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Prenatal stress differentially affects habituation of corticosterone responses to repeated stress in adult male and female rats

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Abstract

Environmental factors operating early in life have long-lasting and important consequences for the mental and physical health of the adult organism. In particular, prenatal exposure to stress represents one category of adverse early environmental events that are associated with development of depression and schizophrenia in adulthood. In the present studies, we examined whether prenatal stress alters the habituation of hypothalamic–pituitary–adrenal (HPA) activity that occurs with repeated stress exposure in adulthood. We compared corticosterone responses to the first vs. the eighth restraint, with lower responses to the eighth vs. the first considered evidence of habituation. In males, prenatal stress prevented the habituation of corticosterone responses to repeated restraint that was observed in non-prenatally stressed rats. Limited evidence of habituation was seen in either group of females and prenatally stressed females did not exhibit the enhanced corticosterone response during recovery from the eighth restraint that was seen in non-prenatally stressed females. Together, these results suggest a sex-specific interaction between prenatal stress and adult chronic stress on HPA activity.

Keywords: Chronic stress; Hypothalamic–pituitary–adrenal; Restraint; Early environment; Sex differences

Introduction

Considerable evidence suggests that environmental factors operating early in life have long-lasting and important consequences for the mental and physical health of the adult organism. Early environmental events that are adverse may render an individual more vulnerable to illness later in life (Kessler, 1997). In particular, prenatal exposure to stress represents one category of adverse early environmental events that are associated with development of depression and schizophrenia in adulthood (Kessler, 1997; Koenig et al., 2002; Quenstedt and Parshall, 1998). Various animal models of prenatal stress have been developed over the years. Adult animals that have been prenatally stressed exhibit many characteristics similar to those in humans with depression. These include dysregulation of the stress-responsive hypothalamic–pituitary–adrenal (HPA) axis, anhedonic and anxiogenic behaviors, and alterations in circadian rhythms (e.g., Carroll et al., 1976; Mortola et al., 1987). Together, results from animal studies suggest that stress during late gestation affects fetal development which may lead to increased propensity to develop depression and schizophrenia in adulthood (Weinstock, 1997). Therefore, prenatal stress may represent a relevant animal model for the study of vulnerability to develop psychiatric illness related to exposure to adverse early environmental events.

There is strong evidence that episodes of schizophrenia and depression in adults can be precipitated or exacerbated by life stressors occurring in adulthood (Kessler, 1997; Post, 1992) such as physical abuse, low socioeconomic status, and lack of social support. Some evidence from animal models indicates that adverse early life events interact with chronic stress in adulthood to alter physiology and behavior (Bhatnagar and Meaney, 1995). However, little is known about changes in behavior and physiology of prenatally stressed animals when they are exposed to chronic stress in adulthood.

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Chronically stressed animals often exhibit decreased HPA responses to repeated exposure to the same or homotypic stressor. This decrement, termed habituation, has previously been shown with repeated exposure to restraint (Hauger et al., 1990; Cole et al., 2000; Viau and Sawchenko, 2002) as well as cold (Bhatnagar and Meaney, 1995), noise (Armario et al., 1986), water immersion (De Boer et al., 1990), immobilization (Garcia et al., 2000; Giralt and Armario, 1989), repeated ethanol injections (Spencer and McEwen, 1990), and repeated handling (Dobrakovova et al., 1993). In the present studies, we examined the effect of prenatal stress on HPA responses to repeated restraint in adult male and female rats. Smythe et al. (1996) have suggested that one of the primary effects of prenatal stress is to increase sensitivity to other manipulations, such as chronic stress. Little is known about the effects of prenatal stress on HPA responses to chronic stress in adulthood. We expected that prenatally stressed males and females would demonstrate disruptions in HPA responses to chronic restraint compared to chronically stressed rats that have not been prenatally stressed.

In addition, we monitored body weight gain from post-weaning to the onset of stress as an index of general growth and development. Since we administered prenatal stress during the third trimester, our discussion of other studies is limited to those that also administered stress during the third trimester, unless otherwise noted.

Materials and methods

General housing conditions

All rats were Sprague–Dawley rats and were housed in plastic tub cages. Rats were allowed ad lib access to food and water and maintained on a 12:12-h light–dark schedule (lights on at 07:00 h) and ambient temperature maintained at 21 ± 1°C. All experiments were approved by the University Committee on Care and Use of Animals at the University of Michigan.

Prenatal stress

Young adult female rats (n = 7) were purchased from Harlan Sprague–Dawley (Indianapolis, IN). They were housed with males and monitored twice daily for presence of vaginal plugs. The day that vaginal plugs were detected was considered day 0 of pregnancy and the females were then separated and individually housed. Some pregnant female rats (n = 4) were randomly assigned to the stress group and exposed to stress in the third trimester (days 15–21 of gestation). Stress consisted of placing the females in a Plexiglas restrainer for 45 min three times per day, beginning at 9 a.m., 12 p.m., and 4 p.m. The other pregnant females were assigned to the no stress, control group and these females were only exposed to weekly cage changes as were the stressed females. All litters were born within 12 days of one another. Litter sizes ranged from 8 to 14 at birth and litters were not culled. After birth, the female and her litters were undisturbed, except for cage changes until day 21. On this day, pups were weaned from their mothers and housed in same sex groups. Pups were tail marked and body weights were recorded at regular intervals. One week prior to onset of repeated restraint in adulthood, male and female rats were singly housed in plastic tub cages. Daily vaginal smears were conducted on the female rats starting 1 month prior to the onset of repeated restraint to determine stage of estrous cyclicity at the time of blood sampling for hormone responses to acute or repeated stress.

Adult stress paradigm

Adult offspring from each litter were randomly assigned to one of two groups, acute restraint or repeated restraint. At approximately 85 days of age, some male prenatally stressed (PS) and non-prenatally stressed (NPS) rats were exposed to 7 days of repeated restraint and blood was sampled for corticosterone on days 1 and 8 (described further below). Other male PS and NPS rats were exposed to a single acute restraint only and also sampled as described below. PS and NPS females were similarly exposed to repeated or acute restraint but starting at approximately day 105 of age. Acute stress only groups were included to assess effects of acute stress on other measures not reported here.

Adult male and female NPS and PS rats were repeatedly stressed by placing them in a Plexiglas restrainer for 30 min a day (between 09:00 and 10:00) for 8 consecutive days. HPA activity habituates to repeated restraint exposure during this period (Bhatnagar et al., 2002a). On days 1 and 8, blood was collected via nicking of the tail vein within 60 s following placement in a Plexiglas restrainer. This is a standard procedure for collecting blood allowing for repeated sampling without the necessity of surgical implantation of indwelling catheters and provides consistent results (Akana et al., 1996; Bhatnagar et al., 2002a,b). Corticosterone levels in blood are not affected by placement in the restrainer if samples are collected within 60 s. On day 1, all animals were placed in a Plexiglas restrainer and a blood sample taken immediately from the tail vein (the 0-min sample), and also at 15 and 30 min during restraint. After collection of the 30-min sample, the animals were re-placed in their home cages. 30 min later (60 min after onset of 30 min restraint), samples were taken again from the tail vein by placement in a restrainer and the animals returned to their home cages. All blood samples were collected within 60 s of opening of the cage to remove the rat. The next day, day 2, animals were exposed to 30 min restraint, but not sampled. They were subsequently exposed to restraint every day until day 8 without being sampled. On day 8, rats were sampled as on day 1.

Plasma testosterone was also measured on days 1 and 8 of repeated restraint in NPS and PS male rats. After plasma was used for analysis of corticosterone, the leftover plasma