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Predator and Restraint Stress During Gestation Facilitates Pilocarpine-Induced Seizures in Prepubertal Rats

ABSTRACT: *Stress during gestation can result in early and long-term developmental aberrations. This study aimed to assess the impact of prenatal restraint or predator stress on pilocarpine-induced epileptic behavior. Pregnant rats were exposed to stressors on gestational days 15, 16, and 17. Restraint stress consisted of daily restraint of the dam. During predator stress, caged rats were exposed to a cat in a cage. On postnatal day 25, male pups were injected with pilocarpine and the behavior of each rat was observed. Prenatal stress led to low birth weight and increased blood corticosterone levels. Both stressors significantly potentiated pilocarpine-induced seizures. Predator-stressed pups exhibited significantly severe tonic–clonic seizures compared with restraint-stressed animals. These data emphasize the impact of prenatal stress on fetal growth, and neural and endocrine function. The results also suggest that psychosocial stressors have a greater impact on neural and endocrine function than physical stressors do.* © *2011 Wiley Periodicals, Inc.* Dev Psychobiol 53: 806–812, 2011.

Keywords: *prenatal stress; restraint; predator; seizure; epileptic behavior; rat*

INTRODUCTION

Prenatal environmental factors exert a profound influence on the development of an organism and can predispose it to adaptive disturbances later in life (Heinrichs, 2010). In humans, this phenomenon has been associated with severe birth outcomes, including preterm birth, fetal growth retardation, delays in early motor development, behavioral abnormalities, infant sleep disturbances, and the development of psychiatric disorders, such as schizophrenia and depression (Edwards, Dortok, Tam, Won, & Burnham, 2002). In rats, prenatal stress leads to impaired sexual function (Secoli & Teixeira, 1998), vulnerability to anxiety, increased the propensity to self-administer drugs (Edwards et al., 2002), and impaired feedback regulation of the hypothalamic-pituitary-adrenal (HPA) axis due to decreased hippocampal corticosteroid receptor expression (Sadaghiani & Saboory, 2010). The appearance of such changes depends on the timing of the maternal stress, its intensity and duration, gender of the offspring and is associated with structural changes in the hippocampus, frontal cortex, amygdala, and nucleus accumbens (Weinstock, 2008). Prenatal stress can affect susceptibility to seizures in rats during postnatal development that can persist until adulthood (Slamberova, Schutova, Matejovska, Bernaskova, & Rokyta, 2009). Previously, we have demonstrated that prenatal restraint stress increases the susceptibility to seizures in male and female rats (Sadaghiani & Saboory, 2010). The effect of stress on epilepsy is controversial; a number of reports have documented findings contradictory to those previously described in the literature. Although the underlying mechanisms are poorly understood, emotional stress is well recognized as affecting seizure control in epilepsy and other seizure syndromes (Heshmatian, Roshan-Milani, & Saboory, 2010). However, experimental stressors, including swim stress,

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have been shown to elicit anticonvulsant effects in animals (Reddy & Rogawski, 2002). Thus, both proconvulsant (Edwards et al., 2002; Frye & Bayon, 1999) and anticonvulsant (Reddy & Rogawski, 2002) effects of stress have been reported, depending on experimental conditions. There are other types of human psychosocial stress that approximate predation. Of recent prominence are terrorist attacks. In the aftermath of the terrorist attack on New York, the incidence of affective disorders in many survivors has increased. Clearly, being the target of such aggression, or simply witnessing it, is traumatically stressful, and survivors experience disturbing and lasting changes in affect (Adamec, Blundell, & Burton, 2006). In animal models, predator stress can incite aggression. Studying defensive responses that are elicited by predator stress is an increasingly popular focus in neurobiological studies of fear and stress (Staples, McGregor, & Hunt, 2009). Predator odors elicit powerful defensive behaviors and characteristic patterns of neuronal activation in rodents (Blanchard et al., 2003; Staples et al., 2009). In rats, cat odor activates a ''medial hypothalamic defensive system'' (Canteras, 2002). Predator stress is anxiogenic in the elevated plus maze, light/dark box, and acoustic startle tests, and appears to potentiate right and depotentiate left hemisphere afferent amygdala transmission (Adamec, 1990). Previous studies have shown that status epilepticus (e.g., pilocarpine-induced seizure) early in life results in multiple effects in the developing brain. These changes, coexisting in the nonepileptic brain, can result in a maladaptive combination to produce the diseased state of epilepsy. The consequences of early seizure activity in immature animals are influenced by both the developmental stage and the method of seizure induction (Sankar, Shin, Liu, Wasterlain, & Mazarati, 2002). The extent of neuronal injury in the hippocampus produced by experimental status epilepticus is age dependent and is not readily demonstrable in many models of neonatal seizures (Sankar, Auvin, Mazarati, & Shin, 2007). Therefore, we used the same experimental seizure model in rats of the same age for the behavioral assessments in this study.

Although the effects of predator stress on animal behavior have been examined, very little is known about its influence on epilepsy and seizures. Therefore, this study was designed to investigate the impact of prenatal predator or restraint stress on pilocarpine-induced seizures in rats and compare the effects of the two stressors on epileptic behavior.

METHODS

Male and female Wistar rats (weight, 200–250 g; age, 10 weeks on delivery) were obtained from our animal facility (Urmia University of Medical Sciences, Urmia, Iran). These rats were housed in groups of four per cage and maintained under standard conditions as follows: 12-hr light/dark cycle, $22 \pm 2^{\circ}C$, and food and water ad libitum. All experimental protocols and procedures complied with the guidelines of the 1975 Declaration of Helsinki, as reflected in the guidelines of the Medical Ethics Committee, Ministry of Health, I.R. Iran. All females were mated at 12 weeks with a sexually experienced male of the same genotype. Each female was paired with one male at 0900 hours, and we checked for plugged females at 1500 hours; plugged females were immediately housed individually in cages for the entire gestation. If a plug was not observed, the animal was returned to her home cage until the next morning for a new mating session. Pregnant rats were divided into three groups ($n = 28$ in each): control, predator-stressed, and restraint-stressed. In the control group, pregnant females were transported to the experimental room on gestational days 15, 16, and 17 (E15, E16, and E17, respectively) and were handled similarly to the stressed groups, except for stressor exposure. Both stressed groups were exposed to stressors on E15, E16, and E17. Our previous study showed that stress during E15, E16, and E17 alters feedback regulation of the HPA axis and affects epileptiform activity in the offspring in vitro (Heshmatian et al., 2010). The restraint-stressed group was stressed daily. The stress involved transport of the home cage to the experimental room and placement of the pregnant female in a restraint chamber (a transparent, plastic, cylindrical chamber; diameter, 6 cm; length, 16 cm) under normal room conditions. Animals were restrained for 120 min, twice daily (between 0800 and 1100 hours, and 1500 and 1800 hours). This procedure causes alterations in regulation of the HPA axis in the offspring (Edwards et al., 2002).

The predator-stressed group was stressed daily. This stress entailed transport of the home cage to the experimental room and placement of the pregnant female in its cage, 30 cm from the cage of a cat, which facilitated visual contact between both animals, once daily for 2 hr for 3 consecutive days. The stress procedure was conducted between 0800 and 1200 hours.

At the end of the stress procedure (E17), both stressed and control animals were divided according to the experimental day into four subgroups ($n = 7$): E18, P2, P6, and P25 (Tab. 1).

Group E18 contained pregnant mothers that were examined on day 18 of gestation. Groups P2, P6, and P25 comprised both dams and pups that were examined on postnatal days 2, 6, and 25, respectively.

All dams ($n = 7$) in groups E18, P2, and P6, as well as two male pups from each litter ($n = 14$) in groups P2 and P6, were decapitated under halothane anesthesia at 0830 hours to collect truncal blood. Samples were kept on ice and centrifuged for 15 min at 9,000 rpm at $3^{\circ}C$. Plasma samples were stored at $-80^{\circ}C$ until the corticosterone (COS) levels were measured (Rangon et al., 2007), using a commercial radioimmunoassay (RIA) kit (Isotope, Budapest, Hungry); the values were expressed in ng/ml.

After parturition, the pups in each litter (control and stressed) were counted and weighed at 0900 hours on the first

Table 1. Grouping of Animals

Groups	Sub-Groups: All Dams in Same Sample Size, $n = 7$; All Pups in Same Sample Size, $n = 14$			
Control dam, $n = 28$	cdE18	cdP2	cdP6	cdP25
Restraint-stressed dam, $n = 28$	rsdE18	rsdP2	rsdP6	rsdP25
Predator-stressed dam, $n = 28$	psdE18	psdP2	psdP6	psdP25
Control pup, $n = 42$	Not available	cpP2	cpP6	cpP25
Restraint-stressed pup, $n = 42$		rspP2	rspP6	rspP25
Predator-stressed pup, $n = 42$		pspP2	pspP6	pspP25

cd, control dam; rsd, restraint-stressed dam; psd, predator-stressed dam; cp, control pup; rsp, restraint-stressed pup; psp, predator-stressed pup.

postnatal day (P1). The weight of each pup was recorded again at 0900 hours on P6, P15, and P25. The male pups from each litter in group P25 were sorted into one group, and the members were injected with pilocarpine on P25. To reduce possible litter effects, two pups from a random litter were also included in this experiment.

Pups whose behavior was to be assessed were allowed to remain with their dam until weaning on P21. On P25, these pups were injected with pilocarpine at a dose rate of 150 mg/kg SC (Gulec & Noyan, 2001; Sadaghiani & Saboory, 2010). Following injection, the behavior of each rat was observed and documented at least every 15 min for 120 min, and a seizure rating was made using a previously defined scale: stage 1, immobility; stage 2, forelimb and/or tail extension; stage 3, repetitive movements and head bobbing; stage 4, rearing and falling; stage 5, continuous rearing and falling; and stage 6, severe tonic–clonic seizures (Samland et al., 2003). Other parameters included latency to first behavioral change and latency to first maximal seizure. In addition, fatalities due to pilocarpine were recorded until 24 hr after injection.

Results are expressed as mean ± SEM. Data on normally distributed COS blood levels, pup weights, and litter sizes were analyzed using parametric techniques. Two-group comparisons were made using the *t*-test, whereas multiple-group comparisons were made using one-way analysis of variance (ANOVA). When appropriate, post hoc analyses were performed using the Tukey test. Behavioral assessment data that were not normally distributed were analyzed by the Mann–Whitney *U*-test and Kruskal–Wallis one-way ANOVA. When appropriate, post hoc analyses were performed using Dunn's test. All tests used a significance level of $p < .05$.

RESULTS

Effects of Prenatal Stress on Pup Weight and Litter Size

No significant difference in litter size was detected between experimental groups. The mean number of pups per group ± SEM was 8.1 ± .69 (control), 7.7 ± .54 (restraint stress), and 7.2 ± .63 (predator stress). Pups that were born to dams that were stressed during gestation had reduced weights compared with controls (ANOVA, $F_{(2)} = 10.47$, $p < .001$; Tukey, $p = .001$). The effect of restraint or predator stress on pup weight at various times is illustrated in Figure 1.

The difference in pup weight disappeared by P15, and, on average, the pups weighed 22.46 ± 1.36 g (mean ± SEM) at that time. On P1, the mean ± SEM weight (g) per group was 6.56 ± .19 (control), 5.46 ± .17 (restraint stressed), and 5.42 ± .22 (predator stressed).

Effects of Prenatal Stress on Corticosterone (COS) Blood Levels

The effects of gestational restraint or predator stress on blood COS levels were determined in two male pups from each litter in groups P2 and P6. Both restraint and predator stress significantly increased COS levels in pups at P2 and P6 ($p < .001$). Uneven elevation of COS levels between different stressed groups of P6 pups is an indicator of the type-dependent impact of prenatal stress on brain structure and function. The effects of gestational restraint or predator stress on COS blood levels are illustrated in Table 2.

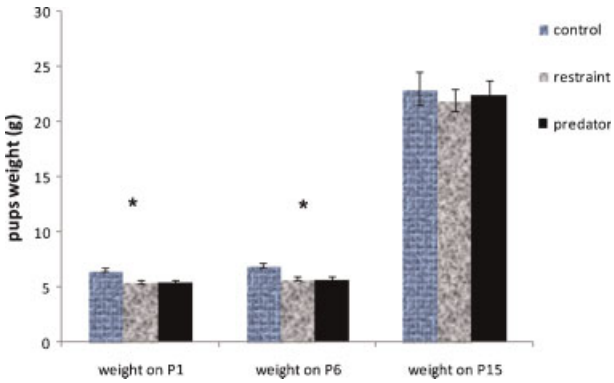

FIGURE 1 The effect of exposure to restraint or predator stress during gestation on offspring weight in different time points. Both stresses led to low birth weight, which disappeared by P15. The weight at birth was significantly lower in stressed animals compared with the control group ($p < .001$). [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/dev]

Table 2. Effect of Gestational Restraint or Predator Stress During the Third Week of Pregnancy on COS Blood Levels in Dam and Male Pup Rats (ng/ml)

Groups	E18	P2	P6
Control dams	4.18 ± .54, $F_{(2)} = 14.72$	3.55 ± .47, $F_{(2)} = 36.45$	1.26 ± .2, $F_{(2)} = 63.7$
Restraint-stressed dams	14.09 ± 1.8, $p < .001$	9.99 ± .51, $p < .001$	7.4 ± .35, $p < .001$
Predator-stressed dams	13.48 ± 1.64, *Tukey* $p < .001$	9.6 ± .77, *Tukey* $p < .001$	7.72 ± .63, *Tukey* $p < .001$
Control pups	Not available	.204 ± .059, $F_{(2)} = 277.98$	.068 ± .033, $F_{(2)} = 517.26$
Restraint-stressed pups		5.12 ± .25, $p < .001$	2.66 ± .043, $p < .001$
Predator-stressed pups		5.05 ± .13, *Tukey* $p < .001$	3.08 ± .11, *Tukey* $p = .002$

Note. There are significant differences between control group and all stressed animals. Moreover, there is a significant difference between restraint- and predator-stressed pups at P6.

Effects of Prenatal Stress on Pilocarpine-Induced Seizures

After subcutaneous administration of 150 mg/kg pilocarpine, all rats experienced comparable seizures, but the time to onset of the first epileptic behavior differed significantly between the control and stressed groups ($p = .01$). The first epileptic behavior was followed by myoclonic twitching, and frequent rearing and falling; and all rats experienced continuous tonic–clonic seizures, but at different times, as shown in Table 3. Concerning epileptic behavior, such as *duration of tonic–clonic seizure*, there was a significant difference ($p = .03$) between restraint- and predator-stressed groups (Figs. 2 and 3).

DISCUSSION

In this study, we subjected normal pregnant rats to acute restraint or predator stress. Thereafter, their male pups were examined for pilocarpine-induced epileptic behavior on P25. Notably, both prenatal acute stressors had proconvulsant effects on pilocarpine-induced seizure activity in pups. Blood COS levels increased significantly in both stressed dams and their pups (Tab. 2). Pups that were born to dams that were stressed during gestation weighed significantly less compared with controls (Fig. 1).

Our observation that acute restraint stress potentiates seizures in rats is consistent with studies that have demonstrated that acute stress is associated with proconvulsant effects on seizures that are induced by pilocarpine (Edwards et al., 2002; Sadaghiani & Saboory, 2010), pentylenetetrazol, and other GABAA receptor antagonists (Cremer et al., 2009; Suchecki & Palermo Neto, 1991).

The potentiation of seizures by prenatal stress has been reported and is presumably caused by an imbalance between the excitatory and inhibitory systems (Sadaghiani & Saboory, 2010). One determinant for stress-induced susceptibility to seizures relates to hippocampal plasticity. Stress attenuates the neurogenesis of dentate gyrus neurons, and long-lasting stress decreases the size and number of dendrites in the CA3 region (Pavlides, Nivon, & McEwen, 2002). A prominent physiological state of the hippocampus, the theta rhythm, often accompanies voluntary motor behavior output and is associated with resistance to seizure. Similarly, pharmacologically induced hippocampal theta activity correlates with behavioral arousal in freely

Table 3. Classification of Seizure Parameters in 25-Day-Old Male Rats Prenatally Exposed to Restraint or Predator Stress After Subcutaneous Administration of 150 mg/kg Pilocarpine

Epileptic Behavior	C	RS	PS	*p*-Value
Time to onset (min)	5.35 ± .75	3.21 ± .43	3.2 ± .24	$p = .01$, C vs. RS and PS
Number of tonic–clonic seizures	5 ± 1.2	8.2 ± 2.6	5.15 ± .6	$p = .03$, C vs. RS
Duration of tonic–clonic seizure(min)	.53 ± .1	1.29 ± .5	16 ± 3.8	$p = .03$, PS vs. C and RS
Number of immobility	3.45 ± .5	2.8 ± .5	2.33 ± .45	$p = .08$
Duration of immobility (min)	35.57 ± 12.6	37 ± 12.8	3.8 ± .3	$p = .02$, PS vs. C and RS
Number of head bobs	5.25 ± 1	4.9 ± 1.1	8.64 ± 1.78	$p = .002$, PS vs. C and RS
Duration of head bobbing (min)	.68 ± .08	1.05 ± .2	1.26 ± .2	$p = .04$, C vs. PS
Latency to tonic–clonic seizure	41.25 ± 3.24	22.4 ± 2.54	15.22 ± 1.88	$p = .037$, all groups
Number of rearing and falling	6.1 ± .87	15.64 ± 1.56	17.12 ± 1.84	$p = .001$, C vs. RS and PS
Duration of rearing and falling	.14 ± .03	.31 ± .08	.18 ± .04	$p = .35$

C, control; RS, restraint-stressed; PS, predator-stressed.

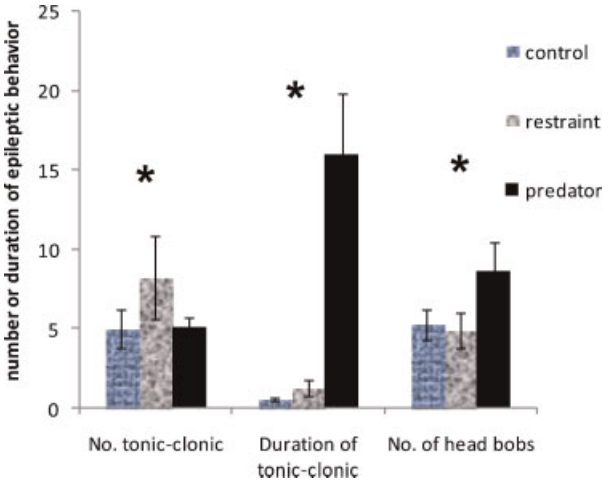

FIGURE 2 Effect of prenatal (restraint or predator) stress on pilocarpine-induced seizure in 25-day-old mal rats. All animals were injected with pilocarpine 150 mg/kg. *Epileptic behavior in one of the groups differed significantly from the other groups. The number of tonic–clonic seizures was higher in restraint-stressed than in control and predator stress animals ($p = .03$), but the duration of tonic–clonic seizures ($p = .03$) and number of head bobs ($p = .002$) were higher in predatory-stressed animals than in control and restraint-stressed rats. [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/dev]

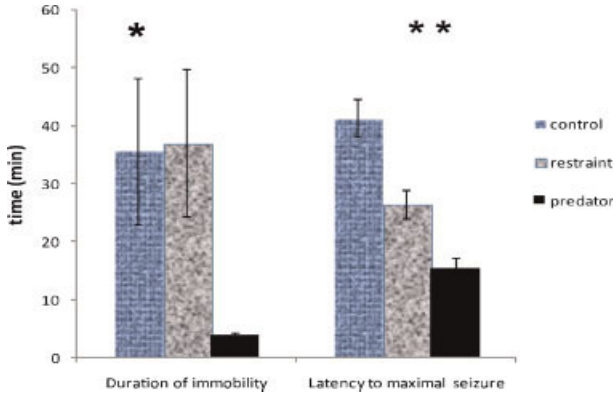

FIGURE 3 The effect of prenatal (restraint or predator) stress on pilocarpine-induced seizure in 25-day-old male rats. All animals were injected with pilocarpine 150 mg/kg. *Duration of immobility in the predator-stressed group differed significantly from the other groups ($p = .02$). **Latency *Latency to maximal (tonic–clonic) seizure differed significantly in all three groups ($p = .037$). [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/dev]

moving rats (Heinrichs, 2010). These results suggest that the arousal-like effects of a stressor modulate seizure-related behavioral output and the onset of seizures through a mechanism that involves electrophysiological activation of the hippocampus (Heinrichs, 2010; Sadaghiani & Saboory, 2010).

Our findings are consistent with these data. As illustrated in Figures 2 and 3, the duration of immobility and latency to maximal seizure decreases in predator-stressed animals compared with controls and restraint-stressed rats. Furthermore, the duration of tonic–clonic seizures and number of head bobs increased in predator-stressed animals compared with control and restraint-stressed rats. Alterations in hippocampal structure and function might constitute the underlying mechanism of rapid induction of seizures in stressed rats. Our current and previous findings demonstrate that prenatal restraint stress potentiates pilocarpine-induced seizures. However, this study indicates that predator stress affects epileptic seizures much more potently. As shown in Figures 2 and 3, latency to tonic–clonic seizure (maximal seizure) decreased markedly in predator-stressed animals compared with restraint-stressed rats, while duration of tonic–clonic seizures increased significantly in these subjects. The different mechanisms by which these two stressors act are unknown. It appears that psychosocial stress (predator stress) affects epileptic behaviors more severely than physical stress (restraint stress) in rats. No previous study has compared the impact of two kinds of stressors on seizures.

The chief pathway that coordinates the consequences of stress in most mammalian species is the HPA axis (Heshmatian et al., 2010; Sadaghiani & Saboory, 2010). Stressors that trigger seizures increase glucocorticoids levels, which, in turn, lower the threshold for seizure induction. Prenatal stress also alters feedback regulation of the HPA axis, effecting higher basal secretion of corticotropin releasing factor (CRF) and associated adrenal corticosteroid production in the offspring (Sadaghiani & Saboory, 2010; Viltart et al., 2006). CRF is a potent proconvulsant in pups, which lowers seizure threshold. Prenatal stress is reported to increase plasma COS levels from 100% to 800% (Sadaghiani & Saboory, 2010). Thus, it appears that seizure severity is in part a function of the sensitivity to the excitatory effects of glucocorticoids. Our findings are consistent with these data. As shown in Table 2, blood COS levels increased in both restraint- and predator-stressed groups compared with control rats. Therefore, the excitatory effect of prenatal stress on infant rats might reflect greater glucocorticoid production. Collectively, prenatal stress increases COS levels and alters neurotransmitter systems in the hippocampus, including the serotonergic, cholinergic, and noradrenergic systems (Sadaghiani & Saboory, 2010). These alterations could affect brain excitability and, hence, pilocarpine-induced seizures.

Furthermore, there is strong evidence that stress during gestation influences fetal growth; leads to low

birth weight (LBW); and produces long-term metabolic, behavioral, and neuroendocrine changes that are consistent with prenatal programming of adult biology and pathophysiology (O'Regan, Kenyon, Seckl, & Holmes, 2008, 2010). Harmful events during the fetal period can induce lifelong changes in various organs, predisposing one to the development of disease (Lesage et al., 2002). Similarly, individuals that are born with a LBW are insulin-resistant and experience increased rates of type 2 diabetes (Mairesse et al., 2007). The mechanisms of the changes that are associated with LBW are unknown.

Recently, fetal stress and high plasma levels of glucocorticoids have been suggested to cause HPA axis hyperactivity, which may result in chronically excessive adrenal glucocorticoids secretion and an increased risk for abnormal neuronal plasticity, susceptibility to seizures and LBW (Mairesse et al., 2007; Sadaghiani & Saboory, 2010). Collectively, these findings indicate that maternal stress ''signals'' the developing fetus to adjust multiple facets of its development to alter the adult phenotype. These changes broadly parallel the human phenotype that is associated with LBW populations (Barker, 2004). It has been postulated that the origin of such altered developmental plasticity is the in utero exposure to glucocorticoids, which increase during maternal chronic stress (Mairesse et al., 2007). Our findings are consistent with these data. As outlined in Figure 1, a significant reduction in birth weight was present in pups born to dams that were stressed during gestation, as compared with controls. Also, blood COS levels, as shown in Table 2, were significantly higher in stressed animals. Therefore, we conclude that elevated blood COS levels may lead to growth retardation and LBW.

Another mechanism that may explain our findings is that the maternal behavior of stressed dams impacts pups during juvenile development. The quality of parent–child relationships in humans predicts vulnerability to psychopathology in adulthood, an effect that might be mediated by the influence of parental care on the development of individual differences in stress responses (Bagot et al., 2009). In rats, variations in maternal care directly influence the development of corticolimbic systems that regulate endocrine and emotional responses to stress (Champagne & Meaney, 2006). Bagot et al. (2009) reported that a morphological analysis of dentate gyrus neurons revealed greater dendritic arborization in adult offspring of high- versus low-licking/grooming (LG) mothers. Although total dendritic length did not differ, the dendrites of high- versus low-LG rats had significantly more branching points. Moreover, the dendritic complexity index was greater in high-LG rats. Dendrites of high-LG rats also had significantly more spines versus low-LG rats (Bagot et al., 2009). Therefore, we conclude that prenatal stress influences maternal care, leading to changes in neuronal plasticity of the hippocampus, which potentiates pilocarpine-induced seizures in stressed pups.

In conclusion, our data highlights the impact of prenatal stress on fetal endocrine and neural function. Besides HPA axis alteration, prenatally stressed pups exhibit increased susceptibility to pilocarpine-induced epileptic behavior. Moreover, stressed pups have LBW, which disappears by P15. Possible mechanisms of this altered neonatal phenotype include (1) diminished maternal food intake and weight gain, (2) increased maternal gestational COS levels during restraint and predator stresses, (3) increased fetal COS levels after exposure to stress, lasting at least until P6 (in this study), and (4) altered maternal care, which can alter subsequent responses to stress.

Because the action of glucocorticoids on homeostasis is widespread, affecting most body compartments as well as the brain, we speculate that acute stress in mothers generates a deleterious environment for fetal development. The early-altered phenotype in this study might subsequently be the origin of the adult pathophysiology that is programmed in prenatally stressed offspring.

NOTES

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