Alterations in Behavioral and Striatal Dopamine Asymmetries Induced by Prenatal Stress[1]

ESTER FRIDE AND MARTA WEINSTOCK[2]

Department of Pharmacology, The Hebrew University-Hadassah Medical School, Jerusalem, Israel

FRIDE, E. AND M. WEINSTOCK. Alterations in behavioral and striatal dopamine asymmetries induced by prenatal stress. PHARMACOL BIOCHEM BEHAV 32(2) 425–430, 1989.—We investigated the effects of maternal noise and light stress, randomly applied throughout pregnancy, on the development of behavioral and neurochemical asymmetries in the rat offspring. This form of maternal stress resulted in a rightward positioning of the tail of both sexes soon after birth as opposed to the leftward bias in controls. At adulthood, prenatally stressed offspring showed a change in directional bias compared to controls with a preponderance of left turns after amphetamine. In the males, this was expressed as a reduction in directional preference, while in females a reversal occurred of their dominant turning direction from right (controls) to left. We also observed a reduction in dopamine turnover rates in the left corpora striata of stressed offspring of both sexes. Again, in the females, this change was particularly marked and resulted in a reversal towards the right hemisphere. The findings from this study are consistent with the possibility that the alterations in cerebral asymmetries induced by prenatal stress may underly the decrease in the ability of the offspring to cope with anxiety provoking situations.

Prenatal stress   Cerebral lateralization   Tail posture   Turning behavior   Dopamine turnover
Neurochemical asymmetry   Corpus striatum

IT has been shown that stress during pregnancy induces alterations in early motor development of the offspring (4,17) and increases emotionality at adulthood (3, 14, 15, 43). Maternal stress has also been found to interfere with sexual behavior in the male and reproductive function in the female offspring (25, 26, 44, 45). These changes were associated with the appearance of the characteristic peak level of testosterone in the male fetuses of stressed dams (46,47) one day earlier than in controls. Prenatal testosterone has also been implicated in the development of lateralized functions of the cerebral hemispheres (19–21, 35).

Lateralization of spatial processes is increased by daily handling of neonatal male rats (10,40), but the effect in females is less clear (6, 12, 41). Such handled animals are also less emotional at adulthood (9,30). In contrast to neonatal handling, maternal stress, randomly applied throughout pregnancy, reduces the ability of the offspring to cope with stressful situations (14,15) as indicated by the appropriate behavioral measures (18). One may therefore predict that this type of prenatal stress would induce alterations in the development of lateralization for spatial functions, but in the opposite direction to that seen after a neonatal handling. This may result in either a reduction in side-preference

or a switch to lateralization in favor of the opposite side. In order to substantiate this suggestion, we investigated the development of lateralization in prenatally stressed offspring for asymmetry of tail posture during the neonatal period. At adulthood, we measured left-right choices in an open-field and amphetamine-induced turning. Since tail posture (36) and amphetamine-induced rotations have been shown in some studies to correlate with dopaminergic activity of the nigrostriatal system (22,36), we also measured the rate of dopamine turnover in the left and right corpora striata.

METHOD

Animals

Female virgin albino rats (Sabra strain) were kept four to a cage on a 12-hour light/dark cycle. Two to four females were left overnight with 1–3 male rats. Vaginal smears were taken the following morning. The day that spermatozoa were found in the smear was designated day 1 of pregnancy. Food and water were provided ad lib.

Maternal Treatment

On day 1 of pregnancy, females were housed singly and

randomly assigned to control (C) or stress (E) groups. Rats in the E group were kept in a stress chamber as described previously (17). The room in which the stress chamber was situated had a similar ambient temperature and light/dark cycle to that of the animal house in which the control animals were left undisturbed except for routine cage cleaning. The stress chamber was open to the room at all times except during stress sessions. In addition, the stress chamber was continuously aerated throughout the stress periods.

Stress Treatment

The stress stimulus employed consisted of flashing lights and sound from a bell, as previously described (17). The flashing lights were regular 75-W incandescent bulbs (with plastic covers) giving a light intensity of 20 foot-candles when measured inside the rat cage. The noise source was an electric bell, which gave a sound volume of 90–95 dB SPL at its peak frequency between 5000 and 25000 cps. The rat cages were arranged so as to insure a similar distribution of light and sound to all animals. The bell and lights were controlled electronically to deliver intermittent noise bursts and light flashes (at a rate of 2/sec) for alternating 5-min periods. Each stress session lasted for 4 hours and was delivered between 0800 and 1500 hr on three randomly distributed days of each week of pregnancy.

Litters

Thirty-one stressed and 31 control litters were bred in our laboratory. Within 24 hr after birth (day 1 of age), litters were culled to 8 pups with equal numbers of males and females, as far as possible. Offspring were weighed on day 1 and at 4 months of age.

Measurements on individual offspring within a given litter may be correlated (1). Hence, neonatal data were tested for the presence of litter effects. Since we found that these effects were indeed significant for birth weights and tail posture ($p<0.001$), the neonatal data were analyzed using litter means as the unit of analysis. In order to prevent litter effects from biasing the outcome of observations on adult offspring, only 1 male and 1 female from each litter were used in these experiments.

Behavioral Observations

Neonatal tail posture. Methods described by Ross *et al.* (38) and Denenberg *et al.* (11) were used. On days 1, 2 and 3, the mother was removed from the litter and pups were individually placed on a wooden surface, facing away from the experimenter. Upon release, the pup was observed for 5 sec at the end of which it was recorded whether the tail positioned leftward, rightward or in line with the spinal axis. After testing, pups were sexed, so that expected male-female differences in tail posture (11,38) would not influence the observation.

Scoring. When the majority of pups in a litter showed a leftward bias on a given day the litter was scored as "left" and "vice versa." When there was an equal number of left and right-biased pups, it was recorded as neutral.

Initial turn in open-field. At 10–12 weeks of age, 30 male and female offspring from each group were tested in a 1 m × 1 m × 40 cm high black open-field. Animals were confined for 15 sec in one corner by an L-shaped barrier as described by Sherman *et al.* (40). The initial choice after the barrier was lifted (along the left wall, right wall, or into the diagonal

square) was recorded. Testing took place during the dark period of the 24-hr cycle under red light. In order to account for possible unequal light distribution, the barrier was rotated over the 4 corners so that equal numbers of C, E, male and female animals started from each corner. Cages were coded to insure blind testing. The proportion of rats turning left was computed.

Amphetamine-induced rotation. At 4 months of age, amphetamine-induced rotational behavior was recorded in 14 to 16 male and female offspring of each group according to the method described by Robinson *et al.* (34). Becker *et al.* (5) have shown that for females, the strength of rotation varies during the estrous cycle. Therefore, prior to testing, the stage of the estrous cycle was determined by vaginal smears and only females in estrus were used. In order to control for the handling involved in this examination, males were also handled daily for the time taken to perform the vaginal smears.

The apparatus used for assessing rotational behavior was a transparent spherical bowl, with a diameter of 30 cm, located in a testing cubicle with black walls. The bowl was divided into quadrants by lines on the outside and was cleaned between observations. Each rat was acclimatized to the bowl for 10 min, prior to IP injection of dl-amphetamine.

In order to achieve similar brain levels of amphetamine in males and females, relative doses were extrapolated from the data of Becker *et al.* (5), who measured d-amphetamine levels in the brains of male and female rats after the injection of a series of different doses. Our preliminary observations indicated that 9.6 mg/kg for males and 6.8 mg/kg for females of dl-amphetamine [the equivalents of about 3.4 and 2.4 mg/kg, respectively, of d-amphetamine (2)] induced maximal net rotation (i.e., the number of left minus right turns) with minimal variability within 30 min after injection. This observation agrees with Jerussi and Glick's (26) findings in females that 1.25 to 2.5 mg/kg of d-amphetamine induced maximal rotation within 25–45 min after injection. Observations started immediately after injection. A record was made of every $1/4$ turn made to the left or right. From these data, we calculated for each rat the number of 1) total $1/4$ turns ($1/4$ turns to the left and right summed), 2) left rotations (full left turns), 3) right rotations (full right turns) and 4) index of symmetry, as a measure of the direction of turning behavior, according to the formula: $(R - L)/(0.5(R + L))$ (39).

Measurement of Dopamine Turnover Rates in the Corpus Striatum

Two weeks after amphetamine-induced rotation was performed, 8 C and 8 E male and female offspring were removed from their home cages and immediately decapitated in a separate room.

Their brains were partially frozen and the left and right corpora striata were punched (33) (1.5 mm diameter) from the slice between 8030 and 10300 which was made in a brain block according to the atlas of König and Klippel (28). Samples were sonicated for 3 sec at 230 W in 100 l perchloric acid 0.1 M, containing $4·10^{-3}$ M sodium bisulfite, and stored at $-70°C$ until assay a few days later. Dopamine (DA) and dihydroxyphenylacetic acid (DOPAC) were measured by high performance liquid chromatography (HPLC) with electrochemical detection. The mobile phase (30) consisted of citrate buffer pH 4.25 containing 8% methanol and 10 mg/ml of the sodium salt of 1-octanesulfonic acid (Eastman Kodak). Epinine (Sigma) was used as the internal standard. Recovery

TABLE 1
NEONATAL TAIL POSITION % LITTERS WITH LEFT OR RIGHT PREFERENCE

		Males			Females	
	N[a]	Left	Right	N[a]	Left	Right
Day 1						
control	20	60	40	28 cont	71	29
exp.*	25	20	80	26 exp	58	42
Day 2						
control	25	56	44	25 cont	72	28
exp.†	27	15	85	26 exp*	31	69
Day 3						
control	27	78	22	28 cont	68	32
exp.†	27	26	74	24 exp*	33	67

*Different from controls, $p<0.05$.
†Different from controls, $p<0.01$.
Different from preference for opposite side in same treatment group, $p<0.05$.
Different from preference for opposite side in same treatment group, $p<0.01$.
[a]Number of litters which showed left or right directionality.

rates were between 80 and 100%. Before assay, the homogenates were centrifuged for 2–3 min at 12000×g and the supernatants injected for HPLC. Proteins were measured according to Lowry et al. (31). Dopamine turnover was assessed by DOPAC/DA ratios.

Statistical Analyses

Body weights, amphetamine-induced rotation and DA, DOPAC data were analyzed by two-way analyses of variance (ANOVA) for split-plot designs (groups × sex, with sex as the correlated factor, since the males and females used included littermates). Individual comparisons were made by a priori contrasts. Left-right differences within treatment groups were tested for significance by paired t-tests. Bartlett-Box F-tests were performed to test for homogeneity of variances (48).

Pearson's mean square contingency coefficient (7) was used to assess male-female littermate correlations on open-field data.

Neonatal tail posture and open-field data were initially analyzed by overall chi-square tests for all 4 groups (C and E male and female offspring). When these were significant, individual chi-square tests were performed between the groups and within the groups for left-right preferences (41).

RESULTS

Body Weights

There were no significant differences in the weights of control and experimental pups at birth (C: 6.78±0.09, E: 6.60±0.108 males; C: 6.44±0.089, E: 6.30±0.089 females), n=31 (each group) or at adulthood (C: 428±10 g, E: 411±8 g, males; C: 252±6 g, E: 245±5 g, females). These results replicate our data from a previous study (17).

TABLE 2
INITIAL TURN IN OPEN-FIELD

		Percent of Animals	
Treatment Group	N	Left	Right
Control males	27	48	52
Exp. males	29	43	57
Control females	28	21	79*
Exp. females	27	67	33

*Significantly different from left of same group $p<0.05$.
Experimental females show significant difference in proportion of left or right turns from controls $p<0.001$.

Neonatal Tail Posture (Table 1)

Similar results were obtained when litters showing no bias ("neutral") were excluded from the analysis. Hence, only the latter data are presented in Table 1. The proportions of litters of each sex and group showing left, right or no bias, differed on each day [day 1, $\chi^2(6)=19.1$, $p<0.005$; day 2, $\chi^2(6)=21.7, p<0.05$; day 3, $\chi^2(6)=24.3, p<0.001$]. About 15% of the pups in each group showed no side preference on any of the first 3 days of life. Overall, there were no significant differences between the proportions of litters showing no bias. However, in order to compare our control animals with the literature, the degree of neutral tail position in male and female pups was also analyzed separately for the control groups. Thus we observed more male than female pups displaying neutral tail posture on day 1, $\chi^2(1)=4.52$, $p<0.05$, which is consistent with observations by others (11).

As can be seen, tail position also differed significantly between the 4 groups on each day after the neutral litters were eliminated from the analysis [day 1, $\chi^2(3)=14.5$, $p<0.005$; day 2, $\chi^2(3)=19.2$, $p<0.001$; day 3, $\chi^2(3)=20.9$, $p<0.001$].

Furthermore, both male and female E pups placed their tails in directions opposite (right) to that in the C groups (left). These differences were significant for the males on each day and for the females on days 2 and 3. C females and E males had significant biases on each day, whereas preferences in C males and E females only occurred on days 3 and 2 respectively.

Initial Turn in Open-Field (Table 2)

Data from male and female littermates were not correlated. Analysis for all 4 groups indicated an overall difference between the groups, $\chi^2(3)=12.3, p<0.01$. Neither C nor E males showed a side preference. The C female group, on the other hand, was significantly biased towards more rightward turns, $\chi^2(1)=10.0$, $p<0.01$. In contrast, E females tended, $\chi^2(1)=3.0$, $p<0.1$, towards the left. These proportions were highly different from each other, $\chi^2(1)=12.1$, $p<0.001$.

Amphetamine-Induced Turning

We found no sex or group differences in the amounts of total ¼ turns (data not shown). There were no differences in the strength of asymmetry between the groups. However, the index of symmetry differed for stressed as compared to

TABLE 3
AMPHETAMINE-INDUCED ROTATIONS

| Treatment Group | N | No. of Full Turns ± SE | | Symmetry Index | No. of Animals Turning | |
		Left	Right		Left	Right[a]
Control males	16	14 ± 6	39 ± 13	+0.65 ± 0.29	4	11
Exp. males	16	20 ± 6	25 ± 9	+0.24 ± 0.37	5	10
Control females	14	12 ± 4	32 ± 9	+0.73 ± 0.31	3	11
Exp. females	15	30 ± 6*	21 ± 4	−0.6 ± 0.30	9	6

*Significantly greater than left turns for controls, $p < 0.02$.
Significantly different from zero, $p < 0.05$.
Significantly different from control, $p < 0.05$.
[a]No. of animals that turned preferentially to left or right (irrespective of magnitude of left-right difference. Two rats (1 control male and 1 control female) turned an equal number of times to left or right.

TABLE 4
DA AND DOPAC LEVELS IN THE LEFT AND RIGHT CORPORA STRIATA OF PRENATALLY STRESSED OFFSPRING

| Treatment Group | N | DA Concentration ng/mg Protein ± SE | | DOPAC Concentration ng/mg Protein ± SE | |
		Left	Right	Left	Right
Control males	8	56.7 ± 6.5	56.2 ± 9.6	11.1 ± 1.7	9.7 ± 1.6
Experimental males	6	37.5 ± 5.5	57.3 ± 9.0	6.0 ± 0.7*	9.4 ± 1.3
Control females	8	61.8 ± 8.8	61.6 ± 4.5	13.5 ± 0.8	10.6 ± 1.0
Experimental females	7	57.1 ± 8.7	63.8 ± 6.2	8.5 ± 1.2*	9.7 ± 0.9

*$p < 0.05$ controls of same sex.

control offspring, $F(1,27) = 5.4$, $p < 0.03$ (see Table 3). This was apparently due to an increase in left turns, $F(1,27) = 4.6$, $p < 0.04$, because the number of right turns was similar to that in controls. Inspection of the data from the individual groups reveals that the increase in the number of left turns was only significant for the females. Moreover, C males and females rotated preferably to the right ($p < 0.05$) (Table 3). The E males made an equal number of left and right turns, but E females tended to make more leftward turns. This reversal of direction was significantly different from C females ($p < 0.05$).

DA and DOPAC in the Corpus Striatum

DA and DOPAC levels are presented in Table 4. The control levels are in the range reported by others [see for example (37)]. Although both DA and DOPAC levels were lower in the left striata of E as compared to C rats of both sexes, this reduction was only significant for DOPAC values, $F(1,20) = 30.2$, $p < 0.0001$.

The reduction in DA activity in the left striata of E rats is also evident when DA turnover is expressed as the DOPAC/DA ratio (Table 5), $F(1,22) = 7.1, p < 0.02$. Individual comparisons revealed that this difference was only signifi-

cant in the female C and E striata ($p < 0.01$). In E animals the right-left difference was close to zero and different from controls, $F(1,22) = 4.1$, $p < 0.005$, whereas the ratios in the E females differed significantly from their C counterparts ($p < 0.05$).

DISCUSSION

The results from this study demonstrate that randomly applied prenatal noise and light stress induces consistent alterations in behavioral and neurochemical asymmetries in the offspring, which last into adulthood. In addition, the effect on cerebral lateralization in females was more evident than in males.

By cross-fostering stressed pups onto control mothers and vice versa, we have shown previously that the retardation in early motor development seen after this treatment was prenatally determined (16). There is ample evidence in the literature that postnatal handling influences the development of cerebral lateralization (6, 10, 21, 40). Since we did not compare asymmetries in cross-fostered offspring with those in animals reared by their own mothers, we cannot dissociate prenatal from postnatal effects on cerebral lateralization at adulthood. However, the present observa-

TABLE 5
DOPAC/DA RATIO IN CAUDATE NUCLEUS

Treatment Group	N	Left	Right	Right Minus Left
Control males	8	0.20 ± 0.03	0.18 ± 0.01	−0.022 ± 0.024
Exp. males	8	0.16 ± 0.02	0.16 ± 0.01	−0.002 ± 0.013
Control females	8	0.25 ± 0.04	0.17 ± 0.01	−0.081 ± 0.043
Exp. females	8	0.15 ± 0.01†	0.15 ± 0.01	+0.006 ± 0.031*

Values are SE.
*Significantly different from value for control females, $p<0.05$.
†Significantly different from left side value for control females, $p<0.01$.

tion that maternal stress induced reversal of postural asymmetry from the first day of life (see Table 1) strongly suggests that development of cerebral lateralization can also be influenced prenatally.

In previous studies the direction of tail posture in neonates was the same as that of turning preference at adulthood (11,38). In our study, using Sabra rats, the direction of neonatal tail position in control pups (left) was the opposite of the right bias in the adults. This may be due to strain differences, which have been reported for both neonatal tail posture (11, 12, 37) and adult turning behavior (12, 23, 40, 41).

The direction of neonatal tail posture has been shown to be predictive of striatal dopamine asymmetry at adulthood, but only in animals which had a preferred tail position (36). This is also suggestive of a complex relationship between the different measures of asymmetry. However, irrespective of the initial turning preference, our observations on the prenatally stressed offspring also indicate that the neonatal-adult correspondence may be disrupted by gestational, nongenetic factors. Thus, while the prenatally stressed female offspring had a right tail bias as neonates, which corresponded to leftward turning at adulthood, the experimental male pups had not reversed their neonatal rightward bias at adulthood.

No attempt was made in this study to correlate the directions of amphetamine-induced turning to that of striatal dopamine turnover in individual rats. Correspondence between higher DA activity in the striatum contralateral to turning preference may not be as universally present (8,34) as previously thought (22, 24, 49). Therefore, we cannot be certain whether the selective increase in the number of amphetamine-induced left turns in the stressed offspring was associated with the reduction in DOPAC levels in their left striata. However, the consistency with which prenatal stress induced a behavioral shift towards the left, together with reduced DA turnover in the left striatum in the adult offspring at the group level, tempt us to suggest that these behavioral and neurochemical changes are functionally associated.

Several studies suggest that daily handling of neonatal rats, which reduces emotionality (9,30), increases spatial asymmetry in the male adults (10,40), while this effect on the females is less clear (6, 12, 41). The reduced lateralization found in prenatally stressed male offspring, which accompanied their increase in emotionality (14, 15, 18), is consistent with our expectation. The alterations in lateralization in the stressed females are harder to interpret. However, when viewed on a continuum of left to right preferences, their consistently displayed reversal of the dominant direction of rotational behavior may be an expression of a greater effect of the gestational treatment, resulting not only in a reduction of asymmetry as in the males, but also in a switch towards dominance of the opposite side. Studies on changes in lateral preferences as a result of birth stress in human adults are consistent with this interpretation. Thus, a reduction in right-side preferences, rather than outspoken left-sidedness, was associated with birth stress (8).

Testosterone has been implicated as a possible mediator both in the sequelae of prenatal stress (46,47), and in the development of cerebral lateralization (19,21). Direct testosterone injection to pregnant female rats caused a reversal of the direction of tail posture in female pups, but not in males (35). Therefore, it is possible that the development of cerebral lateralization in the females is more strongly influenced by uteral testosterone. This is in agreement with the interpretation offered above, that hemispheric asymmetry in the female offspring was more affected by prenatal stress than in the males.

To the best of our knowledge, this study is the first demonstration of alterations in hemispheric asymmetries after prenatal environmental stress. The functional significance of these alterations is not yet clear. However, in view of the possible role played by altered hemispheric specialization in abnormal emotional states (13), we suggest that the changes in cerebral lateralization after prenatal stress may play a role in the increased emotionality and level of anxiety which we have reported previously (14, 15, 18).

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