chow and water. A maximum of two (one male and one female) animals from each litter were used for each experiment. Within 24 h of birth, the culls from each litter were weighed, sacrificed, and brain and liver weights determined.

Dowel Rod Walking

At 45 days of age, an animal was taken from its home cage and trained to walk on the wooden dowel without falling off. The dowel consisted of a wooden rod 5 cm in diameter that was elevated 60 cm above the table top. The training involved placing the rat on the dowel and replacing them on the dowel when they fell off. Following the training period, all animals were eventually able to stay on the dowel for a 5-min period without falling off. The time required to train an animal to stay on the dowel did not differ among the various treatment groups. An animal learned to stay on the dowel within one or two falls and this did not appear to vary among the different treatment groups. Within 15 min of training, an animal was given a subanesthetic dose of ethanol (2.5 g/kg, IP) as a 50% v/v solution and placed on the wooden dowel (14). The length of time an animal was able to stay on the dowel was measured. When it was determined that an animal was unable to stay on the rod (fell off rod when replaced), trunk blood was collected for blood alcohol determinations. Serum alcohol levels were determined according to the method described by Lundquist (22), which utilizes alcohol dehydrogenase (ADH) and nicotinamide adenine dinucleotide (NAD). The enzyme, ADH, catalyzes the conversion of ethanol to acetaldehyde with the concomitant conversion of NAD to NADH. The increase in NADH becomes a measure of the amount of ethanol present in the reaction mixture. A typical reaction mixture is as follows: 3.0 ml pyrophosphate buffer, pH 9.2 (tetrasodium pyrophosphate, 0.075 M; semicarbazide, 0.075 M; and glycine, 0.022 M), 0.1 ml serum, 1.8 μmol NAD, and 150 U ADH. Alcohol levels were reported as mg of alcohol per 100 ml serum.

Sleep Time

Another group of rats was tested for sensitivity to alcohol at 45 days of age in a temperature-controlled room (27°C ± 1). Sleep time following an anesthetic dose of alcohol was used as a measure of sensitivity to alcohol (36). Animals were given an IP injection of alcohol (3.4 g/kg) as a 20% (v/v) solution prepared in water. Following alcohol injection, rats were judged to have lost their righting reflex (LORR) when they could not right themselves twice within a 30-s period after being placed on their backs. Once the righting reflex was lost, the animal was timed until it regained its righting reflex (RORR). They were judged to have regained their righting reflex when they could right themselves twice within a 30-s period. The interval of time between LORR and RORR was considered to be the sleep time (12).

Alcohol-Induced Hypothermia

The effects on alcohol-induced hypothermia were measured following administration of alcohol (3.4 g/kg). Rectal temperatures were monitored with a Harvard TM99A Temperature Probe (Harvard Apparatus, South Natick, MA) before injection and every 10 min until rats regained their righting reflex.

Rate of Alcohol Elimination

Another group of rats was tested to determine the rate of elimination of alcohol. Rats were given an IP injection of 2.5 g/kg alcohol as a 20% (v/v) water solution. Animals were placed in plastic animal constraints and blood samples collected from the tail vein at 30, 60, 90, and 120 min after administration of alcohol. Alcohol concentration in the blood was determined as described above. The disappearance rate of blood alcohol was calculated from the slope of the linear descending portion of each curve (20,21).

Statistical Analysis

The data from each experiment was analyzed by analysis of variance (ANOVA) using Human Systems Dynamics Statistical Analysis Software. To prevent an undue influence of a particular litter on the data, no more than one animal of a particular sex was used from a single litter (2).

RESULTS

Morphological Characteristics

Pregnant female rats on the 35% EDC diet consumed an average of 16.8 g alcohol/kg/day. The blood alcohol concentration (BAC) of pregnant rats receiving a liquid diet containing 6.7% (v/v) alcohol (35% EDC) throughout gestation have been determined previously in our laboratory to be 170 mg % at 0700 h and 30 mg % at 1700 h on day 21 of gestation (28). The characteristics of the litters used in this study are presented in Table 1. These characteristics are similar to those of litters used in our laboratory in other studies describing the effects of in utero exposure to alcohol (31,32). There was a significant effect of alcohol treatment on birth weight, brain weight, liver weight, and litter size. Offspring from the 35% EDC-treated mothers were smaller than controls (0% EDC) and came from smaller litters.

Effects of Alcohol on Dowel Rod Performance

The length of time an animal was able to stay on a wooden dowel following an IP injection of alcohol (2.5 g/kg) is shown in Fig. 1. Statistical analysis by ANOVA showed a significant effect due to treatment of mothers during pregnancy, $F(2,$

TABLE 1
CHARACTERISTIC OF OFFSPRING OF MOTHERS EXPOSED TO ALCOHOL DURING PREGNANCY

Characteristic	Treatment Group			F-value
	LC	0% EDC	35% EDC	
Birth weight (g)*†	6.66 ± .83	6.03 ± .61	4.67 ± .80	$F(2, 58) = 37.3$
Brain weight (mg)†	268 ± 22	256 ± 16	234 ± 23	$F(2, 58) = 14.6$
Liver weight (mg)†	285 ± 48	280 ± 42	217 ± 48	$F(2, 58) = 13.3$
Weight at 32 days (g)	104 ± 26	114 ± 18	100 ± 11	$F(2, 38) = 1.4$
Litter size†	11.3 ± 3.3	10.5 ± 3.7	9.2 ± 3.0	$F(2, 324) = 9.2$

*Values are presented as means ± SD.
†Significance at $p < 0.05$. Statistical analysis by two-way analysis of variance.

39) = 4.571, $p < 0.05$. There were no effects due to sex or to a treatment × sex interaction. Animals born to mothers on a 35% EDC diet were able to stay on the wooden dowel longer than their appropriate pair-fed controls. Male and female animals within the same treatment group had similar fall times; for example, male rats from 35% EDC mothers had a fall time of 104 s while corresponding females had a fall time of 100 s. In the absence of a sex effect, statistical analysis was done on the data without regard to sex. Figure 1 shows the effect of mother treatment on fall time and BAC when sexes were combined. Single-factor ANOVA showed that offspring of 35% EDC mothers stayed on the dowel longer than did pair-fed controls, $F(2, 46) = 6.55$, $p < 0.01$. The 35% EDC group fell off at 101 s, the 0% EDC group at 74 s, and the LC group at 91 s.

The mean BAC of offspring at the time they fell off the wooden dowel is also shown in Fig. 1. Initial multifactor ANOVA showed that there was no difference in BAC due to sex and therefore BAC of males and females were combined. After combining, single-factor ANOVA showed that the 35% EDC group had a significantly higher BAC than did pair-fed controls, $F(2, 37) = 3.85$, $p < 0.05$. Animals born to mothers on a 35% EDC diet had an average BAC of 284 mg % as compared to pair-fed controls, which had a BAC of 196 mg %.

Effects of Alcohol on Sleep Time

The length of time an animal slept following administration of an anesthetic dose of alcohol (3.4 g/kg, IP) is shown in Fig. 2. A multifactor ANOVA showed that alcohol treatment of mothers during pregnancy produced a significant increase in sleep time of offspring following an anesthetic dose of alcohol, $F(2, 46) = 5.20$, $p < 0.05$. There was no effect due to the sex of offspring nor was there a treatment × sex interaction effect. As seen in Fig. 2, male offspring of 35% EDC-treated mothers sleep the longest and males of the 0% EDC group sleep the least (67.4 and 41.3 min, respectively).

There was a significant difference found in the time to LORR between the different treatment groups due to treatment of mothers, $F(2, 46) = 9.19$, $p < 0.05$, and sex, $F(1, 46) = 5.28$, $p < 0.05$. Male offspring of the 35% EDC mothers required 2.9 min to LORR and corresponding pair-fed controls required 1.8 min. Male offspring of mothers fed ad

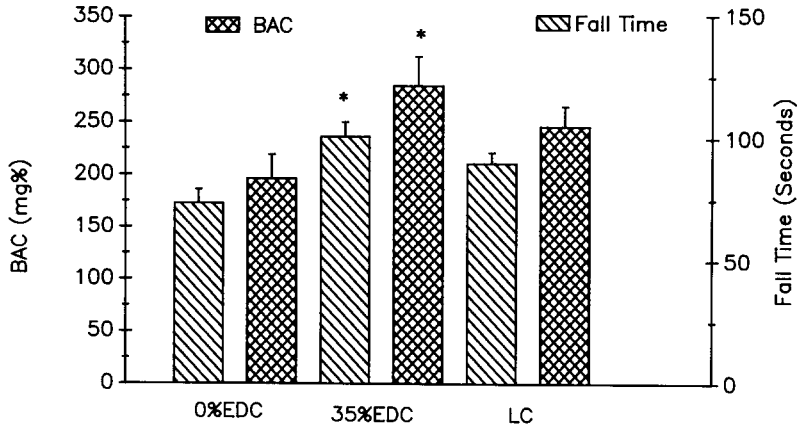

FIG. 1. Effects of in utero administration of alcohol on fall time and blood alcohol concentration (BAC). Fall times and BAC at time of fall of offspring of mothers maintained on a 35% EDC, 0% EDC liquid diet, and ad lib lab chow during pregnancy are presented. Values are reported as the mean ± SEM. Asterisks denote statistically significant differences between 35 and 0% EDC controls. A minimum of six litters is represented by each value.

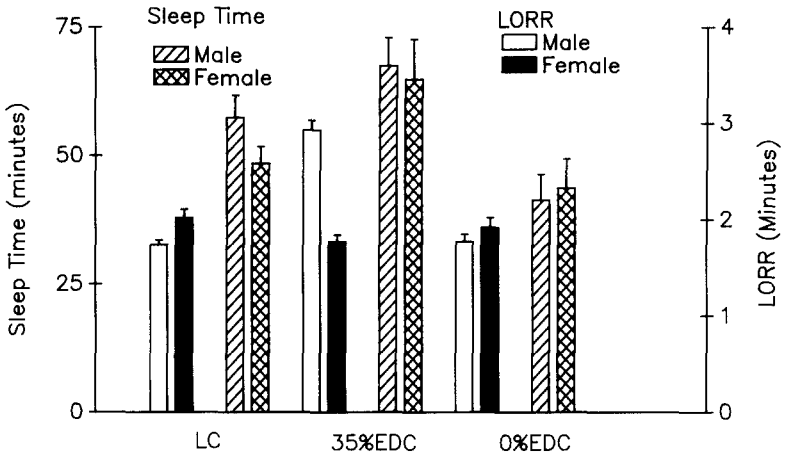

FIG. 2. Effects of in utero administration of alcohol on sleep time. Sleep times and time for loss of righting reflex are reported as the mean ± SEM. A minimum of six litters is represented by each value.

lib lab chow required 1.7 min. There was no difference found between female offspring, $F(2, 31) = 1.41$, $p > 0.05$. Females in LC, 0% EDC, and 35% EDC groups required 2.0, 1.9, and 1.8 min, respectively, to lose their righting reflex.

Effects on Alcohol-Induced Hypothermia

The alcohol-induced hypothermic effects were determined following administration of alcohol (3.4 g/kg, IP) to offspring of mothers in the various treatment groups from LORR to RORR. The average age of these animals was 96 days. Because animals in the various treatment groups slept different amounts of time, the body temperature was plotted at 10% time intervals based upon their total sleep time. The body temperature of animals was plotted as a percentage of total sleep time to compare their body temperatures at various times in their sleep cycle. The increased time to RORR in 35% EDC animals does not necessarily account for the lower body temperatures because a comparison of female and male groups, which slept the same length, still shows a difference in body temperature. A between-within ANOVA design showed that in utero exposure of the fetus to alcohol or the sex of offspring (between groups) had no effect on alcohol-induced hypothermia. However, there was a significant within-groups effect of percent of sleep time, $F(9, 177) = 238$, $p < 0.05$, that is, the body temperature of all animals decreased following an alcohol challenge from time of LORR to time of RORR. Figure 3 illustrates this comparison between males and females in the 35% EDC, 0% EDC, and LC group of animals. At the time animals regained their righting reflex, the body temperature of female offspring in the 35% EDC group had fallen to a greater extent than had the body temperature of all other groups.

Effects on Rate of Alcohol Elimination

The effects of in utero exposure to alcohol on the rate of alcohol elimination was determined in 45-day-old rats. Figure 4 shows the curves for mean BAC in 35% EDC ($n = 5$), 0% EDC ($n = 8$), and LC ($n = 5$) offspring after a test dose of 2.5 g/kg alcohol. The elimination rates for alcohol were calculated from the slope of the linear descending portion of each curve (20) and found to be 52 mg/100 ml/h and 50 mg/100 ml/h in the 35% and 0% EDC groups, respectively. As evident by examination of Fig. 4, there was no difference in the rate of alcohol elimination between the 35 and 0% EDC groups. Throughout the elimination phase of the curve, 0% EDC animals consistently displayed lower BACs than did animals in the 35% EDC group.

DISCUSSION

In utero administration of alcohol produces morphological and dysmorphic changes in the rat as it does in the human. Besides the growth retardation evident at birth, there are behavioral effects that last into adulthood. These behavioral effects have been seen in adult rats and include delayed kindling, learning deficits, hyperactivity, cross-tolerance to

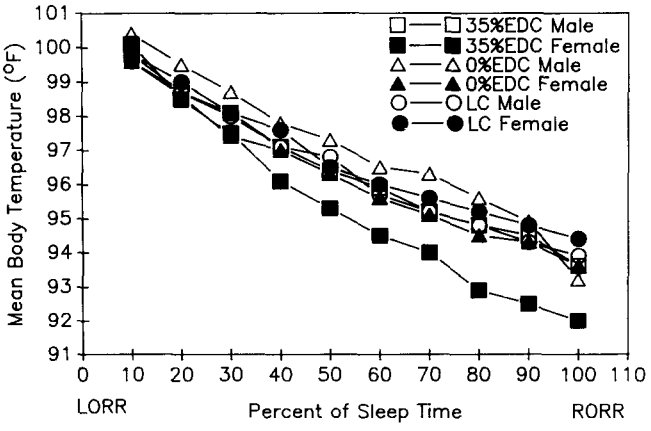

FIG. 3. Effects of in utero administration of alcohol on alcohol-induced hypothermia. The rectal temperature was measured every 10 min from LORR to RORR using a Harvard Tm99A temperature probe and is reported at 10% intervals of total sleep time. The body temperature of animals was plotted as a percentage of total sleep time to compare their body temperatures at various times in their sleep cycle.

drugs, and increased preference for alcohol. The increased preference for alcohol may be due to changes in tolerance and sensitivities to alcohol produced by in utero administration of alcohol.

A rat's performance at a time following administration of alcohol is influenced not only by the initial sensitivity of the animal's CNS to alcohol but also by the development of tolerance (resistance) to alcohol's effects. Acute tolerance has been defined as the development of tolerance during the time a single dose of alcohol is present in the body. In the present study, we believe that administration of alcohol during development constitutes a form of chronic alcohol administration that results in the development of tolerance.

A resistance to the effects of alcohol on dowel walking was demonstrated in rats given alcohol during development. The higher levels of alcohol found at the time rats in the 35% EDC group fell off the dowel rod indicate the presence of a resistance to the effects of alcohol on motor impairment. The brief differences in fall times (25 s) argues against the higher BACs of the 35% EDC group being entirely due to the fact that they stayed on the dowel longer (and thus were sacrificed longer after receiving an injection of alcohol). These results appear to be in agreement with other studies that demonstrate that in utero administration of alcohol results in behavioral changes that decrease an animal's response to alcohol (23). Mature mice exposed to alcohol in utero, for example, were less responsive to injected alcohol as evidenced by a reduced effect of the drug on response rates and a reduction in their ability to discriminate the presence of injected alcohol (23).

A longer period of time was required for males in the 35% EDC group to LORR and these animals slept longer than corresponding controls. This data appears to suggest that in utero administration of alcohol may affect the CNS and the ability to develop acute tolerance. Brain alcohol levels need to be determined at both LORR and RORR before it can be said that these animals differ in their ability to develop acute tolerance (36). Animals in the 35% EDC group slept longer than did controls, which suggests that in utero administration of alcohol increases sensitivity to alcohol. Differences in rates of alcohol metabolism do not account for the differences in sleep time in these groups of animals.

Another action of alcohol that has been used to determine tolerance to its effects is alcohol-induced hypothermia (36). The increased time to RORR in 35% EDC animals does not necessarily account for the lower body temperatures because a comparison of female and male groups, which slept the same length, still shows a difference in body temperature. In males, in utero administration of alcohol had no effect on alcohol-induced hypothermia. However, in females there was a greater alcohol-induced hypothermic effect produced by in utero administration of alcohol. However, it has been demonstrated

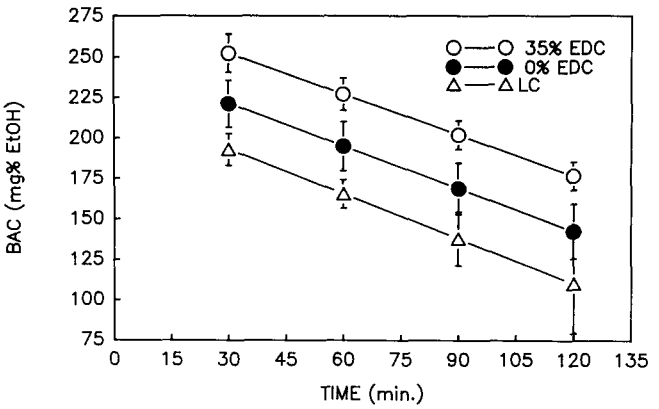

FIG. 4. Effects of in utero administration of alcohol on rates of alcohol elimination. Blood alcohol concentrations were determined at 30, 60, 90, and 120 min following administration of alcohol (2.5 g/kg, IP) in 35% EDC (n = 6), 0% EDC (n = 5), and LC (n = 6) rats.

that alcohol produced less of a hypothermic response in females than in males (4). This apparent contradiction may be due to a difference in methodologies in both studies. In the present study, alcohol was not given to the offspring after birth but only during gestation. This may imply that females born to drinking rats are less tolerant to at least some of the effects of alcohol and therefore less apt to develop a preference for alcohol. Preference studies have shown that indeed females exposed to alcohol in utero have a lower preference for alcohol than do males (28). These studies suggest that tolerance to the hypothermic effects of alcohol may be influenced not only by genetic makeup of an individual but also by in utero administration of alcohol.

In summary, these studies show that in utero administration of alcohol produces long-lasting effects that result in increased tolerance to the motor impairment effects of alcohol without producing an increase in rate of metabolism of alcohol. In utero administration of alcohol appears to result in increased sensitivity to alcohol; however, brain alcohol levels must be determined before this can be positively established. It is important to note that these changes in tolerance to alcohol are without administration of alcohol after birth to cause tolerance as has been done in several studies. Further studies must be conducted to define the sources of these differences.

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