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Motor Lateralization, Behavioral Despair and Dopaminergic Brain Asymmetry After Prenatal Stress

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ALONSO, S. J., E. NAVARRO, C. SANTANA AND M. RODRIGUEZ. *Motor lateralization, behavioral despair and dopaminergic brain asymmetry after prenatal stress.* PHARMACOL BIOCHEM BEHAV **58**(2) 443–448, 1997.—This paper presents data suggesting a relationship between rat behavioral despair in the Porsolt test and motor lateralization in the T-maze test. In addition, experimental evidence suggests a functional coupling among dopaminergic systems, behavioral despair and motor lateralization. In the first experiment, female, not male, rats with a high level of behavioral despair showed a low level of behavioral lateralization. The inverse relationship was found in female offspring of mothers stressed during gestation. In comparison with unstressed-mother rats, the female offspring of stressed mothers showed an increase of dopamine (DA) and a decrease of dihydroxyphenylacetic acid (DOPAC) and Homovanillic (HVA) levels and of DOPAC:DA and HVA:DA indexes in the n. accumbens of the right side of the brain. No significant differences were found in the n. accumbens of the left brain. Taken together, the present data provide evidence of a relation between behavioral despair and motor lateralization, suggesting that the biological dopaminergic inervation of n. accumbens could be the basis for this functional coupling. Because the stress of gestant mothers modified these biochemical and behavioral variables, the present study also suggests that lateralization of behavior and emotion during adulthood can be modified by prenatal variables. © 1997 Elsevier Science Inc.

Lateralization Behavior despair Stress Dopamine

THERE is some indirect evidence suggesting a biological asymmetric distribution of human emotion in the right and left brain (21,34,36). Poor right-hemisphere performance has been reported in both depressive patients (18) and normal students with a transitory depressed mood (39). This brain lateralization of emotion also has been associated with an asymmetric organization of motor behavior (36). The biological mechanisms associated with the brain asymmetry of emotion remain unknown. We reported that prenatal (2) and postnatal (31) stress modifies motor lateralization in animals. There is no direct procedure to evaluate emotions in animals. Porsolt et al. developed an animal model for human depression that has been very useful for the experimental evaluation of new antidepressant procedures (25–29). One of the aims of the present study was to evaluate in rats the possible relationship between the emotionlike phenomenon quantified by the Porsolt test and the lateralization of the motor behavior quantified by the T-maze test procedure developed in our laboratory (2,12,13,15,31). Both behavioral lateralization (2,12,13, 15) and depression (5–7,22,28,38,40,41) have been associated with dopaminergic ascending systems (17,23,24,35,40), and the asymmetric distribution in the brain of these systems could be based on the functional lateralization of both emotion and motor behavior. The other aim of the present study was to evaluate a possible relationship among dopaminergic systems, behavioral despair and motor lateralization.

MATERIALS AND METHODS

Experiments were performed on male and female Sprague–Dawley rats (Letica, Barcelona) weighing 180–250 g. Animals were housed under normal laboratory conditions of 22 ± 1°C on a standard light–dark schedule (12-h light:12-h dark; lights on: 0300–1500) and were allowed free access to the standard laboratory food and water.

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Behavioral Despair Test

Rats were forced to swim in a confined space in an immobile posture after an initially frenzied attempt to escape. On subsequent immersion, the onset of immobility was more rapid and marked. Porsolt et al. (25–29) named this phenomenon "behavioral despair" and offered it as an animal model of depression. This test has the following advantages over other animal models of depression. (a) The antidepressant procedures useful in humans (including atypical antidepressant drugs such as iprindole and mianserin, electroconvulsive shock, deprivation of rapid eye-movement sleep, etc.) delay the onset of immobility. (b) There is a significant correlation (not found in any other model) between clinical potency and potency of antidepressants in the behavioral despair test. (c) The test is widely used and much information is now available about it (10,46). Thus, in the present study, we use the "behavioral despair" test as an animal model of depression.

Rats were plunged individually into a vertical glass cylinder (height = 30 cm, diameter = 15 cm) containing 15 cm of water maintained at 23°C. After 15 min in the cylinder, the animals were removed and allowed to dry for 30 min in a heated enclosure (28°C) before being returned to their individual cages. One day later, the rats were plunged into the cylinder, and the duration of immobilization was quantified for the next 5 min (25–29).

T-Maze Side-Preference Test

The materials used for the task were placed in the center of a sound-attenuated room that was cleaned regularly to eliminate odors. The behavioral tests were done during 3–8 h of the light period at room temperature (22°C) and under red light illumination. Testing consisted of five consecutive trials, with 3 s between trials, for each task. All the rats were tested in an electrified glass T-maze. The stem was 30 cm long, each arm was 25 cm long and the walls were 8 cm high. The floor of the stem was a grid of 0.4-cm stainless steel rods, spaced 1.3 cm apart. Rats were placed in the stem of the T-maze, and a scrambled 0.4 mA current was applied to the grid with a Letica LI-100-20 shocker. The shock was terminated when a rat entered either the left or right arm of the T-maze; the rat was then removed from the arm and placed in the stem. Because lateralization increases during the first few days of the test (12,13,31), the T-maze test was repeated over 8 consecutive days (5 trials/day). Because the internal consistency of the test is low during the first few days, only the data recorded after the 4th day of testing were used. Absolute laterality (AL) is defined as the preference for either the right or left side. It is an indicator of the degree of asymmetric behavioral choices. Following previous studies (2,31), AL was computed from the side choices in the trials performed between days 5 and 8 (from the 4th day, the side choice remains stable) (2). AL was calculated as the absolute value of (right side − left side) divided by (right side + left side) and multiplied by 100.

Stress Procedure

Young female rats (150–200 g body weight before gestation) were crossbred (two males and one female per cage) with young male rats (250–300 g) until sperm was found in the vagina (day 0). Only females that copulated during the first 4 days were included in the study. Between days 15 and 21 of gestation, females rats were exposed to daily sessions of suspension stress. The stress procedure was similar to that previously reported (2,4,5). Pregnant rats (stress group) were suspended by the thorax with a tight belt so that they remained suspended with their hindlegs 100 mm over a table surface. Animals in the suspension stress control group remained with their food cups and water bottles removed from the cages for the same period of time the stress group was denied access to food and water. The stress duration in this procedure was 3 h/day. On day 21 after birth, prenatally stressed and nonstressed offspring were weaned, segregated by sex and housed 4 per cage. Starting at 90 days of age, rats were examined for behavioral lateralization or behavioral despair. To avoid litter effects on the results, each selection in the different experiments contained at least 7 different mothers.

Preparation of Tissue

Rats were decapitated (at 4–6 h into the light period), and the brains were quickly removed and dissected on ice. The regional dissection of the nucleus accumbens was carried out according to Gonzalez et al. (20). Brain pieces were weighed in conical 1.5-ml test tubes, and 300 μl of 0.1 M perchloric acid containing 4×10^{-5} M sodium metabisulphite were pipetted into the tubes. The mixture was sonicated at 100 W for about 12 s while on ice, and the homogenate was centrifuged for 15 min at 15,000 × *g*. The supernatant was used to quantify monoamines, and the pellet was used to determine total proteins. The protein in each sample pellet was determined according to the method of Bradford (11).

Biochemical Analysis

Dopamine (DA), dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were measured by liquid chromatography with electrochemical detection using a procedure developed in our laboratory (1,20). An aliquot of the supernatant was injected into a chromatographic column (300- × 3.9-mm stainless steel column packed with μBondapack c18, 10 μm particle size; Waters Associates, Milford, MA). The mobile phase consisted of 0.07 M NaH_2 PO_4H_2O, 0.1 mM EDTA-methanol (92:8 v/v) containing heptyl sulphate 1.7×10^{-3} M. The final solution (acetic acid was added until the pH of mobile phase was 3.1) was filtered (0.45-μm Millipore filter) before use. Standard solutions of DA, DOPAC and HVA (Sigma, St. Louis, MO) were dissolved in 0.1 M perchloric acid containing 4×10^{-5} M sodium metabisulphite and kept as stock solutions at −20°C. Quantification was based on standard curves of peak height. All separations were performed isocratically at a flow rate of 1.0 ml/min at room temperature.

Statistics

The statistical analyses were performed with the Complete Statistical System (StatSoft) with a two-way analysis of variance (ANOVA) followed by a Scheffé post hoc test (experiments 1 and 3) or a *t*-test (experiment 2). The value of $p \leq 0.05$ was considered to be significant.

EXPERIMENTAL PROCEDURE

Experiment 1: Relationship Between Behavioral Despair and Behavioral Lateralization in Male and Female Rats

The behavioral lateralization of rats showing high or low behavioral despair was studied in 19 male and 26 female adult rats (90–110 days old). The behavioral lateralization was quantified in the T-maze test over 8 successive days. Twelve days after the end of this initial study, the behavioral despair was quantified with the Porsolt test. Both male and female

rats were divided into two equal groups: the high-immobility group (animals that remained more seconds without movements) and the low-immobility group (animals that showed persistent escape behavior during the test).

Experiment 2: Behavioral Despair and Behavioral Lateralization in the Female Offspring of Rats Stressed During Pregnancy

Previously, we reported (2,4) that stress of pregnant rats induces masculinization in female offspring. In the present experiment, the relationship between behavioral despair and behavioral lateralization was studied in 15 female rats whose mothers were stressed during pregnancy and in 14 female rats whose mothers were not stressed. Approximately 90–100 days after birth, the behavioral lateralization of all rats was quantified in the T-maze test over 8 successive days. Twelve days after the end of this initial study, the behavioral despair of all rats was evaluated with the Porsolt test.

Experiment 3: Dopaminergic Neurotransmission in the Nucleus Accumbens, Behavioral Despair and Behavioral Lateralization in the Female Offspring of Rats Stressed During Pregnancy

We studied the DA, DOPAC and HVA levels in the n. accumbens of 15 rats whose mothers were stressed during gestation and 14 rats whose mothers were not stressed. Because we did not find a relationship between laterality and behavioral despair in male rats in experiment 1, we used only female rats in experimetn 3. All animals were killed 105–110 days after birth. The simultaneous measurement of a metabolite and its neurotransmitter precursor has been used as a turnover index (23). In the present study, the DOPAC:DA and HVA:DA ratios were computed as an index of DA turnover.

RESULTS

Experiment 1: Relationship Between Behavioral Despair and Behavioral Lateralization in Male and Female Rats

Figure 1 shows the degree of immobility in the Porsolt test and the behavioral lateralization in the T-maze test of animals included in the low- and high-immobility groups. Significant differences were found in the Porsolt test for both sex [ANOVA, $F(1, 42) = 40.94$, $p < 0.0001$] and degree of immobility [ANOVA, $F(1, 42) = 57.98$, $p < 0.0001$]. In both female (Scheffé test, $p < 0.0001$) and male (Scheffé test, $p < 0.0001$) rats, the high-immobility group in the Porsolt test showed a higher degree of immobility than did the low-immobility group. Sexual differences were found in the T-maze test [ANOVA, $F(1, 42) = 17.97$, $p < 0.0001$], with the sex × degree of immobility interaction showing significance [ANOVA, $F(1, 42) = 4.14$, $p < 0.05$]. The high-immobility female rats showed a low level of behavioral lateralization in the T-maze test (Scheffé test, $p < 0.05$).

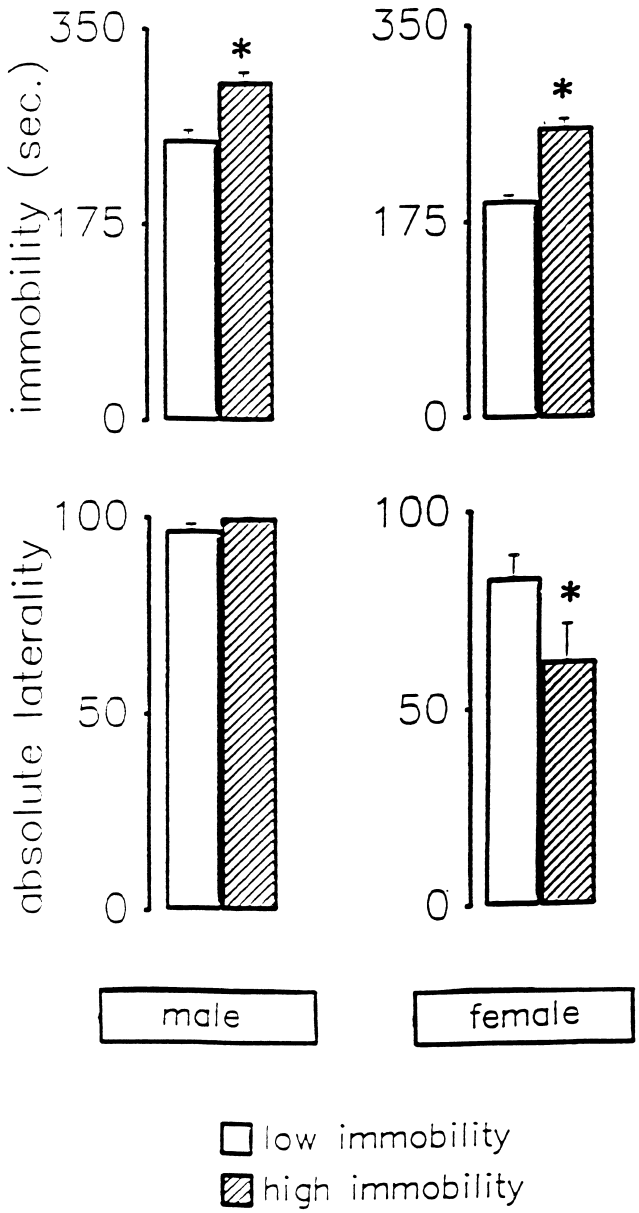

FIG. 1. Behavioral despair and behavioral lateralization in male and female rats with low and high levels of despair. Values are means ± SEM of seconds of immobility in the Porsolt test (left side) or absolute lateralization in the T-maze test (right side). $p < 0.05$ vs. low-immobility group.

Experiment 2: Behavioral Despair and Behavioral Lateralization in the Female Offspring of Rats Stressed During Pregnancy

Figure 2 shows the degree of immobility and the behavioral lateralization of female rats whose mothers were stressed or sham-stressed during gestation. The prenatal stressed group showed a level of immobility [$t(10) = -2.35$, $p < 0.05$, control vs. stress group) and AL [$t(10) = -2.64$, $p < 0.02$, control vs. stress group) that was higher than that showed by the prenatal sham-stressed group. Thus, prenatally stressed females showed a behavior similar to that found in experiment 1 for males and opposite to that found for females.

Experiment 3: Dopaminergic Neurotransmission in the Nucleus Accumbens, Behavioral Despair and Behavioral Lateralization in the Female Offspring of Rats Stressed During Pregnancy

Figure 3 shows the DA, DOPAC and HVA levels and the DOPAC:DA and HVA:DA indexes in the right and left n. ac-

cumbens of female offspring of control and stressed mothers. The DA level was lower in the right accumbens of the stress group [ANOVA for control × stress, $F(1, 18) = 4.91$, $p < 0.05$; ANOVA for right × left side, $F(1, 18) = 5.15$, $p < 0.05$; Scheffé test, $p < 0.05$ for control vs. stress group in the right brain site]. The DOPAC level was lower in the right accumbens of stress group [ANOVA for control × stress, $F(1, 18) = 7.32$, $p < 0.01$; ANOVA for right × left side, $F(1, 18) = 13.01$, $p < 0.002$; Scheff test, $p < 0.002$ for control vs. stress group in the right brain site]. Similar results were found for the HVA level [ANOVA for control × stress, $F(1, 18) = 5.43$, $p < 0.05$; ANOVA for right × left side, $F(1, 18) = 0.12$, $p < 0.05$; Scheffé test, $p < 0.05$ for control vs. stress group in the right brain site]. The DOPAC:DA index was lower in the right accumbens of the stress group [ANOVA for control × stress, $F(1, 18) = 6.13$, $p < 0.05$; ANOVA for right × left side, $F(1, 18) = 6.25$, $p < 0.05$; Scheff test, $p < 0.05$ for control vs. stress group in the right brain site]. The HVA:DA index also was lower in the right accumbens of the stress group [ANOVA for control × stress, $F(1, 18) = 17.02$, $p < 0.01$; ANOVA for right × left side, $F(1, 18) = 0.007$, NS; Scheffé test, $p < 0.05$ for control vs. stress group in the right brain site].

DISCUSSION

The present study shows a relationship among the mesolimbic dopaminergic system, behavioral lateralization and emotion. The functional relationship between behavioral lateralization and emotion is supported by two experimental findings: (a) the animals with a high response to stress during adulthood (group with the highest levels of immobility during the second day of the Porsolt test) were also the animals with the lower degree of behavioral lateralization in the T-maze test (Fig. 1), and (b) the offspring of mothers stressed during gestation showed an alteration of behavioral lateralization during adulthood (Fig. 2). The relationship between emotion and the mesolimbic dopaminergic system is supported by data showing different DOPAC and HVA levels and DOPAC:DA index in the n. accumbens of offspring of stressed and sham-stressed mothers (Fig. 3). The relationship between emotion and the biochemical lateralization of the dopaminergic system is supported by data showing that the biochemical difference between the offspring of stressed and sham-stressed rats during gestation was found in the right but not in the left n. accumbens (Fig. 3). Taken together, the present data suggest that emotion is the base of both biochemical and behavioral lateralization.

We reported that stress during T-maze testing modifies behavioral lateralization in rats (2,31). The previous studies and the present data suggest that in animals an emotion-like phenomenon is asymmetrically disposed in the brain and may influence the lateralization of motor behavior. This hypothesis also agrees with previously reported data for humans. The depression of mood modifies the right and the left brain activity in a different way (18,39). In addition, the right and left brain lesions have different effects on the expression of emotion or on the ability to understand the emotions of other people (21,34,36). Considering that a brain side often has an unilateral action on behavior (one side of the brain modifies the motor behavior of one side of the body), it is not surprising that the brain lateralization of the neural basis of emotion correlates with the lateralization of motor behavior.

We reported sex differences for both behavioral lateralization in the T-maze test (2) and behavioral despair in the Por-

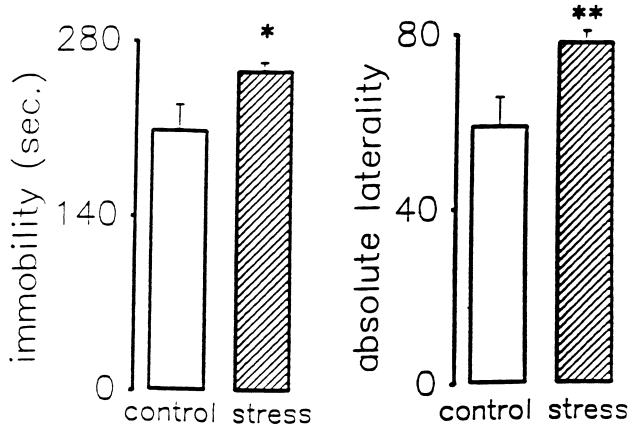

FIG. 2. Effect of stress during gestation on behavioral despair and absolute laterality of adult female offspring. Data represent means ± SEM seconds of immobility in the Porsolt test (left side) or absolute laterality in the T-maze test (right side). $p = 0.04$ vs. control group; *$p = 0.0240$ vs. control group.

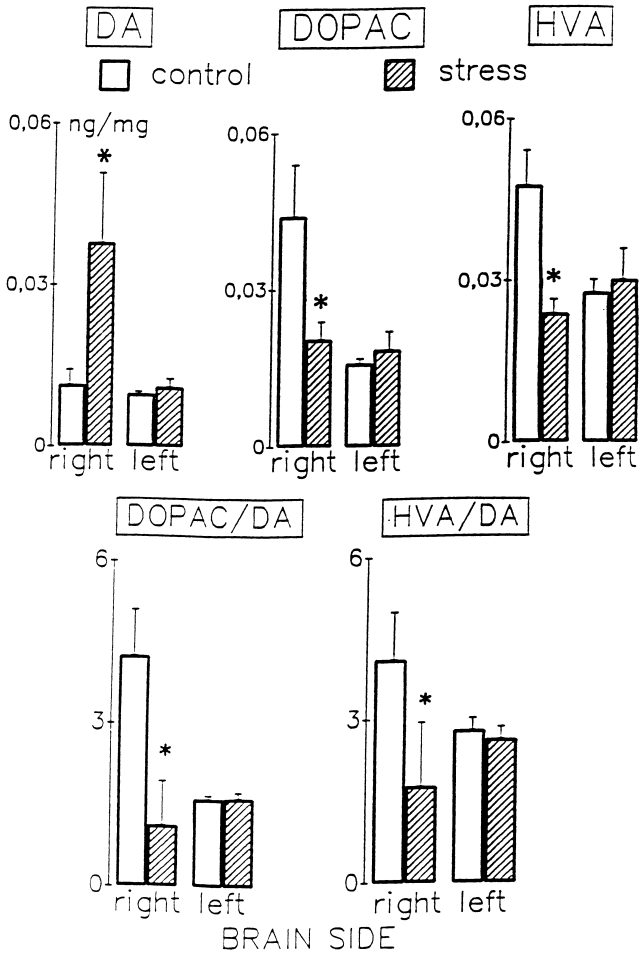

FIG. 3. Effect of stress during gestation on DA, DOPAC and HVA levels (top) and DOPAC:DA and HVA:DA indexes (bottom) in the n. accumbens of the right and left sides of the brain in adult offspring. Data represent means ± SEM. $p < 0.05$ vs. control group.

solt test (3) in adult rats. Because sex differences for behavioral motor asymmetry are present in rats during neonatal life, we proposed that behavioral lateralization in animals is conditioned by prenatal factors (31). The present data support this hypothesis. The stress of mothers during gestation alters behavioral laterality of the adult offspring (Fig. 2). In addition, experiment 1 showed a sex-related relationship between behavioral lateralization and emotion. This relationship was found for female but not for male rats (Fig. 1). In addition, this inverse relationship between behavioral lateralization and behavioral despair changes after prenatal stress of females.

Many data have been adduced in favor of the hypothesis that human depression is related to an alteration of monoaminergic systems and particularly of dopaminergic neurons (38). Clinical (22,38,40,41) and experimental (6,7,28) data in animals strongly suggest that brain dopaminergic neurotransmission is decreased during depression. The brain location of dopaminergic alteration in depressive patients remain unknown. However, studies in animals suggest that the dopaminergic system alteration takes place in the DA innervation of n. accumbens by the mesolimbic system (17,23,24,35,40). Figure 3 shows that prenatal stress, the procedure that increased behavioral despair in the offspring (Fig. 2), decreases the metabolization of dopamine in the n. accumbens of the right brain side. Because behavioral lateralization in the T-maze test also is related to the brain asymmetry of dopaminergic ascending systems (12,13,15), the specific action of prenatal stress on the n. accumbens of the right brain side could be based on the alteration induced by maternal stress on both the lateralization of behavior and behavioral despair.

The biological basis for the action of prenatal stress on the behavior of the offspring remains unknown. The gonadal steroids released by the gestant mother during stress exposure (42–44) could be the cause of persistent morphological and biochemical modifications of different brain nuclei (14,32,45), thereby inducing the behavioral disruptions observed in the offspring. However, unlike humans, rats do not release significant amounts of sex steroids from the maternal adrenal gland in response to stress (16). We previously reported evidence that catecholamine in addition to their role as neurotransmitters during adulthood have an important neurotrophic action during early development (8,19,33,37). Because the paradigm used in the present study results in dramatic changes of monoamines, the behavioral disruption found in the offspring may be directly induced by the action of catecholamine released from the maternal adrenal gland in response to stress on the fetal brain. Because monoamines modulate steroid action on brain development (9,30), gonadal steroids also could be involved.

In summary, the present data show that maternal stress during gestation induces an asymmetric modification of DA neurotransmission in the n. accumbens. This persistent action is the basis of the alteration found in the adult offspring for motor lateralization and behavioral despair.

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