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Effects of prenatal stress on motor performance and anxiety behavior in Swiss mice

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Abstract

Stressor presence during the last weeks of gestation has been associated with behavioral disorders in later life. In this study we support further research on the long term effects of prenatal stress on *Swiss mice* descendant's behavior. Prenatal stress procedure consisted on restraining the dams under bright light for 45 min, three times per day from the 15th day of pregnancy, until birth. After weaning, offspring's motor performance and spontaneous exploratory behavior were measured by the tight-rope and T-maze tests, respectively. We also evaluated anxiety behavior using elevated plus maze test. We found that maternal stress improves the performance of the animals in the tight rope test and that this effect was sex and age dependent: prenatal stressed males obtained the best scores during the first month of life, while in females the same was achieved at the second month. Spontaneous exploratory behavior analysis revealed that it was elevated in prenatal stressed males and that this effect persisted on time. However, we did not find significant differences on this behavioral response among both females groups. Finally, differences on anxiety behavior were found only in females: prenatally stressed animals showed a higher proportion of entries into the open arms of a plus maze (reduced anxiety) compared to the control group. Our results show that prenatal stress modifies the normal behavior of the progeny: prenatal stressed animals have a better performance in the carried out test. These notably results suggest the existence of an adaptive response to prenatal stress.

Keywords: Prenatal stress; Restraint; Swiss mice; Sex differences

1. Introduction

In recent years, new evidence has been published supporting the fact that chronic exposure to stressful events during prenatal development can induce long-lasting alterations upon a variety of behavioral and neuroendocrine systems' functions of the newborn [1,2]. In humans, prenatal stress induces low birth weight, delay in walking and speech, sleep disturbances and emotional alterations such as an increased emotionality during childhood [1,3,4]. Moreover, in experimental animals, chronic maternal stress has been shown to induce alterations in the progeny which are consistent with those observed in humans [1,5]: gestational stress seems to be associated with increased emotional responses when faced to novel or averse stimuli, depressive-like alterations, learning and memory deficits in adulthood [6–8]. Additionally, abnormalities were found in early motor development, exploratory activity and locomotor behavior and in some cases, these differ in a sex-specific way [9]. The sexual behavior is also affected by prenatal stress in males [10].

Evidence from previous researches revealed that the maternal stress hormones, the glucocorticoids (GC), that can also reach the foetuses after passing through the placenta, are one of the responsible for the aforementioned effects [1,11–14]. Indeed, the brain is very sensitive to so called prenatal programming, and excess of GCs at critical stages of development can modify neuroendocrine functions and also the morphology of several brain structures, particularly the limbic system (including the amygdale, hippocampus and hypothalamus) [2]. By this way, GCs effects can modulate the behavior of adult animals' offspring. However, other systems are implied on these. For example, the midbrain dopaminergic system, involved in the control of motor activity, and also

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cognition and emotion, was found to be affected by prenatal stress [9,15–17].

Based upon these observations, the aim of the present study was to further evaluate how prenatal stress may affect the behavioral reactivity of the descendants, using for that purpose a mouse model. While much of the investigations on this concern were realized with rat animal models, it is well known that prenatal stress may also exert effects on mice. Differentially behavior has been reported between both rodents. Moreover, their stress response also differs [18,19]. This study might contribute to generate new data on the effect of prenatal stress on mice behavior. The Swiss mice strain was chosen on the basis of its widespread use in behavioral research and well validated behavioral test are being performed on this strain.

2. Materials and methods

2.1. Subjects and prenatal procedure

Three month old virgin Swiss female mice (*Mus musculus*) bred in our colony were mated with sexually experimented males. The presence of vaginal plug was counted as day 1 of pregnancy and then males were removed [20]. Pregnant females were housed in individual cages under standard laboratory condition (sound attenuated and temperature −22 °C-controlled room, light from 7 a.m. to 7 p.m.). Food and water were provided *ab libitum*. In all cases, the manipulation of animals was performed according to the principles and directives of the European Communities Council Directives (86/609/EEC).

At day 15th of pregnancy, females were randomly assigned to Control (C) (N=4) or Stress (S) group (N=4).

Control group pregnant females were left undisturbed, while the others received a stress treatment that consisted in placing the animal in a ventilated plastic restraint tube (inner diameter: 3.5 cm) under a bright light for 45 min, three times per day (at 10:00, 14:00, and 18:00 h), until birth [20,21]. It is important to point out that when placed into the tube, the mice were able to move back and forth, but they could not turn around.

2.2. Behavioral analyses

After birth, dams and their offspring's were left undisturbed, except for cage changes until weaning. Then, they were separated and randomly distributed in groups of 5–7 animals per cage, according to their sex and the prenatal treatment they had received.

Tight-rope and T-maze behavioral tests were carried out at the first and second month of life (*i.e.* 30 and 60 days of age) with a four-day interval between each test. Elevated plus-maze test was performed when the animals reached the age of three months.

All the behavioral tests were performed from 12:00 to 14:00 h, and the experimental apparatuses were cleaned and dried after each between animals.

2.2.1. Tight rope test

Briefly, the procedure consisted in placing the animal on the middle of a 60 cm long horizontal rope suspended 30 cm above the floor and time was recorded until the animal reached either end of the rope or fell down. A score was assigned accordingly: animals reaching the end of the rope in ≤6 s were given 1 point and an additional point was given for every additional 6 s needed to complete the test. Animals that stayed on the rope for 60 s without reaching the end were given 11 points. Mice falling down before 60 s were given 1 point in addition to the 11 points for every 6 s falling earlier than 60 s [22]. It is important to remark the following: the test assesses the motor performance as a mean of the animals' intrinsic neuromuscular coordination [23]. They not only must reach the end of the rope in a predefined time, they must also use it four extremities, as well as the tail, in a coordinated way. For that reason, the animals that do not carry out with these, were discarded (*e.g.* animals that reach the end of the rope in less than 60 s, but using only it both fore limbs) [22–24].

The test was performed in two consecutive days, being the first day a pre-test session that was not scored; and the second day, the test session.

2.2.2. T-maze test

Spontaneous exploratory behavior was tested in a T-shaped maze (110 cm × 60 cm of transverse and longitudinal arms, respectively). Animals were placed on the base of longitudinal arm, and the time it needed to reach the intersection of the three arms with both hind legs was registered. The proportion of animals that completed the test in less than 20 s was evaluated [23,24].

2.2.3. Elevated plus-maze test (EPM)

The plus maze consists of two open arms (30 × 7 cm), alternating in right angles with two closed arms (30 × 7 × 30 cm). The surface of the central area delimited by the four arms was 49 cm^2. The whole maze was elevated 60 cm above the floor. Before the start of the test, animals were individually placed in a rectangular plastiglass arena (40 × 40 cm) for 5 min in order to habituate them to the test environment. Mice were placed in the center of the elevated plus-maze, facing the closed arm, and were allowed to explore the maze for 5 min. The animal's behavior was videotaped and following a four-paw criterion, percentages of entries and time spent in each arm over the total exploration in both open and closed arms were calculated. This test model is based on the natural aversion the rodents show to the open surfaces. In this case, they present behavioral and physiological manifestations of fear (*i.e.* freezing, defecation, etc). A higher anxiety is estimated by a reduction in open arm entries [25].

2.3. Statistical analyses

Behavioral data from the tight rope and T-maze tests were established to be nonparametric according the Kolmogorov–Smirnov test (P<0.05). For that reason, the data from the first test were analysed by a Mann–Whitney *U-test* for comparisons between groups, while the proportions of success obtained by the T-maze test were analysed by the *Chi-Square* test.

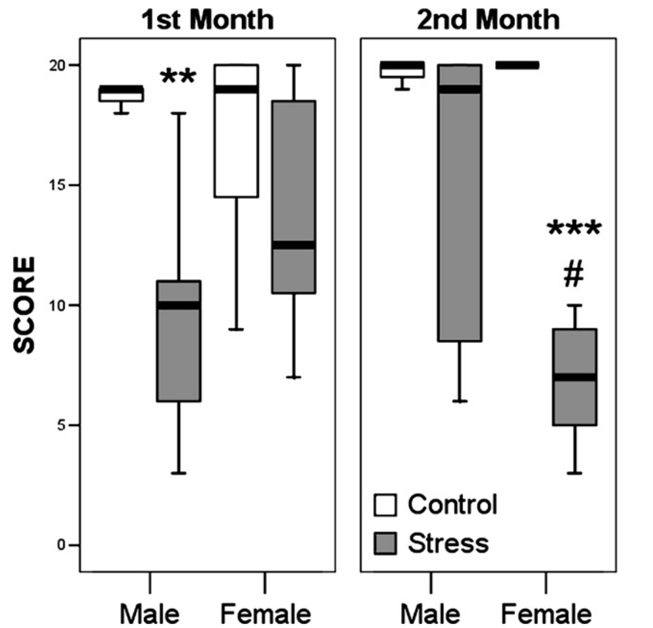

Fig. 1. Effects of prenatal stress on motor activity during the first and second month of life on offspring of both sex. As described in the test, the lower the score, the better the performance in the test was. Boxes represent the median (horizontal dark bars) and quartiles (25 and 75%) of the scores obtained in the tight rope test. $^{**}P \ll 0.05$ (C *vs* S in males 1st month); $^{***}P \ll 0.001$ (C *vs* S in females 2nd month); $\#P \ll 0.05$ (S group, males *vs* females, 2nd month). *N*: C=7, S=13 and C=7, S=11 (for males at firs and second month of ages, respectively). For females, *N*: C=8, S=9 (first month) and C=9, S=10 (second month).

The EPM data followed a parametric distribution, and because none interactions of the factor Sex and Treatment were found ($P > 0.05$), the data were processed by means of a *One-way ANOVA test*.

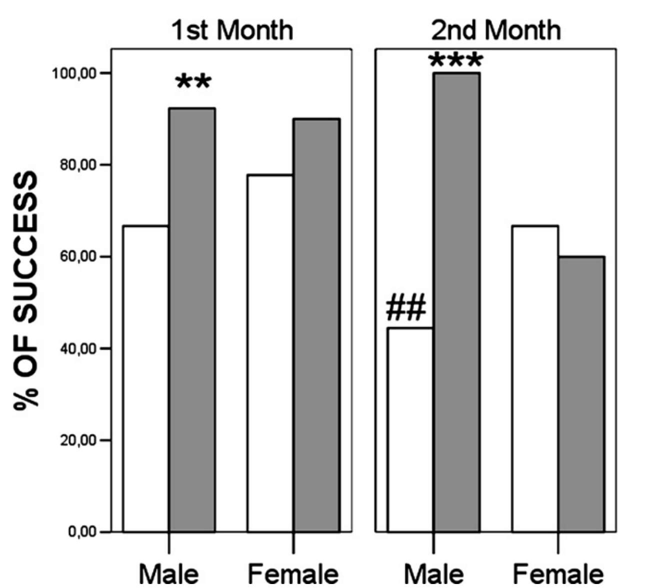

Fig. 2. Effects of prenatal stress on spontaneous exploratory activity. Bars represent % of success achieved by offspring of both sex at first or second month of life, that received (solid bars) or not (white bars) prenatal stress. $^{*}P < 0.05$ (S *vs* C, males 1st month); $^{***}P \ll 0.001$ (S *vs* C, males 2nd month); $\#\#P \ll 0.05$ (1st *vs* 2nd month, C group). *N*: C=9, S=13 for males; and *N*: C=9, S=10 for females.

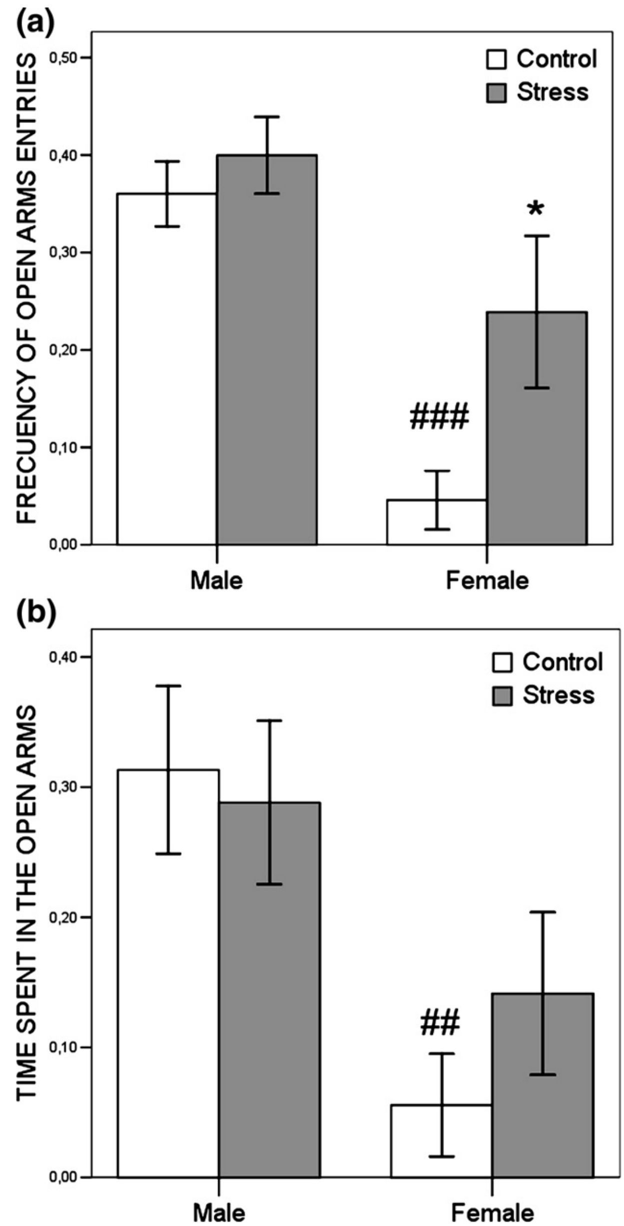

Fig. 3. Effects of prenatal stress on the anxiety behavior. Values are Frequency of open arms entries (a) or time spent in the open arms (b), means±SEM. In (a)$^{*}P = 0.05$ (S *vs* C, in females); $\#\#\#P \ll 0.001$ (males *vs* females, C group). (b) $\#\#P \ll 005$ (males *vs* females, control group). *N*: C=7, S=12 for males; and C=8, S=10 for females.

A difference was considered to be statistically significant when $P < 0.05$ (SPSS 13.0 version).

3. Results

Not differences were found on litter size or sexes distribution between the offspring belonging to the prenatal stress or control group.

3.1. Effects of prenatal stress on motor performance

Motor performance was evaluated by the tight rope test. Results demonstrated the existence of differences in the effects of prenatal stress depending on the age and sex of the progeny (Fig. 1): prenatal stressed animals' scores were lower than those of controls; but, while in male offspring the best performance was achieved during the first month [$P=0.008$], in prenatal stressed females, the same effect was observed during the second month also [$P \ll 0.001$]. Moreover, the performance of S group females at this age was significantly better compared with S group males of the same age [$P=0.007$].

3.2. Effects of prenatal stress on spontaneous exploratory activity

Interestingly, the analysis of the spontaneous exploratory activity by the proportion of control males that successfully completed the T-maze showed that there is a reduction of this during the second month [$\chi^2=4.766$; $df=1$; $P=0.029$]; however, it persisted elevated in prenatal stressed males, at both ages [$\chi^2=3.931$; $df=1$; $P=0.047$ and $\chi^2=21.778$; $df=1$; $P \ll 0.001$ respectively, Fig. 2]. Nevertheless, the proportion of success on completing the T-maze in females belonging to S or C group was similar.

3.3. Effects of prenatal stress on anxiety behavior

Anxiety behavior was estimated by the number of open arm entries over the total arms entries and the time spent in them compared with the total time that the animal stayed in the EPM (Fig. 3). We did not find differences in anxiety behavior between males of either group. However, control females exhibited a lower frequency of open arm entries and less time spent on them, indicating higher anxiety compared with control males [$F_{(1;13)}=49.183$, $P \ll 0.001$ Fig. 3A and $F_{(1;13)}=12.352$, $P=0.004$ Fig. 3B]. Nevertheless S group females showed a higher frequency of open arms entries than C group [$F_{(1;16)}=4.402$, $P=0.05$, Fig. 3A].

4. Discussion

The results of the present study show that prenatal stress modifies the descendants' behavior. Indeed in this work, prenatal stress improves the offspring's behavior in a sex- and age-specific way: prenatal stressed animals obtain a better performance in motor task, without increasing their anxiety-like behavior.

Prenatal stressed animals' behavioral reactivity has been the focus of numerous researches since the prenatal exposure to a stressful agent was associated with developmental delays, behavior abnormalities and alterations on the correct function of the adult stress response system of the progeny [1,3,6,7,11,13,26]. However, the severity of these conditions depends on the genetic vulnerability of the organism, as well as the nature and the timing of the stressful event [27,28].

The present study also supported further investigation on prenatally stressed animals' reactivity, of both sexes, in front of novel situations.

In order to investigate the animal's capacity to perform a motor task, we measured their motor performance with the tight rope test, by assessing their ability to achieve a goal by correctly utilizing its four extremities and tail in a predefined time [22–24]. On the other hand, we also studied the spontaneous exploratory activity by determining the time the animal took to explore the T-maze [23,24].

We repeated both tests on the same animals at first and second month of age (*i.e.* adolescent and young adult animals [29,30], in order to follow if the animals' stress response vary according their age. Previous studies demonstrate that adolescent animals behave in a differential way respect adults ones [30]. And the stress response also varies according the age of the offspring [29,31]. Whenever we are conscious that the repetition of the tests could affect the results we obtained due to a several kind of "learning process" between both measures at the same animals, on the other hand, the tests are not linked with any learning task and no reward or any other kind of stimuli was offered to the animals during the test; they only measure several aspects of the intrinsic animal locomotor behaviour. However, we keep on mind investigating the possible effects of this concern.

Our results indicate that prenatal stress resulted in a better performance of the offspring in the tight rope test, compared to the control, none prenatally stressed animals, and this effect persisted in time. Nevertheless, while in males the best performance was achieved during one month of age, in females the best performance is observed during the second month of life (Fig. 1).

Furthermore, the evaluation of exploratory activity in prenatal stressed males revealed an increased response compared to the control group, but we did not find significant differences between females belonging to C or S group, on this issue (Fig. 2).

It is well known that gonadal hormones participate in the control and maturation of several motor activities [9] and most of the alterations observed in adult offspring start after puberty. Although these issues need to be explored more meticulously, the difference in the onset of sexual maturation inherent to each gender may explain the discrepancies observed in the tests.

As for the dimorphic effects of prenatal stress in motor activity results, these are consistent with previous investigations that support the fact that locomotor activity is strongly sex dependent [32]; furthermore, prenatally stressed rodent males were found to display an enhanced motor response (*i.e.* locomotion and exploratory activity) to novelty [9].

The fact that all the animals used on these tests presented normal motor behavior (*i.e.* normal coordination and marching) when undisturbed in their cages, suggests that these differences on test performances should be attributed to alterations in specific brain regions responsible for motor and spontaneous activities. The mesolimbic and mesostriatal dopamine (DA) pathways are some of the circuits implied. Additionally DAergic neurons are also involved in the normal extinction of fear responses. Although there exists little information concerning the effects of the adrenal steroids on the prenatal development on these pathways, several researches demonstrated that restraint stress applied to the mother during the last week of gestation affects DA-Glutamate receptor expression of numerous forebrain regions [9,15–17], providing a possible substrate for the explanation of more than a few of the well-known abnormalities on motor activities and behavior induced by prenatal stress [1].

The other major focus of this investigation was to assess the animals' reactivity by evaluating the anxiety behavior in the EPM test. A low time spent in the open arms, as well as a reduction in the number of open arm entries, is indicative of this behavior [25,33]. Generally, investigations on prenatal stress models reported that prenatally stressed animal's exhibit increased "anxiety" compared to prenatally undisturbed animals [11]. Moreover, this response is generally gender dependent. Prenatally stressed females were more sensitive than males: they are less anxious and exhibit a higher corticosterone response in front of acute stress treatment or novelty [33,34].

In this study, prenatal stress did not exert differences in the anxiety behavior of males offspring compared to controls (Fig. 3). Probably, the EPM test is not a sufficiently sensitive test to reveal differences in this parameter in response to a prenatal treatment in this gender. Nevertheless, S group females showed a higher frequency of open arm entries in the EPM compared to control females, indicating that prenatal stress seems to reduce the anxiety behavior in this sex. Moreover, there were no differences in this behavior between males (C or S group) *vs* S group females (Fig. 3).

Anxiety behavior abnormalities are also linked to an alteration in amygdale function. Moreover the hippocampus is also implicated because of its important role on the negative feedback of the HPA under stress situations [26,34]. Moreover in females the HPA axis' response to acute stress, such as an exposure to a novel situation, varies over the oestrus cycle [35]. A high oestrogen level (as occurs during the proestrus and oestrus phase) is associated with increased HPA axis activity even in non-fearful situations (as could be the home cage). However high levels of these steroids are also associated with increased anxiety [36]. We did not monitor the oestrus cycle in this study because it would have required subjecting the animals to the additional stress of sample collecting associated with those procedures. We did not discard the fact that probably the effects observed on the anxiety-like behavior should be due to abnormal corticosterone levels in plasma between prenatally stressed or not animals. However the aim of this study was to support behavioral observations of the prenatal stress effects on the progeny and unfortunately we did not measure the animal's corticosterone levels in plasma.

Despite the prenatal stress model utilized in this work was a chronic severe stress procedure [21], the kind of behavior observed in our investigation has been found in other models of early development stress such as Postnatal Handling in rats [28,37]. Nonetheless, we cannot exclude a genetic background on the effects of prenatal stress [18] as well as procedural differences.

In conclusion, we provide evidence on a new aspect of the effects of chronic prenatal stressful agent exposure on the descendant's behavior. Prenatally stressed animal shows a better motor performance in the tight rope test, and males also show an enhanced spontaneous exploratory activity, compared with control animals. We did not find increment on the anxiety-like behavior due to a prenatal stress treatment. Accordingly to our results, it appears to be unlikely that those effects can be a consequence of a probably enhanced reactivity of prenatally stressed animals. Even when mice strains were reported to be more reactive to stressful conditions, as could be a new environment or the suspension on a rope, than other rodent models [19]. For that reason, we think that an adaptive or protective effects of prenatal stress possibly enable offspring to respond better to a novel situation. Therefore, we cannot rule out this possibility. Then, further research is currently being performed in our lab to clarify the intimate mechanisms involved.

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