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Chronic Prenatal Stress Affects Development and Behavioral Depression in Rats

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We have used the approach of Willner *et al* (1987), which consists of transitory and variable changes in the rat's living conditions, to investigate the influence of chronic prenatal stress on pup development and their susceptibility to behavioral depression at adult age, as assessed by the learned helplessness model. Pregnant female Wistar rats were divided into either stressed (S; N = 35) or non-stressed (NS; N = 35) groups during the last two weeks of pregnancy. The male and female pups of both groups were either handled to test for physical development up to weaning (H; N = 25 litters) or left undisturbed (NH; N = 10 litters) until adult age, at which time the males from all four experimental groups were divided into two subgroups (N = 10 each) and were submitted to the learned helplessness model of depression. Prenatal stress reduced the number of male pups per litter, decreased the anogenital distance, and produced earlier earflap and eye opening dates, as well as a faster righting. Behavioral depression was induced in all cases, except in the NS-H animals. The prenatally stressed, non-handled pups showed greater escape latency than the NS subgroups. We conclude that the stress schedule used in this study was stressful to dams and sufficient to affect the pups' development and to increase the intensity of induced behavioral depression at adult age.

Keywords: behavioral depression, prenatal stress, rats

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INTRODUCTION

Environmental factors to which a mother is exposed during pregnancy influence the behavioral formation of the offspring (Joffe, 1969). Such factors include drug consumption, certain nutritional states and emotionally stressful events (Joffe, 1978; Swaab and Mirmiram, 1984; Weinstock *et al*, 1988; Stott, 1973). It has been observed that children born to mothers who suffered stress during pregnancy have a low birth weight, an altered sleep pattern, neophobia, irritability, social fear and anxiety (Knipschild *et al.*, 1981; Schell, 1981). Such children also show a low weight gain and a delay in walking and speech development (Stott, 1973; Meier, 1985).

Numerous studies in rodents have examined the effect of intense prenatal distress induced by electric shocks, prolonged physical contention and prolonged exposure to intense light, noise or heat, applied during pregnancy (for review see Weinstock *et al.*, 1988). In

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this regard, feminization and a pronounced reduction in sexual maturation have been reported for male rat pups (Dahlof *et al.*, 1977; Meisel *et al.*, 1979), including a decrease in the anogenital distance and testis weight at birth (Dahlof *et al.*, 1977, 1978). In female pups, changes in the estrus cycle, a reduction in fertility and alterations in nursing behavior have been observed at adult age (Herrenkohl and Politch, 1978; Herrenkohl and Whitney, 1976; Herrenkohl, 1979). Physical or behavioral alterations arising from prenatal stress have also been observed (Thompson et al., 1962; Meisel *et al.*, 1979, Fride *et al.*, 1986; Takahashi *et al.*, 1992). Such changes as have been described may (Dahlof *et al.*, 1977; Ward, 1972 a,b; Masterpasqua *et al.*, 1976; Meisel et *al.*, 1979; Herrenkohl and Whitney, 1976) or may not (Barlow *et al.* 1978; Fride and Weinstock, 1984) be related to sexual activity.

In this work, we have investigated the influence of prolonged (12 days) prenatal chronic unpredictable stress on the physical and behavioral development of rat offspring. We employed a form of chronic, mild psychological stress described by Willner et al. (1987), that evokes physiological and behavioral responses but does not produce direct tissue damage. Such a great stress regime, which is well established in the literature and widely used as a model of depressions (for a review see Willner, 1997), has the added advantage in that it prevents the animals from adapting to the stimulus. The stress regime consist of transitory and variable changes in the rat's living conditions, and is applied during the last two thirds of the rat's pregnancy.

Stress is known to reveal latent mental disease, although the stressing event need not always immediately precede manifestation of the disease (Weiss and Kelts, 1995). Since we were interested in investigating the possibility that prenatal stress could precipitate a state of depression in adulthood, we chose the learned helplessness model of depression (Maier and Seligman, 1967) for this study as it is widely accepted as a useful animal model of human depression (Willner, 1986). A preliminary report of the work described here has been published (Teixeira and Secoli, 1997).

MATERIAL AND METHODS

Nulliparous adult female Wistar rats (approximately 200 g in weight) were housed with adult males for three days. The rats had access to food and water *ad libitum* throughout the experiments and were housed at a temperature of 26 ± 2°C on a 12 h light:dark cycle with the lights turned on at 6:00 a .m. The date of conception (day 0 of pregnancy) was determined when sperm were detected in expelled vaginal plugs. The pregnant females were then isolated in wire cages (30 cm × 16 cm × 19 cm) and randomly assigned to one of two treatments: 1) 35 dams were housed with no handling during the gestation period (Control group) and 2) 35 dams underwent a schedule of chronic unpredictable stress such as that described by Willner *et al.* (1987), during the last 12 days of gestation (Treated group), starting on the seventh day of pregnancy; in this case it was assumed that the sequencing and timing of the stress was consistent across groups. In brief, the stress regime (per week) consisted of 60 h of food and 78.5 h of water deprivation, 35 h of continuous lighting, 24.5 h of cage tilting, 17 h of paired housing, 17 h in a soiled cage, 2 h of reduced temperature, 10 h of exposure to intermittent white noise (85 dB), 1 h of stroboscopic lighting, 0.5 h of exposure to empty water bottles following a period of water deprivation, 2 h of restricted access to food, 17 h of exposure to a new odor, and 17 h of exposure to objects in the home cage. A full time-scale figure illustrating the stress protocol can be found in Willner *et al*(1987); together with further details of the stress protocol. Three days before the expected parturition date, the females were transferred to solid-bottom polypropylene cages (30 cm × 20 cm × 13 cm) with pine shavings as bedding material. All of the females were left undisturbed during this period. Females near parturition were visually inspected twice daily (at 10.00 a .m and 4.00 p.m.). birth. The offspring were counted, at birth, weighed and examined for external malformations. The number of stillborn offspring was recorded, and the litters were then reduced to eight pups per dam (always four females and four males), in order to provide a standard composition for all litters, independent of the number or sex of the pups born in each delivery.

All tests with dams and pups were performed during day light hours (9 :00–12 :00 a.m.) at a room temperature of 30 ± 2°C, in order to minimize cooling of the pups. Each manipulation involved removing the female from the nest after which each pup was then held by the experimenter, or was tested for its righting reflex or weighed by placing it on a cotton tissue on a balance. The average time of handling of each pup was 30 sec. The litters from groups 1 and 2 were divided into four experimental groups as follows: a) 10 litters were neither stressed prenatally nor handled during the lactating period (NS-NH); b) 10 litters were stressed prenatally but were not handled (S-NH), c) 25 litters were not stressed prenatally but were handled during the lactating period (NS-H), and d) 25 litters were stressed during the prenatal period and were handled (S-H).

At weaning (pups 21 days old), only two male pups from each of the litters were kept and tested at adult age (90 days old) for the induction of behavioral depression using the learned helplessness model (Maier and Seligman, 1967; Teixeira *et al.*, 1995b).

1) Evaluation of offspring

We employed the following tests which are commonly accepted in behavioral toxicology and scored the physical landmarks of development and the pup retrieval measures by conventional means (for details see reference in Teixeira *et al.*, 1995a). As soon as the pups had been tested, they were returned to their mothers.

Physical landmarks of development

Weekly body weights together with the dates of earflap and eyelid opening were recorded. A positive score was assigned to the pup if both pinnae were completely detached by the second day after birth or if both eyes were completely open by the 14th day. A positive score was assigned to the litter if more than five pups had positive scores at each critical date.

Surface righting reflex

At birth, each pup was placed in a supine position and the time required to right itself and to place all four feet in contact with the floor was measured. A maximum of 60 s was allowed for the test.

Pup retrieval

When the offspring were two days old, the dam and litter were placed in another cage and allowed to adapt and build a nest for a 20-min period. The dam was then removed and the litter shifted to the opposite side of the cage. The dam was subsequently returned to the center of cage and the time required to return all pups to the nest was recorded. Positive scores were assigned to those dams that recovered their pups within a maximum period of 15 min.

2) Evaluation of adults

Adult age males from all four subgroups (only one male pup per subgroup) were housed individually in polypropylene cages (30 cm × 20 cm × 13 cm) as described above. After three days of adaptation to the housing conditions, the rats were randomly assigned to one of two subgroups and submitted to the induction of learned helplessness (for details see Maier and Seligman, 1967; Teixeira *et al.*, 1995b).

The rats were placed in a Plexiglas box (25 cm × 25 cm × 30 cm) equipped with a grid floor consisting of stainless steel bars. The first subgroup was subjected to a session of 60 scrambled, unsigned, inescapable 1mA foot-shocks (Sh group) delivered by a personal microcomputer executing a software program (for details, see Teixeira *et al.*, 1995b). The shock on/off period for this group was yoked to an escapable group. The duration of the shocks varied from 0.58 S to 18.18 s, depending on the trial. Each trial was separated by an interval of 5–25 s. The second subgroup was simply confined in the box for the same period of time (NSh group).

Twenty-four hours after the end of the session, all of the animals underwent an escape test in a different shuttle box, in the same room for the inescapable shocks. This box was a two-way automated Plexiglas

box (50 cm × 25 cm × 30 cm) with a grid floor made of stainless steel bars. The box was divided into two equal chambers connected to each other via a small opening (6.0 cm × 7.5 cm) in the dividing wall located 8 cm from the grid floor (Teixeira *et al.*, 1995b). Thirty shocks were presented continuously during each trial and lasted a maximum of 30 s. in each case; the rat was required to jump into the opposite chamber in order to turn off the shock. If no response was evoked, another shock was immediately delivered (random between-trial interval of 5–25 s). The time between the onset and the end of the shocks was considered to be the response latency or trial duration.

STATISTICAL ANALYSIS

We considered the litter culled to eight pups as the unit for statistical analysis (Abbey and Howard, 1973) using the two-tailed test. Student's t-test or Fisher's exact test was applied when comparing two independent groups of pups. Repeated measures ANOVA followed by Tukey multiple comparation tests were used to analyse the results at adult age. Probability values lower than 0.05 were considered to indicate statistical significance.

RESULTS

A delay of one day in the registered parturition date was observed in 80% of all the stressed dams compared to only 10% of the control dams. No malformation was observed in any of the pups. The incidence of stillborn offspring was not significantly different between the two experimental groups (Table I). There was a reduction in the number of males born to mothers stressed during the last two weeks of pregnancy (Student's t-test, $t = 5.77$, $GL = 48$; $p \leq 0.001$) and hence a decrease in litter size (Student's t-test, = 2.80, $GL = 48$; $p \leq 0.01$) (Table I). The male pups born to stressed mothers showed a decrease in the anogenital distance (Student's t-test; $t = 18.03$; $GL = 48$; $p \leq 0.001$) (Table II). There was no change in the proportion of pups with a normal righting reflex at birth (Table III), although the mean latency to perform this test was smaller in prenatal stressed offspring (13.0 ± 7.3 s) compared to control offspring (21.1 ± 12.5 s) (Student's t-test ; $t = 2.8$; $GL = 48$; $p \leq 0.01$).

TABLE I Prenatal Stress Preferentially reduces the Number of Male Offspring per Litter

Group	*Total*	*Males*	*Females*	*Stillborn*
Control	10.7 ± 1.6	5.4 ± 2.3	5.1 ± 1.7	4
Stressed	9.2 ± 2.3*	3.8 ± 1.4*	5.0 ± 2.0	6

The data represent the mean ± SD of the number of pups in each category and the total number of stillborn offspring. * $p \leq 0.05$ compared to the control group (Student's t-test). N = 25 litters per group.

In the pup retrieval test, there was no difference in the average time the two groups required to rescue pups or in the proportion of females which did not recover their pups within the stipulated period (Table IV). The stress treatment had no effect on birth weight nor did it influence the growth rate until weaning (Table II). The prenatal stress schedule affected the critical days of maturation by increasing the proportion of litters with a positive index for the critical day of pinnae detachment (Fisher's test, $x^2 = 6.12$; $p = 0.01$, $df = 1$) and eye opening (Fisher's test, $x^2 = 4.5$ $p = 0.03$; $df = 1$).

Repeated measures ANOVA was performed to compare the variables: time (blocks of trials), group (each of the four treatments) and shock (inescapably shocked rats) in the four possible combinations. The results were as follows: time vs group vs shock: $F = 0.77$, $p > 0.05$; time vs group: $F = 0.88$, $p > 0.05$; shock vs time: $F = 1.58$, $p > 0.05$; shock vs group: $F = 5.61$, $p \leq 0.001$ [G1 (15,72), for all]. Thus, the only significant interactions involved the latter combination. When each of the treatment groups was compared with the variable "shock" [G1 (1,18) for all], the p values were significant for all groups: NS-H ($F = 6.3$, $p \leq 0.05$); S-H ($F = 13.65$, $p \leq 0.001$); NS-NH ($F = 20.91$, $p \leq 0.001$); S-NH ($F = 51.59$,

$p \leq 0.0001$). No significant difference was found for the non-shocked rats ($F(3,36) = 0.32$) but there was a significant difference among the shocked subgroups of rats ($F(3,36) = 6.29$, $p \leq 0.001$). The behavioral depression induced in the learned helplessness model of depression implies the presence of an escape "deficit" in shocked rats compared to non-shocked rats. For this reason, the post hoc Tukey test was applied to each block of trials. The analysis revealed that when adult male pups were submitted to the behavioral depression test, there was a deficit in the escape latency throughout the trials when the shocked vs non-shocked subgroups for all treatments (except the NS-H animals) were compared. The p value in relation to the non-shocked rats of each subgroup are stated in the figures as routinely done in studies using the learned helplessness model of depression, the escape latencies of all the non-shocked sub-groups were compared in order to evaluate whether there was any possible interference of the treatments with the escape performance itself. This analysis revealed that there were no differences in the escape latencies of any of the non-shocked sub-groups, indicating that there was no interference with the ability to escape the shocks. The number of escape failures in each subgroup was 0, 11, 16 and 29 for the NS-H, NS-NH, S-H and S-NH groups.

TABLE II Prenatal Stress reduces the Anogenital Distance at Birth and the Post-weaning Body Weight

		Age (Days)				
Group	*Anogenital distance*	*0*	*7*	*14*	*21*	*28*
Control	0.32 ± 0.03	5.6 ± 0.3	14.0 ± 1.9	26.4 ± 2.6	41.6 ± 4.7	69.0 ± 6.2
Stressed	0.19 ± 0.02*	5.7 ± 0.4	14.7 ± 1.5	26.5 ± 2.4	41.7 ± 3.7	65.9 ± 3.6*

Data represent the mean + SD of the anogenital distance (cm) and the body weight gain (g) from birth (day 0) to the post-weaning period (28 days), in control and stressed pups. *$p \leq 0.05$ compared to control litters (Student's t-test). N = 25 litters per group.

TABLE III Prenatal Stress accelerates the early Maturation Of Pups

	Positive Index		
Group	*Righting Reflex*	*Pinnae Detachment*	*Eye Opening*
Control	84	64	61
Stressed	94	96*	86*

The data represent the frequency (in %) of litters with a positive index for the righting reflex, pinnae detachment and eye opening at critical days. *$p \leq 0.05$ compared to control litters (Fisher test). N = 25 litters per group.

TABLE IV Prenatal Stress has no Effect on the Pup Retrieval Test

Group	*Performance*		*Latency (Sec)*
	+	−	
Control	22	3	18.9 + 2.4
Stressed	19	6	22.5 + 3.8

(+) number of mothers that recovered their pups within a maximum period of 15 min. (-) number of mothers that did not recover their pups. Mean + SD of the time required to return each pup. N = 25 dams per group.

DISCUSSION

Several studies have shown that pre- or post-natal stress can have important, long-lasting morphological, behavioral and physiological consequences in rodents (Weinstock *et al.*, 1988; Dahlof *et al.*, 1977, 1978; Ward, 1972 a,b; Meisel *et al.*, 1979; Herrenkohl and Polich, 1978; Herrenkohl and Whitney, 1976). The effect of such stress is frequently only observed under adverse ambient conditions (Weinstock, 1988). The prenatally-stressed rats are less able to cope with stress in adulthood (Fride *et al.*, 1986) when compared with unstressed rats that suffered mild stress during the post-natal period (Gonzales *et al.*, 1990).

In the present study, the pups born to mothers subjected to chronic stress showed no observable malformations, nor was there any effect on the stillborn rate. The postural reflex of these rats was normal but faster than that of control rats and their weight gain until weaning was normal. In other models of stress during

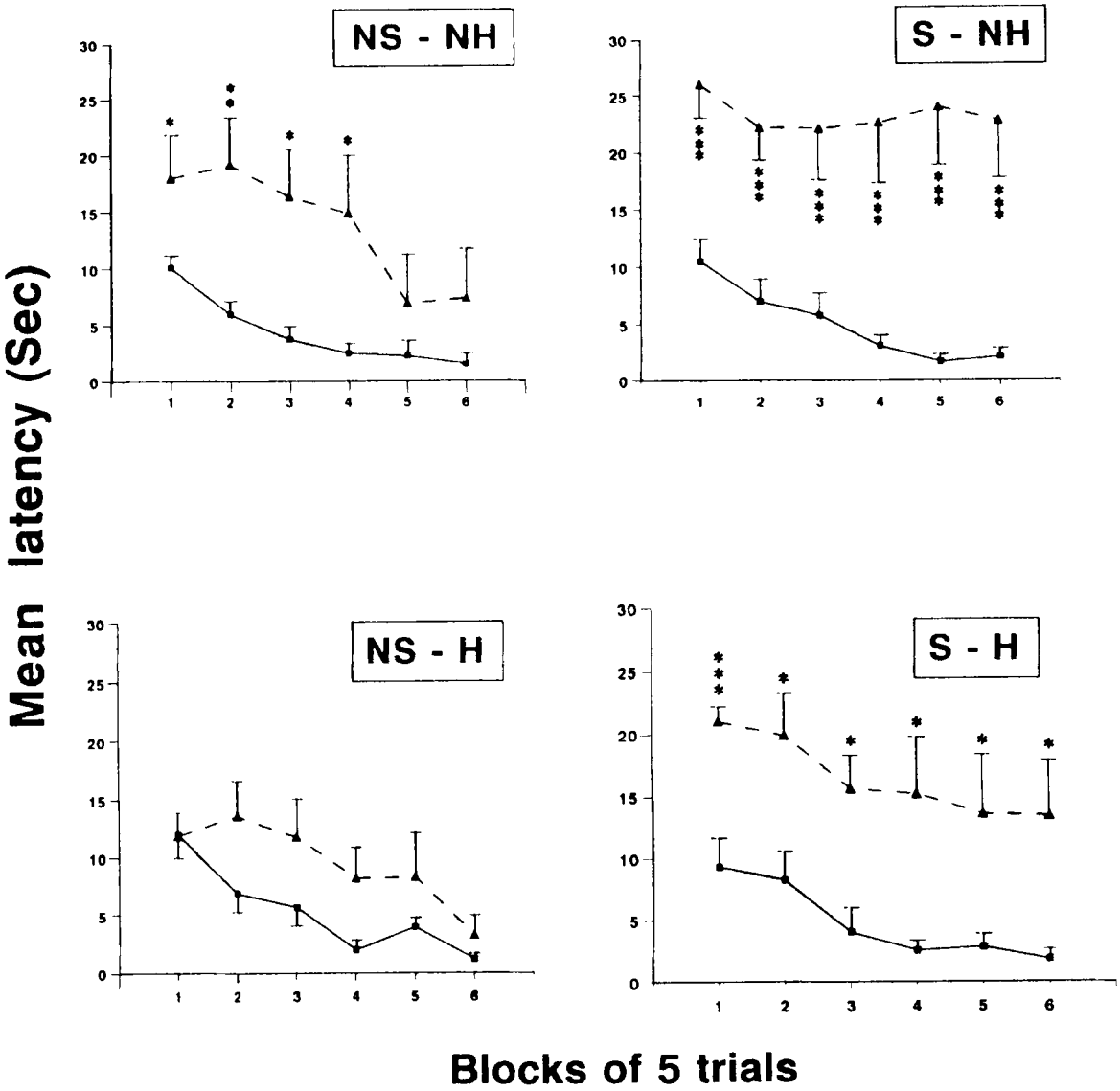

FIGURE 1 Prenatal stress and handling increase and decrease, respectively, the intensity of behavioral depression induced by inescapable shocks the data represent the mean escape latency (sec) ± SEM for blocks of five trials. —, no shocks; - - -, inescapable shocks; NS, non-stressed; S, stressed; NH, not handled; H, handled. $^{*}p \leq 0.05$, $^{**}p \leq 0.01$ and $^{***}p \leq 0.001$, compared to the respective non-shocked group (Tukey test). N = 10 rats per group

pregnancy, these parameters are frequently altered (Weinstock *et al.*, 1988; Herrenkohl and Polich, 1978). The divergence between our results and those of others (Barlow *et al.*, 1978), including the earlier critical dates obtained for the appearance of physical landmarks of development, may be explained by the mean delay of one day in delivery among our rats. Post-term delivery has also been observed in rats

treated chronically with ACTH during pregnancy (Fameli *et al.*, 1995), a procedure that mimics the hyperactivity of the HPA axis, which occurs during stress. Studies using a daily stress paradigm during the last week of gestation have found a faster development of the righting reflex with no difference in the duration of gestation or in body weight (Fride and Weinstock, 1984). The last week of gestation may therefore be the critical period of susceptibility to chronic stress, and may be important in determining the modulation of postural and other physical parameters.

A marked reduction in the anogenital distance of male offspring (Dahlof *et al.*, 1977, 1978) and a reduction in litter size (Fride and Weinstock, 1984) as a result of a decrease in the number of male pups born (Teixeira *et al.*, 1995a), were also observed in our study. However, the pup retrieval test showed that gestational stress did not change the mother's response to the removal of the pups from the nest. The possibility that the treatment employed had a more general effect on the dam's maternal behavior, and consequently affected the quality of offspring care (Ness and Franchina, 1990), cannot be discarded based on the normal results obtained in the pup retrieval test. Detailed studies of the mother-offspring interaction, including measurement of the time expended by dams in anogenital licking of the pups, have shown a reduction in the maternal care of prenatally stressed offspring (Moore and Power, 1986; Power and Moore, 1986). Such a subtle alteration in maternal attention appears to mediate changes in the hippocampus and leads to an abnormal development in many aspects of the pup's adult masculinity (Moore, 1993). Under our conditions of neonatal handling, we observed no increase in the reactivity of adult rats to aversive stimuli (Denenberg and Zarrow, 1974), including in the escape latency to footshocks (Rocha and Vendit, 1990). Had such a response been present, it would have improved the escape behavior of the animals not submitted to inescapable shocks. The rats that were handled only during infancy and submitted to inescapable shocks in adulthood were subsequently the only ones not to show any escape deficit when compared to non-shocked rats. We have therefore confirmed the results obtained by Costela *et al.* (1995) that used the same methodology to induce behavioral depression, although we employed longer periods of neonatal handling. Our data also strengthen the hypothesis of a protective effect of handling against acute stress in adulthood (Pfeifer *et al.*, 1976). In this respect, Weinstock and Wakshlack (1990) found that handling specifically improved the performance in the plus maze and led to a reduction in anxiety in prenatally stressed rats.

To our knowledge, this is the first report to examine the effect of prenatal stress in an animal model of depression. Thus, in rats submitted to inescapable shocks, there was an increase in the escape latency as expected when behavioral depression occurs. This induced depression was completely reversed by handling in prenatally non-stressed pups, but only partially prevented in the offspring of stressed mothers. The prenatally stressed rats which were not handled also showed the greatest escape deficit among inescapably shocked rats for all parameters tested when compared to non-shocked animals. Our results therefore strengthen the argument that pups born to stressed mothers have a higher susceptibility to stress in adult age (Wakshlak and Weinstock, 1990; Weinstock *et al.*, 1992). We conclude that the mild stress schedule used in the present study was sufficient to affect the pups development and to increase the intensity of induced behavioral depression at adult age.

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