Radial arm maze deficits in rats exposed to alcohol during midgestation

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Radial arm maze performance was examined in juvenile and adult rats prenatally exposed to alcohol for the relatively brief period of Gestational Days 7–13. When juvenile animals (26 days of age) were trained in the radial arm maze, alcohol-exposed offspring made significantly more errors than did animals in either nutritional or ad-lib control groups during the second and third blocks of trials. However, by the end of training, alcohol-exposed offspring performed the task at the same level as control animals. When these animals were *retested* at 90 days of age, radial arm maze performance was comparable to that of control animals, suggesting that once acquired, radial arm maze performance is retained into adulthood in animals prenatally exposed to alcohol. When radial arm maze training began in adulthood (90 days of age), rats prenatally exposed to alcohol demonstrated deficient radial arm maze performance. Thus, early behavioral experience may be useful for treating prenatal-alcohol-exposure-induced deficits in learning and memory.

Fetal alcohol syndrome results from in utero exposure to ethanol. The syndrome is characterized by several cognitive, behavioral, and anatomical anomalies (Abel, 1990). The cognitive dysfunctions accompanying fetal alcohol syndrome include impairments in learning and memory, mental retardation, attention deficit disorder, and sensory abnormalities (Clarren & Smith, 1978; Jones & Smith, 1973; Lemoine, Harousseau, Borteyru, & Menuet, 1968; Streissguth, Landesman-Dwyer, Martin, & Smith, 1980; Ulleland, Wennberg, Igo, & Smith, 1970).

Animal models of fetal alcohol syndrome can also demonstrate impairments in learning and memory. For example, rats prenatally exposed to alcohol exhibit poor performance in inhibitory (passive) avoidance (Abel, 1982; Lochry & Riley, 1980; Riley, Lochry, & Shapiro, 1979; Tan, Berman, Abel, & Zajac, 1990), shuttle avoidance (Abel, 1979; Vingan, Dow-Edwards, & Riley, 1986), Y-maze discrimination (Osborne, Caul, & Fernandez, 1980), T-maze (Riley, Lochry, Shapiro, & Baldwin, 1979), Hebb-Williams maze (Bond & DiGiusto, 1978), Morris water maze (Blanchard, Pilati, & Hannigan, 1990; Blanchard, Riley, & Hannigan, 1987; Gianoulakis, 1990), and water T-maze reversal learning (Wainwright et al., 1990). Recent studies show that after prenatal alcohol exposure throughout gestation, adult rats are impaired in the performance of the radial arm maze (Reyes,

Wolfe, & Savage, 1989). Since performance in the radial arm maze is highly dependent on an intact hippocampus (Olton, Becker, & Handelman, 1980), these results are consistent with previous anatomical findings indicating a loss of hippocampal CA1 pyramidal cells after prenatal alcohol exposure during Gestational Days 10–21 (Barnes & Walker, 1981).

To further characterize a “window” for hippocampal damage and subsequent learning/memory deficits induced by prenatal alcohol exposure, we administered alcohol to pregnant rats only during Gestational Days 7–13. During this time in gestation, organogenesis, cell differentiation, and cell migration occur. Thus, it is a period of great vulnerability to prenatal insult. We then tested radial arm maze performance in juvenile and adult offspring in order to determine, in part, the behavioral consequences of prenatal alcohol exposure during Gestational Days 7–13.

METHOD

Animals

Ninety-day-old nulliparous female and 75-day-old male Sprague-Dawley rats (Charles Rivers Farms; Portage, MI) were singly housed in an environmentally controlled vivarium, maintained at $22^{\circ} \pm 1^{\circ}\text{C}$ with lights on at 0700 h and off at 1900 h. The animals had ad lib access to lab chow and water for 2 weeks prior to beginning the experiment.

Breeding

Each female was mated to a randomly assigned male. Mating occurred in each female's cage for 4 h daily and continued for 2 weeks or until a vaginal plug was found (Gestational Day 0). Sperm-positive females were weighed on Gestational Days 0, 8, and 15.

Diet

On Gestational Day 5, females were randomly assigned to one of three groups. One group of rats (35% EDC—ethanol-derived

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calories; $n=21$) had free access to a liquid diet of chocolate Sustacal (Mead Johnson and Co.), supplemented with Vitamin and Mineral Diet Fortification Mixture (ICN Nutritional Biochemicals); 35% of the caloric content of this diet was provided by added ethanol. Another group of animals (0% EDC, $n=15$) was pair-fed to animals in the 35% EDC group. The diet for these animals was similar to the 35% EDC diet, except that no ethanol was added. This diet was made isocaloric to the 35% EDC diet by adding maltose-dextrin. Dams in the 0% EDC and 35% EDC groups were adapted to the liquid diet (0% EDC) on Gestational Days 5 and 6. On Gestational Day 7, the lab chow was removed and replaced with the appropriate liquid diets. Diets were prepared fresh each day and were administered from Gestational Day 7 through 13. On Gestational Day 14, the liquid diets were discontinued. Lab chow and tap water were returned to these animals and provided throughout the remainder of pregnancy ad lib. The third group of animals (ad lib, $n=16$) had ad-lib access to Purina rat chow and tap water.

At birth, the offspring were counted, weighed, randomly culled to 10 per litter, and returned to the dams. The offspring were weighed and weaned at 21 days of age, separated by gender, and group housed (3–4 per cage) prior to behavioral testing.

Task and Apparatus

The radial arm maze is a complex spatial memory task in which rats are required to enter each arm of an 8-arm maze only once in order to obtain a food reward located at the end of each arm (Olton & Samuelson, 1976).

The floor of the maze was made of plywood, painted white. The center of the maze was octagonal (25 cm side to side) and surrounded by clear Plexiglas 30.5 cm high. Each of eight arms (55.5 cm long $\times$ 7.1 cm wide) projected from the center of the maze and had clear Plexiglas walls (15.6 cm high). The entrance to each of the arms was blocked by a clear Plexiglas guillotine door. Recessed cups were located at the end of each arm (2.5 cm in diameter $\times$ 1.8 cm deep). The maze was on a pedestal (75 cm high) in a dimly lit room with several large extramaze cues present (e.g., doors and chalkboards). The maze was cleaned daily prior to training.

Training Procedure and Experimental Design

On Postnatal Day 26, 8 male pups from each diet group were singly housed and placed on a restricted feeding schedule sufficient to ensure continued growth (5–15 g Purina Rat Chow/day). Behavioral procedures were conducted between 1000 h and 1700 h, with no more than 2 animals/litter in any condition (counterbalanced across diet groups). Experimenters collecting behavioral data were blind to the prenatal exposure history of the animals. Maze-naïve animals were initially given five familiarization trials in the maze (one trial/day), during which none of the arms were baited. Each animal was placed in the center of the maze, the guillotine doors were raised, and the animal was allowed 5 min to explore the maze. The total number of arm entries made during each familiarization trial was used to assess locomotor activity levels.

Following familiarization, the animals were trained in the radial arm maze. The rats were allowed a maximum of 5 min/day to consume food rewards (Froot Loops Cereal) located in the recessed cups at the end of each arm. Failure to enter an arm, reentry into a previously visited arm, or entry into an arm but failure to consume the food reward was scored as an error (Altman, Ogren, Berman, & Normile, 1989). The animals were trained for at least 15 days, but not more than 25 days, until they reached a criterion of performance requiring no more than 1 error over 2 consecutive days. The total number of errors made during the first 15 trials was collapsed into five blocks of three trials each and used to assess radial arm maze performance.

Following this period of behavioral testing, the same pups were given ad-lib access to lab chow until 85 days of age, at which time food intake was again restricted to a level that maintained body weights at 80% of the free-feeding weights. On Postnatal Day 90, performance in the radial arm maze was *retested* as before, except that no familiarization period was provided.

Separate groups of maze-naïve male litter mates from the 35% EDC, 0% EDC, and ad-lib lab chow groups ($n=8$) were singly housed at 75 days of age, food deprived, familiarized, and trained in the radial arm maze at 90 days of age as described above.

Data Analyses

Effects on initial animal weights, changes in body weight, locomotor activity levels, and memory performance were assessed by analysis of variance. Newman-Keuls contrasts were used for post hoc analyses of significant effects.

RESULTS

Dams in the 35% EDC group consumed 10.5 ± 0.43 g ethanol/kg/day ($M \pm SEM$). There were no significant differences in maternal weight gain, number of implantation sites, number of live births, birth weights, or litter weights. In the 35% EDC group, there were significantly fewer resorptions (0.5 ± 0.2) and significantly more still births (1.1 ± 0.2) than in ad-lib control animals [1.9 ± 0.4 , 0.0 ± 0.0 , respectively; $F(2,44) = 6.96$, 8.78 ; $p < .01$]. Pinna detachment was significantly delayed in both the 35% EDC (2.8 ± 0.1 days) and 0% EDC (2.8 ± 0.1 days) groups compared with ad-lib (2.5 ± 0.1 days) control animals [$F(2,44) = 6.20$; $p < .01$]. Prenatal alcohol exposure on Gestational Days 7–13 also delayed ear opening (12.9 ± 0.1 days) as compared with either ad-lib (12.6 ± 0.1 days) or 0% EDC (12.2 ± 0.1 days) control animals [$F(2,44) = 26.79$; $p < .01$]. However, there were no significant differences in the time of fur emergence, eye opening, or male pup weights through Postnatal Day 84.

When radial arm maze testing began on Postnatal Day 26, there were no significant between-group differences in initial body weights (ad lib = 71.9 ± 1.8 g; 0% EDC = 75.0 ± 2.4 g; 35% EDC = 78.6 ± 2.3 g) or locomotor activity levels (ad lib = 10.3 ± 0.56 arms/trial; 0% EDC = 9.8 ± 0.61 arms/trial; 35% EDC = 8.6 ± 0.77 arms/trial) for the subset of animals undergoing maze testing. However, there was a significant group effect on weights from the start of maze training through Trial 15 [$F(2,21) = 67.02$, $p < .001$]. Ad-lib lab chow control animals gained more weight (152.2 ± 2.7 g) than did 0% EDC animals (151.3 ± 1.6 g), which gained more weight than did animals in the 35% EDC group (145.1 ± 3.1 g).

Figure 1 illustrates the performance of pups tested in the radial arm maze beginning on Postnatal Day 26. Animals in all three exposure groups demonstrated significant improvements in performance over the five-block period of testing [$F(4,84) = 28.52$, $p < .001$]. There was also a significant group $\times$ block interaction [$F(8,84) = 2.03$, $p = .05$], with significant group differences on Block 2 [$F(2,21) = 3.75$, $p < .05$] and

Figure 1. Prenatal-alcohol-exposure-induced deficits in radial arm maze performance of juvenile rats. Note that alcohol-exposed offspring had significantly poorer performance than did control animals during the second and third blocks of trials. * $p < .05$ versus ad-lib lab chow control group; # $p < .05$ versus 0% EDC control group.

Block 3 [$F(2,21) = 4.41, p < .05$]. Individual group comparisons using Newman-Keuls contrasts indicated that animals in the 35% EDC group made significantly more errors than did animals in the 0% EDC group during Blocks 2 and 3, as well as the ad-lib lab chow group during Block 3. Group differences in trials to criterion (ad lib = 7.37 ± 0.91 ; 0% EDC = 9.63 ± 1.39 ; 35% EDC = 13.0 ± 2.24) approached, but did not reach, statistical significance [$F(2,21) = 3.09, p < .067$].

Animals in these 3 groups (ad lib, 0% EDC, and 35% EDC) were again food deprived beginning on Postnatal Day 85 and retested in the radial arm maze beginning at 90 days of age. At retest, there was a significant difference in initial body weights [$F(2,21) = 4.83, p < .019$], with the 35% EDC pups (431.6 ± 12.3 g) weighing more than the 0% EDC offspring (383.9 ± 11.8 g). The ad-lib lab chow group's initial weight (402.6 ± 8.3 g) was not significantly different from that of the 0% EDC group or the 35% EDC group. However, there were no significant between-group differences in weight losses during the food restriction period.

Figure 2 illustrates the radial arm maze performance of offspring retested beginning at 90 days of age. All groups demonstrated significant memory savings (number of trials to criterion as juveniles – number of trials to criterion when retested as adults: ad lib = $2.37 \pm 0.71, t = 3.35, p < .02$; 0% EDC = $3.87 \pm 1.01, t = 3.83, p < .01$; 35% EDC = $7.13 \pm 2.39, t = 2.98, p < .05$). The animals in all three exposure groups demonstrated significant improvements in performance over the five-block period of testing [$F(4,84) = 26.84, p < .001$]. Radial arm maze performance of animals in the

35% EDC group was comparable to that of animals in both control groups during this testing session, both in terms of number of errors (Figure 2) and trials to criterion (ad lib = 5.0 ± 0.87 ; 0% EDC = 5.75 ± 0.84 ; 35% EDC = 5.88 ± 1.11).

For the maze-naïve litter mates that initially began testing on Postnatal Day 90, there were no significant differences between groups in initial body weights (Postnatal Day 75), weight losses over days, or locomotor activity levels (ad lib = 7.2 ± 0.60 arms/trial; 0% EDC = 6.0 ± 0.52 arms/trial; 35% EDC = 6.9 ± 0.55 arms/trial). Figure 3 illustrates the radial arm maze performance of maze-naïve litter mates when testing began at 90 days of age. The animals in all three groups demonstrated significant improvements in performance over the five-block period of testing [$F(4,84) = 17.96, p < .001$]. There was also a significant group effect [$F(2,21) = 8.21, p < .002$], with significant group differences on Block 1 [$F(2,21) = 10.25, p < .0008$], Block 2 [$F(2,21) = 16.908, p < .0001$], Block 3 [$F(2,21) = 4.7395, p < .0200$], and Block 4 [$F(2,21) = 3.4607, p < .0502$]. Individual group comparisons using Newman-Keuls contrasts indicated that the animals in both the 0% EDC and in the 35% EDC groups made more errors than did the animals in the ad-lib control group during the first, second, and third blocks of testing. In addition, animals in the 35% EDC group also made significantly more errors than did the animals in the ad-lib control group during the fourth block of testing. There was also a significant group effect on trials to criterion [$F(2,21) = 6.76, p < .0054$], with ad-lib (9.63 ± 1.36) offspring requiring fewer trials than did

Figure 2. Radial arm maze performance of adult rats prenatally exposed to alcohol with prior behavioral experience in the maze. Note that alcohol-exposed offspring had performance levels comparable to those of control animals throughout testing.

Figure 3. Prenatal-alcohol-exposure-induced deficits in radial arm maze performance of adult rats. Note that alcohol-exposed offspring had significantly poorer performance than did ad-lib lab chow control animals throughout testing. 0% EDC control animals were also impaired relative to ad-lib lab chow control animals during the first, second, and third blocks of trials. * $p < .05$ versus ad-lib lab chow control group.

the animals in either the 0% EDC (17.13 ± 1.26) or the 35% EDC (15.75 ± 1.91) groups.

DISCUSSION

The results of this study indicate that a relatively brief 7-day period of prenatal ethanol exposure (i.e., Gestational Days 7–13) results in deficits in radial arm maze performance. These results are similar to those reported by Riley, Lochry, and Shapiro (1979) in which 11 days of prenatal alcohol exposure (Gestational Days 6–16) impaired passive avoidance learning in rats. The present results also support previous findings demonstrating similar radial arm maze performance deficits in 60-day-old rats prenatally exposed to alcohol throughout gestation (Reyes et al., 1989) and are consistent with past studies describing learning deficits in animals prenatally exposed to alcohol (e.g., Riley, 1990).

Since juvenile animals prenatally exposed to alcohol were able to acquire the radial arm maze task, albeit at a slower rate, the impairment might result from either a delay in the development of working memory or a deficit in reference memory (Olton et al., 1980). In this regard, several studies suggest that prenatal alcohol exposure delays development (Abel, 1982). Since the hippocampal formation can first be seen on Embryonic Day 14 (Paxinos, Tork, Tecott, & Valentino, 1991), the behavioral deficits seen here might result from damage to, or delayed development of, hippocampal neuroblasts.

It is unlikely that the maze deficits evident in the present study were the result of changes in activity levels due to prenatal alcohol exposure, because there were no

significant differences in the number of arms entered during the habituation trials. However, motivational factors may have contributed to the deficits, since alcohol-exposed animals gained less weight during maze learning than did 0% EDC or ad-lib control animals. These differences in weight gains were small (average = 0.5 g/day), all animals in all groups readily consumed the rewards in the maze, and all daily food rations were consumed in their entirety before the next day's training. This suggests that all animals were highly motivated to seek food reinforcement in the maze, and it lessens the likelihood that radial arm maze performance deficits were motivational in nature.

All animals showed significant savings in radial arm maze performance when *retested* at 90 days of age, indicating substantial long-term retention of earlier training. In addition, alcohol-exposed animals had performance levels comparable to those of ad-lib and 0% EDC animals during retesting. This suggests that once acquired in juveniles, the memory of radial arm maze training remains intact, at least through Postnatal Day 90, even in alcohol-exposed offspring that showed initial maze deficits. The handling of alcohol-exposed animals during initial maze training may also have contributed to the more efficient performance upon retest (Brown, 1968; Greenough, 1976; Hebb, 1949; Weinberg, Krahn, & Levine, 1978).

Alternatively, alcohol-related maze impairments may be transient in nature (Riley, Lochry, & Shapiro, 1979), and at the retest, alcohol-exposed offspring may have been beyond the developmental age at which alcohol effects are most evident. In an attempt to examine this question, we tested maze-naïve rats at 90 days of age. Maze-naïve, 90-day-old alcohol-exposed rats were still impaired in performance on the radial arm maze when compared with maze-naïve ad-lib control animals. This suggests that maze deficits persist into adulthood after prenatal alcohol exposure. However, this interpretation is complicated by the fact that the 0% EDC control animals also showed a significant impairment in comparison with ad-lib control animals and did not significantly differ from the 35% EDC offspring. Thus, the pair feeding of pregnant dams may have contributed to poor maze performance in adult, but not in juvenile, offspring. Possible explanations for pair-feeding effects may be related to nutritional factors, patterns of food intake, or stress associated with the pair-feeding procedure (Mankes, Battles, LeFevre, van der Hoeven, & Glick, 1992; Weinberg, 1984). It is important to note that several others have reported behavioral deficits in pair-fed animals, and such findings highlight the problems associated with finding adequate control groups for prenatal alcohol studies (Weinberg, 1984).

In conclusion, even a brief 7-day period of prenatal alcohol exposure appears sufficient to result in abnormal maze learning in juvenile offspring. In this study, alcohol exposure (Gestational Days 7–13) was delivered just prior to the development of hippocampal pyramidal cells. This period may represent a critical period for dis-

ruption of learning in tasks like the radial arm maze which depend on an intact hippocampus. The fact that performance, once acquired by alcohol-exposed animals, remained stable into adulthood suggests that alcohol-exposed animals can benefit from early training. However, the precise factors that result in continued good performance in adulthood (e.g., handling, behavioral training, further development) need to be clarified.

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