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Differential Effects of Prenatal Stress in Two Inbred Strains of Rats

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STÖHR, T., D. SCHULTE WERMELING, T. SZURAN, V. PLISKA, A. DOMENEY, H. WELZL, I. WEINER AND J. FELDON. *Differential effects of prenatal stress in two inbred strains of rats.* PHARMACOL BIOCHEM BEHAV **59**(4) 799–805, 1998.—The long-term effects of prenatal stress (three times daily restraint stress during the last week of gestation) on the behavioral response to stress, as assessed by novelty-induced locomotion, performance in the forced swim test, and the acquisition of a two-way active avoidance, were investigated in two inbred strains of rats, Fischer 344 (F344/NHsd/Zur) and Lewis (LEW/SsNHsd/Zur). Additional measures included birth weights, pain threshold on the hot plate, and basal and stress-induced corticosterone secretion. In all of the behavioral paradigms strain differences were found: LEW rats showed poorer acquisition of avoidance conditioning, displayed higher levels of activity on the open plate, less immobility time in the forced swim test, and lower pain thresholds in the hot-plate test compared with F344 rats. LEW rats had higher birth weights after prenatal stress, whereas F344 rats were lighter. Following prenatal stress the pattern of behavioral effects obtained in LEW rats in stress-related tests could be interpreted as improved coping abilities with stress, i.e., improved acquisition of active avoidance, less immobility in the forced swim test, and reduced novelty-induced locomotion. Prenatal stress was much less effective in inducing long-term behavioral changes in F344 rats, yielding only one effect, namely, enhanced novelty-induced locomotion in female F344 rats. Pain thresholds were increased as a consequence of prenatal stress, irrespective of strain and gender. Basal and stress-induced corticosterone release differed in the two strains, with LEW rats showing less stress-induced corticosterone release. Prenatal stress did not, however, affect basal or stress-induced corticosterone release. The results suggest that prenatal stress exerts long-term effects on behavior, which depend on the genetic background.

Prenatal stress HPA system Fischer rat Lewis rat Gender differences Genetic differences

THE relative contribution of environmental and genetic factors to normal and pathologic patterns of behavior has been a subject of much research and discussion. Nowadays the importance of both factors is widely acknowledged in both humans and experimental animals. Comparisons of different strains of rats and mice have yielded important information about genetically determined behavioral differences, as well as about the contribution of particular genes or alleles to psychiatric disorders (7–9,17). Likewise, the influence of environmental conditions such as housing and stress on behavioral and cognitive processes and performance in animal models of psychiatric disorders has been widely investigated (2,6,37). Few studies, however, have examined the interaction between genetic and environmental factors. De Fries (10) and Joffe (21) measured locomotor activity in the open-field test in prenatally stressed mice and rats from different strains, respectively. These authors found that animals from the strain that normally exhibits low levels of activity in the open field (C57BL/Crgl mice and Maudsley reactive rats) showed an increase in activity as a consequence of prenatal stress. In con-

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trast, animals from the strain normally exhibiting high open-field activity (BALB/cCrgl mice and Maudsley nonreactive rats) had reduced levels of activity.

The Fischer 344 (F344) and Lewis (LEW) rat strains have been a focus of extensive research due to the marked differences in their hypothalamo–pituitary–adrenal (HPA) axis activity. LEW rats, which are particularly susceptible to inflammatory diseases (35), appear to be deficient in their ability to respond to a variety of stressful stimuli. Further, stress-induced activation of the HPA axis in LEW rats, including the synthesis and secretion of hypothalamic corticotropin-releasing factor (CRH) and plasma corticotropin (ACTH) and corticosterone (CORT), appears to be inadequate compared with other strains (5,13,31,34–36). Conversely, F344 rats, which are relatively resistant to inflammatory diseases, exhibit potentiated CRH, ACTH, and CORT release in response to a variety of stressful stimuli such as open-field exposure, swim stress, restraint, or noise. These differences have been attributed to a deficit in CRH biosynthesis in the LEW compared with the F344 strain (34). In addition, plasma CORT concentrations have been reported to be lower in LEW than in F344 rats at several time points during the circadian cycle [(13,28,32), but see (5)].

Prenatal stress has been shown to exert long-term effects on the behavioral response of animals to stressors as well as on the sensitivity of the HPA system. It has also been reported to increase behavioral suppression by aversive stimuli, increase anxiety in the elevated plus-maze test, and increase immobility in the forced-swim test. These responses have been associated with alterations at the level of the HPA axis, including, for example, impaired negative feedback inhibition of the HPA axis, which results in prolonged secretion of stress hormones such as CRH and CORT [see (40) for review].

We therefore tested whether prenatal stress might differentially affect the hormonal and behavioral response to stress of F344 and LEW rats. In light of previous results (10,21,23) it was of particular interest to see if prenatal stress would abolish or attenuate strain differences in response to stressors. To this end, we examined the performance of prenatally stressed and control male and female F344 and LEW rats in several tests involving stress coping which have been shown to be modulated by alterations of the HPA system: Porsolt's forced swimming test (11,26), two-way active avoidance (14), pain threshold on a hot plate, and locomotor activity following exposure to a novel environment (24,27,30,38).

Because the HPA system might play a critical role in mediating the effects of prenatal stress (3,19,41) we measured basal serum CORT concentrations as well as CORT secretion following stress.

METHOD

Animals and Stress Procedure

The subjects were the offsprings of 14 female F344/NHsd/Zur and 11 female LEW/SsNHsd/Zur rats born during a 3-week period at our institute. Animals were housed in Macrolon cages (type IV) in groups of four under standard temperature (21 ± 1°C) and humidity (55 ± 5%) conditions and a reversed light–dark cycle (lights on 1900–0700 h). Animals received food (Nafag, 890, Nafag Ecosan, Gossau, Switzerland) and water ad lib.

For the assessment of estrous cycle status, vaginal smears were taken daily and preestrous or estrous females were placed with a male of the same strain during the following night. Day 0 of pregnancy was determined by finding spermatozoa in the vaginal smear. On day 14 of pregnancy, pregnant females of both strains were divided into two groups. Mothers of the control group (F344 $n = 8$ and LEW $n = 5$) were left undisturbed, while mothers of the prenatal stress group (F344 $n = 6$ and LEW $n = 6$) were exposed to immobilization stress on days 14–21 of pregnancy three times daily for 30 min. Days 14–21 were selected because this period has been shown to be especially sensitive to the behavioral teratogenic effects of prenatal stress (16). To prevent habituation of animals to the daily procedure, immobilization periods were randomly shifted within certain time periods (0800–1100 h, 1100–1400 h, and 1600–1900 h). The immobilization device consisted of a transparent plastic tube (6 cm diameter) with air holes for breathing. It was closed at one end, and its length could be adjusted to accommodate the size of the animal. Within the first 12 h after birth the pups were weighed and all litters reduced to eight pups (four males and four females when possible). At day 21 all offsprings were weaned and housed four per cage. Rats were 5.5 months old at the start of the behavioral experiments.

Active Avoidance

The apparatus consisted of four identical shuttle boxes (35 × 17 × 21.5 cm, Habitest, Coulbourn Instruments, PA) housed in ventilated, sound- and light-attenuating cubicles. The box was divided into two compartments by an aluminium hurdle measuring 17 × 4 cm.

One day before the avoidance test all animals were given a 60-min habituation session in the shuttle box. On the test day each animal received 100 tone-shock trials with an intertrial interval of 50 ± 40 s. Each trial began with a 10-s tone, followed by 10-s 0.5-mA shock, the tone remaining on with the shock. If the rat crossed into the opposite compartment during the tone, it was terminated and not followed by shock (avoidance response). Crossing to the opposite compartment after the beginning of the shock terminated both the shock and the tone (escape response). If an animal failed to cross during the entire tone-shock pairing, the trial was terminated after 20 s (unfinished trial).

Open Plate

The open plate consisted of a 15-mm thick wooden rectangular plate (110 × 110 cm) painted gray, elevated by a single central support to a height of 94 cm above the floor. Rats were individually placed in the center of the open plate and allowed to explore it for 10 min. Locomotor activity (total distance moved) on the plate was recorded by a videocamera fixed on the ceiling above the plate and relayed to a monitor and a videotracking motion analysis system (Ethovision, Noldus Information Technology bv, The Netherlands).

Forced Swim Test

The apparatus consisted of four identical vertical plastic cylinders (height 44 cm, diameter 29.5 cm) containing 29 cm of water at room temperature. The testing room was dimly illuminated with red light and one 60-watt white light bulb.

Rats were brought into the testing room in their home cages and allowed to acclimatize to the environment. They were then individually lowered into the cylinder with water. After 15 min the rat was removed and wiped with absorbent paper to remove excess water before being placed in a heated enclosure (30°C) for 10 min to dry and then returned to its home cage. On the next day each rat was placed again in the cylinder for 5 min, during which swimming behavior was re-

corded via a videocamera. Behavior was assessed from the videotape recording and measured as the time the rat spent immobile during the 5-min test period.

Hot Plate

The hot plate consisted of a steel plate (Medax, Nagel GmbH, Kiel) measuring 29 × 39 cm. The plate was enclosed in a pentangular tube of clear Perspex to prevent animals from stepping off the plate during the test.

Rats were randomly assigned to two test groups for testing on 2 consecutive days. Prior to testing, animals were put into single cages and taken to the testing room. Each rat was placed on the heated plate (50°C) and the latency to paw lick (hind paw) was recorded. Rats were then immediately removed from the hot plate and returned to their home cage. If a rat failed to demonstrate the paw lick response within a 90-s period the session was terminated and a score of 90 s was recorded. All testing took place between 1200 and 1500 h.

Corticosterone Measurements

To determine plasma CORT levels, blood was sampled from the tail of slightly restrained rats. All animals were habituated to this procedure. Basal CORT was determined in blood samples taken in the evening, shortly before the lights were turned on (diurnal low level). Further samples were collected 0 and 30 min after 30 min of immobilization stress. This time course was selected because previous experiments in our laboratory showed that CORT levels returned to baseline concentrations within this time period. All blood samples were immediately cooled and stored until further processing (−20°C). Total plasma CORT levels were analyzed by radioimmunoassay (3-H Corticosterone Kit, 07-120016; ICN Biomedical Inc.).

Experimental Design

All experiments were performed on the same group of animals except for the active avoidance test for which a separate group of animals was used. The experiments were performed in the following order. The age of the animals at the time of specific tests is indicated in parentheses: group 1 ($n = 4$ per strain, gender, and prenatal stress condition): two way active avoidance (5.5 months). Group 2 ($n = 6$ per strain, gender, and prenatal stress condition): hot plate (6 months), open plate (6.5 months), forced swim test (8 months), CORT measurements (12 months).

In general, tests that were considered to be comprised of a mild stress procedure were performed first (open plate and hot plate). Those tests that were comprised of a more severe stress (forced swimming and stress-induced CORT release) were performed in the latter stages of the studies. At least 2 weeks were allowed to elapse between subsequent tests.

Statistical Analysis

The data were analyzed using an analysis of variance (ANOVA), calculated with the StatView and SuperANOVA software system (Abacus Concepts, Inc., Berkeley, CA). Post hoc tests included the Duncan multiple range and the Student's *t*-test for the comparison of independent and the paired *t*-test for the comparison of dependent samples. All post hoc tests were calculated using the SPSS for Macintosh software package. Level of significance was set at $p < 0.05$.

RESULTS

Body Weight

Litter size and the distribution of males and females did not differ as a function of strain or prenatal stress. The weights at the time of birth (based only on litters that included 8–10 pups) were analyzed by a 2 × 2 × 2 ANOVA with strain, sex, and prenatal stress as main factors. The analysis revealed significant main effects of strain, $F(1, 191) = 268.0$, $p < 0.001$, and sex, $F(1, 191) = 19.0$, $p < 0.001$, as well as a significant interaction of prenatal stress × strain, $F(1, 191) = 23.8$, $p < 0.001$. LEW rats weighed more (5.87 ± 0.05) than F344 rats (4.84 ± 0.05), and males (5.46 ± 0.07) more than females (5.16 ± 0.06). Prenatal stress, irrespective of sex, increased the weight of LEW (males: prenatal stress 6.12 ± 0.08 g, control 5.98 ± 0.11; females: prenatal stress 5.90 ± 0.09, control 5.55 ± 0.11) but decreased the weight of F344 rats (males: prenatal stress 4.76 ± 0.09 g, control 5.13 ± 0.11; females: prenatal stress 4.49 ± 0.07, control 4.89 ± 0.06).

Active Avoidance

A 2 × 2 × 2 × 10 ANOVA with main factors of strain, sex, and prenatal stress and with repeated measurements factor of 10 blocks (each block containing 10 trials) carried out on the number of avoidance responses, revealed main effects of strain, $F(1, 24) = 112.3$, $p < 0.001$, sex, $F(1, 24) = 10.7$, $p < 0.01$, and blocks, $F(9, 216) = 57.4$, $p < 0.001$, and significant interactions of strain × sex, $F(1, 24) = 26.3$, $p < 0.001$, prenatal stress × strain, $F(1, 24) = 5.0$, $p < 0.05$, and prenatal stress × strain × sex, $F(1, 24) = 5.5$, $p < 0.05$. Overall, there was a gradual acquisition of the avoidance response over time. Figure 1 presents the mean number of avoidance responses in the eight experimental groups, collapsed over the factor of blocks. As can be seen, F344 rats made more avoidance responses than LEW rats. In addition, in F344 rats, avoidance performance was not influenced by either sex or prenatal stress, whereas in LEW rats, females avoided better than males, and within females, those prenatally stressed avoided better than controls. Finally, LEW males showed almost no avoidance responses.

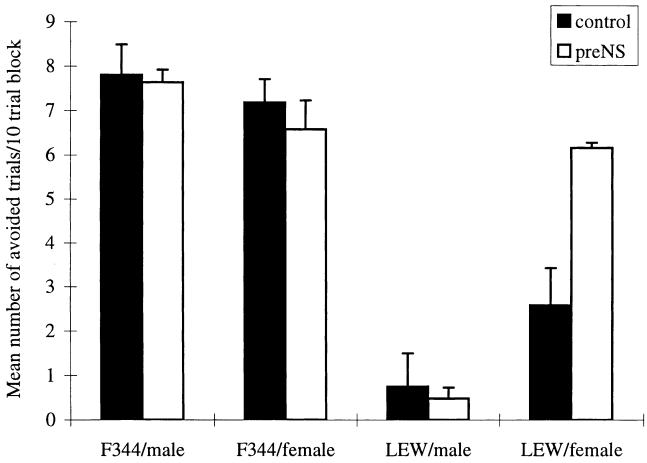

FIG. 1. Means and standard errors of number of avoidance responses collapsed over blocks of 10 trials in prenatally stressed and control, male, and female, F344 and LEW rats.

Open Plate

Locomotor activity, measured as distance travelled in cm, on the open plate was analyzed by a 2 × 2 × 2 × 5 ANOVA with main factors of strain, sex, and prenatal stress and with repeated measurements factor of five bins (each bin = 2 min). There were significant main effects of strain, $F(1, 40) = 4.5$, $p < 0.05$, sex, $F(1, 40) = 5.7$, $p < 0.05$, and bins, $F(4, 160) = 126.2$, $p < 0.001$, as well as significant interactions of strain × prenatal stress × bins, $F(4, 160) = 3.9$, $p < 0.01$, and strain × sex × prenatal stress × bins, $F(4, 160) = 3.4$, $p < 0.01$. As can be seen in Fig. 2, LEW rats displayed higher levels of activity than F344 rats, and females were more active than males. In all groups, there was a marked within-session habituation of locomotor activity. Prenatal stress reduced activity at the beginning of the test in LEW rats irrespective of sex. There was no effect of prenatal stress in F344 males, whereas in F344 females, prenatally stressed rats showed increased activity during the first 2 min of testing.

Forced Swim Test

Immobility time in the forced swim test (second day) was analyzed by a 2 × 2 × 2 ANOVA with main factors of strain, sex, and prenatal stress. This analysis revealed a significant main effect of strain, $F(1, 87) = 114.0$, $p < 0.001$, as well as an interaction of strain × prenatal stress, $F(1, 87) = 4.2$, $p < 0.05$. As can be seen in Fig. 3, F344 spent a higher proportion of time immobile than LEW, and within the LEW strain, prenatal stress reduced immobility, irrespective of sex.

Hot-Plate Test

The latency to paw lick during the hot-plate test was analyzed with a 2 × 2 × 2 ANOVA with main factors of strain, sex, and prenatal stress. The analysis revealed significant main effects of strain, $F(1, 88) = 35.0$, $p < 0.001$, and prenatal stress, $F(1, 88) = 4.4$, $p < 0.05$. As shown in Fig. 4, LEW rats had lower latencies as compared with F344 rats. In addition, prenatal stress increased latencies in all the groups.

CORT Measurements

Basal CORT values were analyzed by a 2 × 2 × 2 ANOVA with main factors of strain, sex, and prenatal stress.

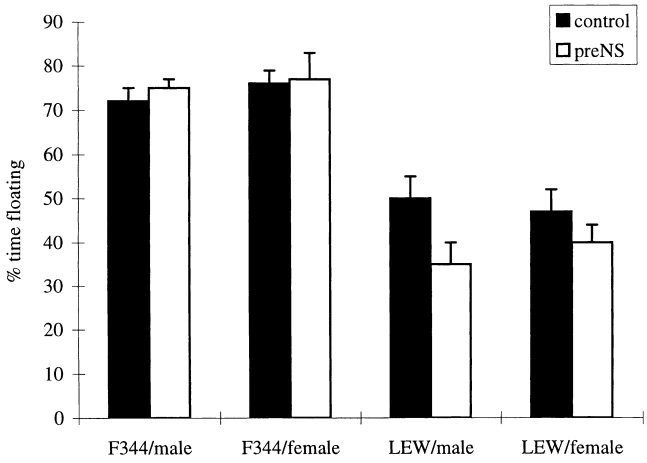

FIG. 3. Means and standard errors of the percentage of immobility time in the forced swim test in prenatally stressed and control, male, and female, F344 and LEW rats.

The analysis revealed a main effect of sex, $F(1, 40) = 30.7$, $p < 0.0001$, as well as an interaction of strain × sex, $F(1, 40) = 4.7$, $p < 0.05$. As can be seen in Fig. 5A, females had higher basal CORT concentrations than males, and these sex differences were more pronounced in LEW than in F344 rats. Prenatal stress did not affect baseline concentrations of CORT.

The percentage change from baseline levels of stress-induced CORT secretion 0 and 30 min following termination of immobilization stress was analyzed by a 2 × 2 × 2 × 2 ANOVA with main factors of strain, sex, and prenatal stress and a repeated measurements factor of time (0 and 30 min after stress). The analysis yielded a significant effect of sex, $F(1, 40) = 4.8$, $p < 0.05$, and significant strain × time, $F(1, 40) = 18.3$, $p < 0.0001$, and sex × time, $F(1, 40) = 7.6$, $p < 0.01$, interactions. The relative increase of CORT values following stress was higher in males than in females. In addition, whereas in female rats, there was a tendency towards a decrease in CORT levels from 0 to 30 min poststress, in male rats CORT values

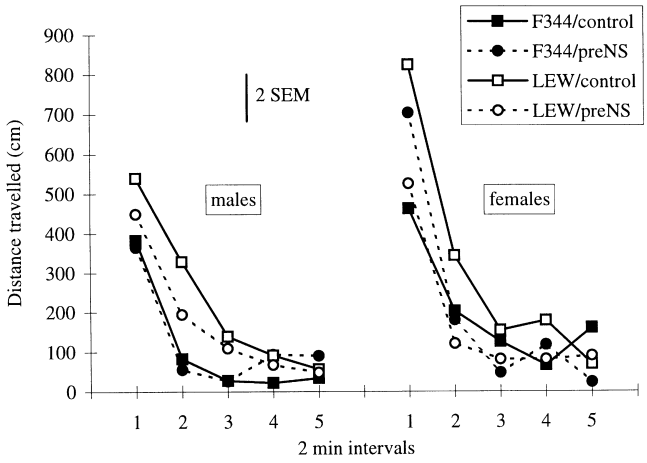

FIG. 2. Means and standard errors of distance travelled in 2-min intervals during a 10-min session in prenatally stressed and control, male, and female, F344 and LEW rats.

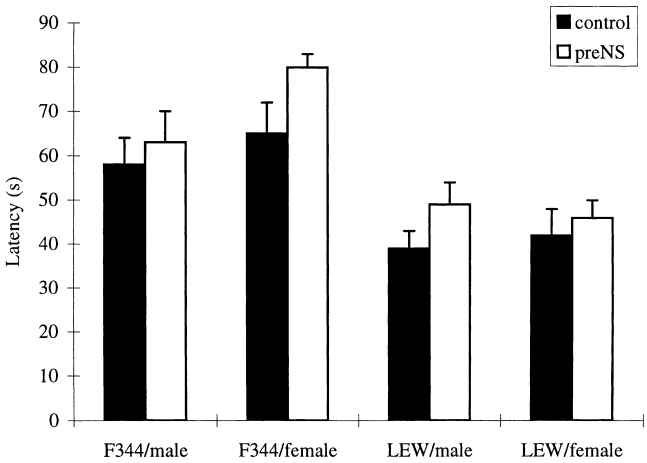

FIG. 4. Means and standard errors of the latency to paw lick in the hot plate test in prenatally stressed and control, male, and female, F344 and LEW rats.

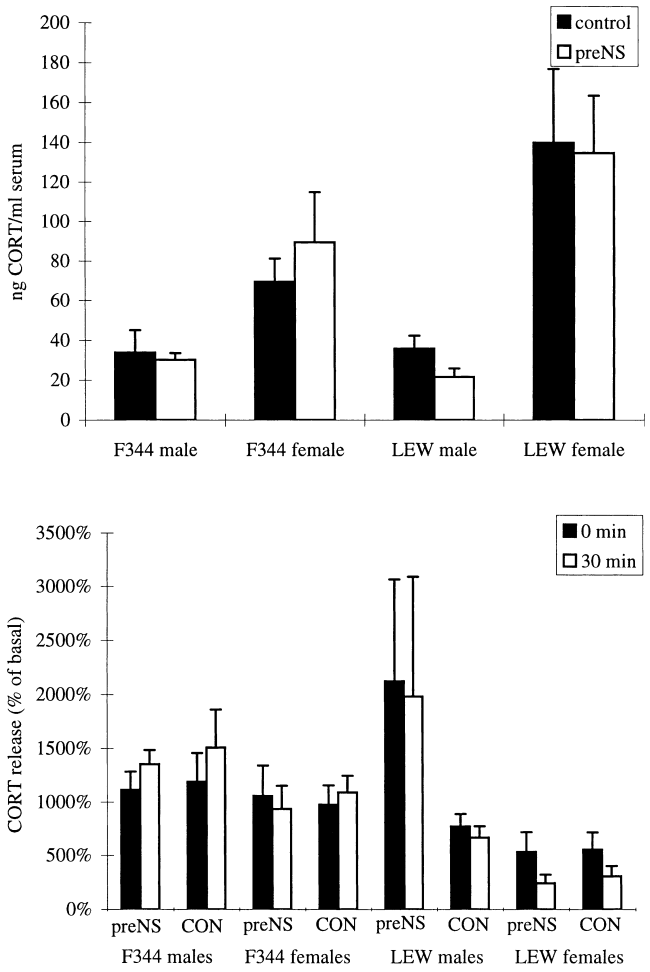

FIG. 5. Basal and stress-induced CORT levels in prenatally stressed and control, male, and female, F344 and LEW rats. A shows means and standard errors of basal serum CORT concentrations. B represents means and standard errors of the percentage increase (relative to basal levels) in serum CORT concentrations following 30 min of immobilization stress.

remained elevated during the 30 min following stress. F344 rats showed a tendency towards an increase of corticosterone levels from 0 min to 30 min poststress, whereas in LEW rats the opposite pattern was found, i.e., a reduction of CORT concentrations from 0 min to 30 min poststress (Fig. 5B).

DISCUSSION

Strain Differences

In the present study, marked differences between F344 and LEW rats were evident in all of the behavioral tests used. These findings are consistent with previous reports in which F344 rats have been compared with LEW rats. For example, it has been reported that LEW rats showed poorer acquisition of two way active avoidance (22), less immobility in the forced swim test (25), greater novelty-induced locomotion (4), and a lower pain threshold in the hot-plate test (42). This behavioral profile is consistent with the suggestion that LEW rats are deficient in coping with a variety of stressful situations (18). The finding that stress-induced CORT secretion was lower in LEW compared with F344 rats probably represents one of the most widely reported physiological differences between the two strains (5,13, 18,34,36). Further, this physiological characteristic may indeed contribute to some of the differences manifest at the behavioral level. It has been suggested that the role of corticosteroids in the processing of stressful life events represents the "consolidation of stressful events and the corresponding coping response" (29). Therefore, the impaired corticosterone secretion following stress in LEW rats might be causally related to their impaired ability to respond adequately to a stressful event. Evidence to support this suggestion can be found in the literature. Thus, the depletion of endogenous CORT by adrenalectomy is reported to impair performance in two way active avoidance (14), and adrenalectomy or the administration of glucocorticoid receptor antagonists to reduce immobility time in the forced swimming test (11,20).

The Effects of Prenatal Stress

Although a dysregulation of the HPA system has been considered to be central in the prenatal stress syndrome [(40) for review], in the present study prenatal stress had no effect on either basal or stress-induced CORT secretion. Alterations in CORT secretion have been reported to vary as a function of several factors, a combination of which may have contributed to the outcome of the results in our study. Of particular significance may be the findings of Maccari and co-workers (3,19), who report that CORT concentrations in prenatally stressed rats were elevated at 90 min but not 30 min following stress. Because CORT levels were determined at 0 and 30 min following restraint stress in the present study (i.e., at time points where CORT concentrations were still elevated compared with basal levels), there remains a possibility that a difference would be evident at a later time point, for example, 60 or 90 min following stress. Of further relevance are the findings of Takahashi and co-workers (39), who reported that prenatally stressed rats exhibit an enhanced CORT secretion during the preweaning period but not in adulthood. In our studies, blood samples were collected from 1-year-old rats, which may be another reason for our negative findings with respect to CORT secretion. That CORT secretion may be influenced by the nature of the prenatal stress has been proposed by Weinstock et al. (41). These authors suggest that random (unpredictable) prenatal stress results in increased CORT secretion, whereas regular (predictable) stress results in the opposite outcome, that is, decreased CORT secretion. It is difficult to define our stress procedure in terms of predictability/unpredictability, because it contained both aspects: a regular stress regimen was employed (restraint three times daily), but the stress events were randomly shifted within time periods of approximately 3 h.

In the hot-plate test, prenatal stress elevated response latencies in both F344 and LEW strains, which is in agreement with previous findings in Sprague–Dawley rats (24,33). In the other tests employed in this study, however, the effects of prenatal stress were evident primarily in LEW rats. Moreover, prenatal stress affected behavioral performance of LEW rats in a way that can be interpreted as improved ability to cope with stress. Thus, prenatally stressed LEW rats showed less immobility in the forced swim test and decreased levels of novelty-induced locomotion during the initial stages of exposure to the open plate. In addition, female LEW rats showed improved two-way active avoidance learning. Alonso et al. (1), using the Sprague–Dawley rat strain, also report decreased levels of ambulation following open-field exposure. In contrast to our results, however, these authors found in-

creased immobility in the forced swim test after prenatal stress in Sprague–Dawley rats. Differences in the results obtained may be related to the stress procedure employed. In the studies of Alonso et al. (1), a once-daily restraint of 3 h during the last week of gestation was used. With respect to active avoidance, Fride et al. (15) also found improved learning after prenatal stress in female Sabra rats, although in prenatally stressed male rats acquisition of avoidance was impaired. That we were unable to observe a similar impairment in this study may be due to the fact that control, male LEW rats already had very low levels of avoidance.

In contrast to LEW rats, the behavior of F344 rats was generally unaffected by prenatal stress. The only exception being that female F344 rats showed increased levels of exploration as a consequence of prenatal stress. This contrasts with the findings in LEW rats, but is in agreement with previously published results using the Wistar rat strain (12,38).

Body weight of the offsprings was also affected by prenatal stress in both strains, but in opposite directions: birth weights of LEW rats were increased, while those of F344 rats were lighter compared with respective control rats. Alterations in birth weights following prenatal stress have been frequently reported, but have been inconsistent. For example, Szuran et al. (38) reported a tendency towards increased birth weights following prenatal stress in Wistar rats, whereas several other authors found lower birth weights following prenatal stress in various outbred strains of rats [see (41) for overview]. Fride and Weinstock (16) have reported increased birth weights after predictable and decreased birth weights after unpredictable prenatal stress in Sabra rats (outbred albino strain). Thus, although prenatal stress apparently affects birth weight, the direction of the effect may vary. To the best of our knowledge, this is the first demonstration within one study that such effects are strain dependent.

The present results demonstrate that prenatal stress exerts different long-term effects in different strains, and points to an interaction of both genetic and environmental factors. Interestingly, there is some support for the hypothesis that prenatal stress might attenuate strain differences in the behavioral response to stress. Although control LEW rats exhibited poorer avoidance in comparison with F344 rats, avoidance in female LEW rats was improved following prenatal stress, thereby attenuating strain differences in females. Likewise, novelty-induced locomotion was higher in control LEW compared with F344 rats; prenatal stress reduced locomotor activity in LEW rats and increased activity in female F344 rats, again resulting in an overall tendency towards attenuation of strain differences. Such attenuation of genetic differences following environmental manipulations is consistent with previous findings (21,23) (see the introductory paragraphs). However, in some of our measures, prenatal stress increased strain differences. Thus, control LEW rats had shorter immobility times in the forced swim test than F344 rats, and prenatal stress further reduced immobility time in LEW rats, while not influencing the immobility response of F344 rats. In addition, normally occurring weight differences (i.e., LEW rats weigh more than F344 rats) were further increased by prenatal stress. In conclusion, our results suggest that prenatal stress exerts long-term effects on behavior, and that such effects seem to be dependent on the genetic background of the animals studied.

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