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Effects of Prenatal Alcohol Exposure on Activity and Learning in Sprague-Dawley Rats

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WESTERGREN, S., B. RYDENHAG, M. BASSEN, T. ARCHER AND N.G. CONRADI. *Effects of prenatal alcohol exposure on activity and learning in Sprague-Dawley rats.* PHARMACOL BIOCHEM BEHAV. **55**(4) 515–520, 1996.—Nulliparous pregnant Sprague-Dawley rats were exposed to ethanol via a liquid diet technique (FAE, fetal alcohol exposure) or administered a fixed amount of control diet from gestational day 11 to day 21. The offspring, at 2–3 months of age, were studied in tests of mechanically monitored motor activity and learning acquisition in an automatized testing cage requiring an instrumental discriminative response, where the ability to learn and relearn correlations of a light signal to water presentation was monitored. A significantly reduced activity (i.e. ramp mounting behaviour) in a novel situation was obtained in the FAE group compared to controls. The initial disruption of ramp mounting behaviour could reflect alterations in either habituation to a novel test situation, altered neophobia, or some retardation in associating these responses with the outcome of water-availability. Adult FAE rats (six months of age) showed a tendency towards a lowered acquisition performance ($p = 0.06$) when tested in a circular Morris-type swim maze, but no detectable differences were shown in a motor activity test chamber situation. **Copyright © 1996 Elsevier Science Inc.**

Rats Prenatal alcohol exposure Liquid diet Visual learning Relearning Activity Residential maze Operant discriminative test Morris-type swim maze Motor activity test chambers

ALCOHOL abuse during pregnancy may cause organic disturbances in children, an effect commonly known as the fetal alcohol syndrome (FAS) (12,13,21). The CNS disturbances of the fetal alcohol syndrome manifest themselves in humans in the form of such syndromes as mental retardation, delayed sensori-motor development, attentional learning deficits, memory disorders, sleep disturbances and hyperactivity (8,24,32,37). However, it is not always easy to detect and interpret functional alterations using standard test batteries. For instance, the children of alcohol- consuming mothers perform at levels that may differ little from that of normal children in global intelligence tests, in spite of easily observed difficulties in specific memory functions (33). At the same time, it should also be mentioned that children with FAS suffer from optic nerve atrophy (34).

The results of animal studies on the perinatal effects of alcohol on functional parameters are mainly in accordance with what would be expected on the basis of the existing clinical evidence. Hyperactivity in measures of spontaneous motor activity is frequently observed following fetal alcohol exposure (FAE), and this feature in particular provides one of the cardinal symptoms of FAS. Interestingly, the observed hyperactivity effect seems to be age-related whereby normal activity levels are obtained during juvenile and adult ages; hyperactive responses have then been evidenced in preweaning and weaning animals (e.g. from 2–4 weeks after birth) on the one hand and in much older age groups on the other hand, suggesting some type of U-shaped function of perinatal alcohol treatment on motor activity (2,4,11). The hyperactivity of FAE may involve a deficit in response inhibition (29), and studies using passive avoidance conditioning situations have confirmed this interpretation (1,16,19,30).

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Other studies have revealed deficits in reversal learning using an appetitively-motivated Y-maze discrimination task (5). Left-right discrimination in a T-maze was, however, not impaired regarding reversal performance (23). At the neonatal and weaning stages difficulties in acquiring associations between taste and odor stimuli are seen (9,28). More complex learning situations cannot reveal any shortcomings in FAE rats, possibly because of compensatory and/or greater habit strength mechanisms. In the Morris water maze test, deficits in spatial learning may be detected in very young FAE rats indicating the likelihood of disturbances of spatial navigation learning function, possibly due to hippocampal and limbic mechanisms; similar studies have not been performed at older ages, a fact that makes it impossible to exclude an age-dependency effect (20).

The aim of the present study was to investigate spontaneous motor activity and maze learning as well as relearning in adolescent and adult FAE rats in comparison with the offspring of control mothers.

MATERIAL AND METHODS

Subjects

Nulliparous Sprague-Dawley dams weighing approximately 240–260 g and with timed pregnancies were purchased from the established breeders (Alab, Sollentuna, Sweden). The rats were housed in a secluded room with an ambient temperature of 22 °C, with a 12 h : 12 h light : dark cycle commencing at 06.00 h. One group of dams was exposed to ethanol by a liquid diet technique (25). Alcohol exposure was initiated on day 11 post conceptionem (p.c.), with an initial alcohol content of less than 2% weight by volume and the amount of alcohol in the diet increased over 3 days to a final concentration of 5%; the exposure regime was maintained until day 22. Initially, we tried to individually pairfeed control and FAE dams but, since only some 50% of the dams in both groups gave birth to litters, this procedure was abandoned. Instead, the mean daily food consumption of alcohol-exposed dams was established and these amounts were then administered to all the control dams using a isocaloric diet. At birth, each of the litters were culled to consist of four pups. Only the male offspring were subsequently used for behavioural testing. The offspring were monitored with regard to body growth.

Apparatus and Analysis

Resident maze. Eleven rats exposed to alcohol (FAE) and eleven control rats were examined by an operant discriminatve testing procedure that was started at 55–80 days of age, and which has been described in detail elsewhere (31). In short, the rats were housed individually in the testing cage which consisted of an animal plexiglass cage with food placed at the roof at one end of the cage. Opposite to where the food was placed the cage was connected to a plexiglass chamber which housed a Y-maze. The right and left arms of this Y-maze formed two ramps each ascending at an angle of 45° to a simplified intelligence panel consisting of a light stimulus (four light diods) and a water dispenser. Each arm of the Y-maze was divided by an opaque wall separating the two ramps and each water dispenser was located 3 cm directly underneath the visual stimulus. Water was presented by opening of an electromechanic valve. The water was sprinkled in front of the nose of the rat in a plexiglass basin with a continous draining. An oval aperture was located in the transparent plexiglass wall dividing the home chamber from the Y-maze chamber, through which the visual stimulus could be observed by the rat. Food was freely accessible and the rat resided in the cage without explicit extraneous interference throughout the extent of the test period.

The side at which water was presented was chosen by a computer on a random schedule and was signalled by the light discriminative stimulus. Information about which side the nose poke was made (in the water dispenser cavity) was recorded and only when this occurred on the correct side was water made available immediately by opening of the valve. Water presentation was immediately terminated when the rat descended the ramp or when the water period was at an end. The correct side was defined as the side at which water was available during any given trial and in this study the light visual discriminative stimulus was used to indicate the side where water was not present during the test period. Hereafter light was used to indicate the side where water was available during the reversal period. The length of the water period, i.e. the period during which water was available at one of the two holes was 10 min and the time between water periods were 60 min. If a drinking attempt was made on the incorrect side the rat was still free to choose the other side for a new attempt. Four cages, simultaneously controlled by one microcomputer, were used, so two experimental and two control animals were tested simultaneously.

The motor activity of the rats was recorded as the number of ramp mounts or drinking attempts, including the activity in relation to each drinking period. Learning acquisition was evaluated as Percent First Choice Correct (PFCC) defined as the number of water periods with the first drinking attempt being correct expressed as the percentage of all water periods with a drinking attempt. PFCC reaches a value of 100 when all first drinking attempts has been made on the correct side.

Automated activity test chambers. Nine control and nine ethanol exposed rats (different to the resident maze-test group), were tested for spontaneous motor activity at six months of age. Plexiglas boxes (70 × 70 × 30 cm) placed within two series of photocell beams (32 photocells, one high level series 13 cm from the bottom and one low level series 3 cm from the bottom, Kungsbacka mät-och reglerteknik AB, Fjärås, Sweden) were applied to measure the locomotion, rearing and total activity parameters of spontaneous behaviour (6,17,18,35). Locomotion was measured by the low level grid of infrared beams. Counts occured when the rat moved around horizontally, showing predominantly locomotory behaviour. Rearing was measured by the high level infrared beams, which registered every interruption of the beams as a rearing count, each time the rat raised itself onto its haunches. Total activity counts were registered when any of the photocells were interrupted, and monitored any type of activity, e.g. those caused by particular rat movements when standing/sitting in one place, like tremors, scratching, head shaking or grooming behaviours.

Circular swim maze (Morris type). Eight control and nine ethanol exposed rats (different to those of the resident maze test, but the same as in the motor activity test chambers) were tested in a circular swim maze at six months of age. The swim maze (Morris-type) was a circular bath (diameter 140 cm) containing clear water thermostatically controlled at 25 °C, apparatus similar but not identical to that described by Morris (27). The bath contained a square platform (10 × 10 cm) placed at a constant position, opposite the initial placement of the animal into the bath, 1 cm below the water level (depth 30 cm). Five trials, each allowing the rat 65 s to swim and

escape the water by finding the hidden platform, were performed on each test occasion, consecutively for three days (17,35).

For all the trials, the rat was placed in the water at the same point and allowed to swim around to find the submerged platform and escape from the water. On reaching the platform the rat was allowed to remain upon it for 30 s before being placed in the water again for the next trial. If the rat failed to locate the platform within 65 s it was lifted out of the water and placed on the platform for the 30 s intertrial interval. Latency to reach the platform and climb onto it was registered for each trial.

Statistical Analysis

For ramp mounts, an habituation quotient, based upon the number of mounts each day divided by the number of mounts on the previous day × 100 was tabulated as described previously (14) in order to indicate an effect upon exploratory behaviour in the test situation. This quotient diminishes the risk of detecting false significances at single days due to temporary variations in activity levels. These data were subjected to the Wilcoxon signed-rank and the Mann-Whitney *U*-tests.

Spontaneous motor activity data was subjected to split-plot ANOVA (22). Swim maze acquisition and the quotient of habituation data were subjected to nonparametric Mann-Whitney *U*-tests for measuring differences between groups. Pairwise differences were tested for using Student *t*-tests. A 5% level of significance (double-sided) was maintained unless otherwise stated.

RESULTS

Food Consumption and Birth Weights

The experimental design allowed a 2-week monitoring of food intake in relation to alcohol exposure which was necessary for controlling intake on the basis of group-yoked controlled procedure. The mean daily food consumption of a separate group of pregnant dams that were allowed free access to the control diet increased from some 55 ml on day 10 p.c. to some 110 ml on the days shortly before birth. (Fig. 1A). Ethanol in the diet resulted in a 50% reduction in daily food intake compared to the freely eating animals (Fig. 1B). The average daily intake of food for the alcohol-exposed dams was 63 ml from day 12 p.c. This amount of the control diet was given to the control dams. Around birth, food consumption was reduced in most dams. Blood alcohol levels were not monitored in this study, but with a similar regime plasma levels have previously been shown to vary widely with a mean of 145 mg/100 ml (15). The food consumption correlated to body weights yields an ethanol intake of about 12 g/kg.

There was a small, statistically significant reduction in birth weight of the AE rats (5.3 g compared to 6.0 g for the control group, $p < 0.05$) but no significant differences could be detected during the suckling period or at weaning. From shortly after 50 days weight gain appeared to be reduced in AE rats but, due probably to the inter-litter variation, no significant differences were found. The body weight at 80 days was higher in both groups compared to rats with eight pups to a mother, indicating that the undernutrition, if any, was limited to the last period of pregnancy.

Activity in the Residential Maze, Adolescent Rats

Ramp mounts. During the first day in the residential maze cage, FAE rats exhibited a significantly lower activity (i.e.

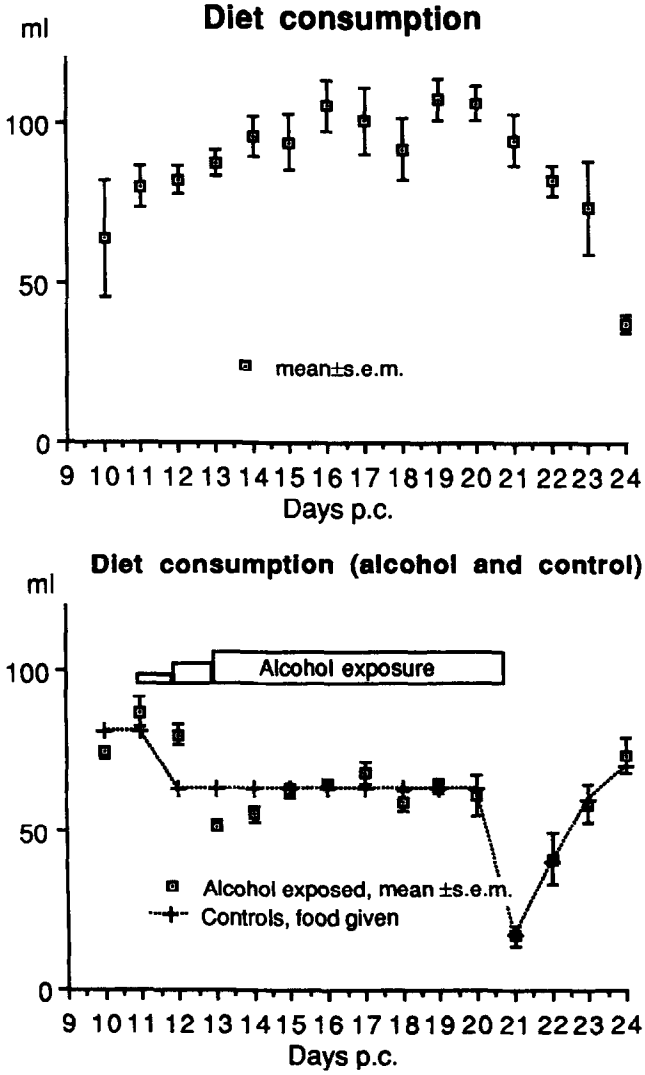

FIG. 1. (A) Food consumption of four rats given free access to the control diet. An increase in the consumption from 55 ml to 110 ml on the days shortly before birth was observed. (B) Ethanol diet consumption in nine FAE rats. Ethanol in the diet resulted in a 50% reduction of food intake.

ramp mounting) score (FAE rats 69.1 vz Controls 180.1 mounts). On the second day, the activity score of the FAE rats increased to 102.1 whereas that of controls decreased to 84.2 (Fig. 2A). Over successive test days (i.e. Day 3 to Day 8) ramp-mounting activity in control rats remained high whereas FAE rats were more variable. After days 6–8 a slight reduction was observed in both groups. Taken over the complete test period, FAE rats appeared to display a lower ramp activity. When the discrimination combination of light/no water was reversed on day 14, FAE rats again showed significantly lower ramp activity scores than controls (FAE rats 56.8 vz C 93.7).

The quotient of habituation in FAE rats was significantly increased on day 2 compared to controls ($p < 0.05$, Mann-Whitney *U*-test), (Fig. 2B), significantly reduced from day 2 to day 3 and significantly increased from day 14 to day 15 ($p < 0.05$, Wilcoxon Signed Rank test). No significant difference between FAE rats and control rats after reversal was obtained.

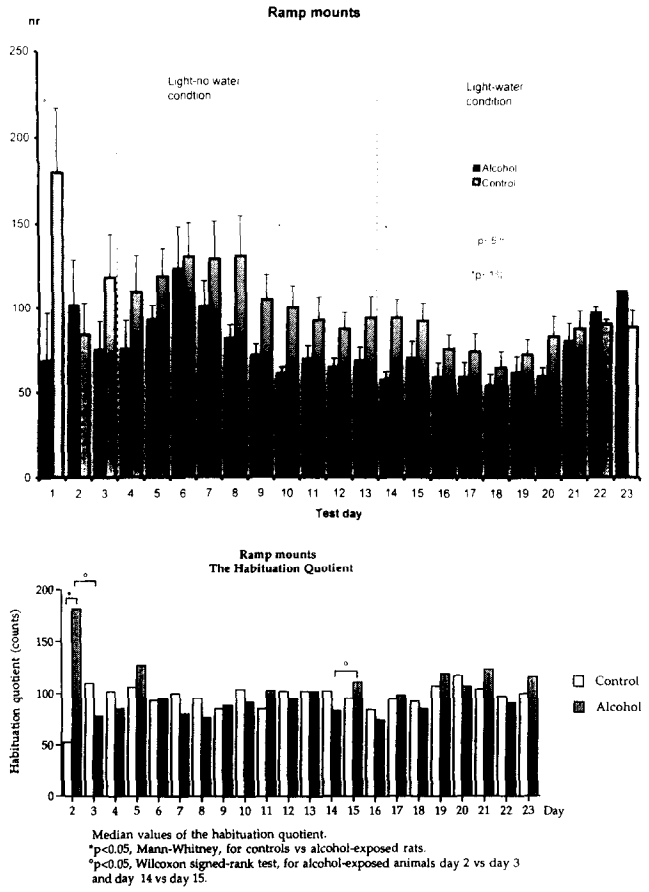

FIG. 2. (A) The mean number of ramp mounts + SEM in 11 FAE rats and 11 controls day by day during the testing period. Activity decreased towards the end of each testing condition, light-no water (Test Days 4–13) and light-water (Test Days 14–23), respectively. Note the statistically significant difference in activity between the two groups at days 1, 9, 10, 12 and 14. Significance levels $p < 5\%$ (days 1, 9, 12) and $p < 1\%$ (days 10 and 14) as indicated in the figure. (B) Habituation quotients for ramp mounting behaviour by the eleven alcohol and control rats over the whole test period. The Habituation quotient represents ramp mounting scores of Day x + 1 divided by Day x times 100. The quotient was significantly increased in the FAE group from Day 2 to Day 1 compared to controls (Mann-Whitney U test, U value = 20). In the FAE group a significant reduction of the quotient was seen from Day 2 to Day 3, finally a significant increase was seen from Day 14 to 15 (Wilcoxon signed-rank test).

Learning in the Operant Discriminative Task, Adolescent Rats

No difference between ethanol-exposed and control rats was obtained (Fig. 3). Ten days of relearning was also tested but there were no statistical differences between the two groups.

Spontaneous Activity, Adult Rats

ANOVA indicated no significant differences in the spontaneous motor behaviour tested in the motor activity test chamber of the control and FAE groups for either locomotor, rearing or total activity ($F(1, 16) = 0{,}937$), (Table 1).

Learning in Circular Water Maze, Adult Rats

The FAE rats seemed to show longer latencies to reach the submerged platform compared to controls. However, when

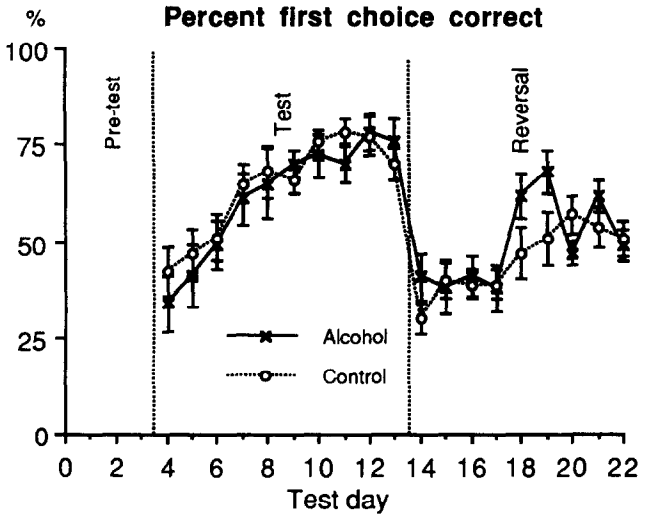

FIG. 3. Mean learning scores ± SEM as reflected by correct choice in 11 control and 11 alcohol exposed rats. The Percent First Correct Choice is indicated as follows: (a) three-day pre-test, (b) test phase, (c) reversal phase. Days 4 to 13 with light indicating no water. Days 14 to 23 with light indicating water. There were no statistically significant differences in learning or relearning scores between the two groups.

tested by the Mann-Whitney U-test a p level of 0.06 was obtained. Thus, a significant reduction in learning in the water maze could not be demonstrated in the FAE rats (Table 1).

DISCUSSION

Many of the functional changes recorded in rats as an effect of fetal alcohol exposure (FAE) appear to be age-related (1,4,11): this is indicated in the present case by differential behavioural changes in adolescent as opposed to adult FAE rats. Following alterations during the suckling period FAE rats show smaller changes as adults and the differences to control groups again increase at the higher age groups (7). This type of alteration in function has been obtained for example with regard to the hyperactivity (1,4,11).

FAE rats also have shown deficits in reversal learning whereby the animal has to suppress the performance of a previously correct response in favour of a previously incorrect response (5,23). This has been interpreted as a deficit in response inhibition caused by the FAE treatment. In complex learning situations, such as certain types of maze learning, the FAE rats have not demonstrated any obvious deficits (3,36). In the present study we could not demonstrate any statistical difference in the operant discriminative learning capacity between prenatally ethanol-exposed rats and the control group. The results were not conclusive regarding the relearning phase which may have been too short since the rats achieved not more than chance performance. The age at testing (55 days or 80 days) may in part be one explanation of the lack of differences. The results of the swim maze learning task, where the latency to locate the platform failed to reach significance ($p = 0.06$) between the FAE and control rats at an adult age suggest that robust alterations in the learning performance capacity of FAE animals may be present only at an earlier stage (20). Apart from the obvious consideration of an appetitive vs mildly-aversive task, there are most certainly differences between the testing situation in the residential maze and the circular water maze, although both cases involve the

TABLE 1

LACK OF EFFECT OF PRENATAL ALCOHOL TREATMENT UPON PARAMETERS OF MOTOR ACTIVITY IN THE AUTOMATED TEST CHAMBERS

	Control (n = 9) (counts)	Ethanol (n = 9) (counts)
Locomotor activity		
15 (min interval)	1032 ± 32	1031 ± 34
30	276 ± 17	420 ± 20
45	195 ± 14	258 ± 19
60	217 ± 14	219 ± 17
Rearing		
15	78 ± 9	93 ± 10
30	24 ± 14	43 ± 8
45	20 ± 8	28 ± 11
60	23 ± 12	16 ± 5
Total activity		
15	1688 ± 51	1722 ± 94
30	520 ± 23	841 ± 39
45	478 ± 41	524 ± 42
60	481 ± 47	447 ± 57
	(n = 8) (s)	(n = 9) (s)
Swim maze performance		
1st test day	35.8 ± 6.1	36.0 ± 6.7
2nd test day	17.8 ± 4.2	24.9 ± 5.5
3rd test day	6.9 ± 2.5	15.1 ± 4.9

For activity tests is $F(9,54) < 1.2$. Motor activity tests: values represent means ± SEM. Circular water maze: values represent medians ± quartiles.

subject's use of an operant response. In the former, a discrimination involving light or no light conditions modulated ramp-mounting responses whereas in the latter swimming responses were modulated by the spatial-navigational orientation of the hidden platform. The consummatory responses were also different: water consumption in the resident maze and platform-mounting in the circular swim maze. Thus despite the relative influence of these different perceptual/operational mechanisms, the resulting less-effective ramp-mounting (Day 1) and platform-mounting (Test Day 3, at $p < 0.06$ level) may have some association with the alcohol consumption.

The alcohol-exposed adolescent rats displayed an initial hypoactivity (Day 1), as reflected by the ramp-mounting behaviour. The initial deficit in ramp activity was followed one day later by increased ramp activity suggesting a possible disruption of an initial habituation response (see Fig. 2B) to the novel residential maze environment and/or the ramp structure itself. A lowered activity on the ramp was observed again after reversal of the visual stimulus. However, other explanations may be considered: it is possible that FAE rats failed to associate the ramp-mount operant response with water as quickly as control rats did although the similar performance of the two groups for the percent first choice correct variable (see Fig. 3) would argue against this. The initial reduction in ramp-mounting activity may also reflect a neophobic response to the novel ramp structure resulting in some degree of avoidance of the ramp during Day 1. Both groups did show similar general habituation with differences only occuring during the initial phase, which if an enhanced neophobia was the case may suggest an altered functional expression of exploratory behaviour in this age group. Unfortunately, the exploratory behaviour of the older rats tested in the open-field test did not disclose any significant differences (for example, with regard to rearing behaviour).

It has been found that amphetamine, methylphenidate and scopolamine affect young adult alcohol-exposed rats differently than control rats (10,11,26). This may be an indication of a disturbance induced in the catecholamine and the cholinergic/inhibitory systems possibly responsible for the hyperactivity in young alcohol-exposed rats. However, the finding of a hypoactivity response in a novel environment at ages 55–80 days in this study are difficult to reconcile with this mechanisms.

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