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# Prenatal stress increases HPA axis activity and impairs maternal care in lactating female offspring: Implications for postpartum mood disorder

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## Summary

Early life stress is believed to constitute a risk factor for the development of mood disorders later in life. In the present study, we hypothesized that prenatal stress (PS) exerts long-lasting effects in female rat offspring, resulting in impaired adaptations to stress during lactation and, as such, may be a contributory factor to postpartum mood disorders. PS increased anxiety in adult virgin females compared with controls. During lactation, PS dams nursed significantly less and spent less time with pups compared with controls, whereas dams did not differ in pup retrieval or maternal aggression. HPA axis reactivity was elevated in response to a mild stressor in PS dams compared to their controls, but not in virgins, with the delta corticosterone response returning to the higher level seen in virgins. Moreover, corticotropin-releasing hormone (CRH) mRNA expression within the parvocellular region of the paraventricular nucleus (PVN) was increased in both virgins and dams exposed to PS compared with the relative controls, while the attenuation in expression in lactating controls was abolished following PS. In addition, arginine vasopressin (AVP) mRNA was increased in the parvocellular, but not magnocellular part of the PVN, in both PS-exposed virgins and lactating dams compared with their relative controls; although expression was also higher in controls during lactation compared with virgins. Thus, the present study demonstrates that exposure to PS results in long-lasting behavioural and neuroendocrine alterations in the female offspring, which are manifested during the lactation period. Furthermore, it implicates PS as a potential risk factor for the development of postpartum mood disorders, and that alterations in the HPA axis reactivity, at least partially, are involved.

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## 1. Introduction

Stress during pregnancy and in the peripartum period has been demonstrated to increase the risk of mood disorders in the offspring later in life (O'Hara and Swain, 1996; Kofman, 2002). Importantly, physiological responses to stress exposure in late pregnancy and lactation are significantly attenuated, as seen both in human and animal studies (Stern et al., 1973; Neumann et al., 1998; Russell et al., 1999; Lightman et al., 2001; Kammerer et al., 2002; De Weerth and Buitelaar, 2005). These adaptations are believed to be necessary to protect the fetus from exposure to excessive levels of glucocorticoids (Welberg and Seckl, 2001). Further, gonadal steroids are important regulators of the HPA axis and the corticotropin-releasing hormone (CRH) system (Kirschbaum et al., 1999; Young et al., 2001). Therefore, the attenuation in stress-related brain circuitries may also be important for the well-being of the mother, providing a protective mechanism against the dramatic fluctuations in circulating sex steroids. Correspondingly, general suppression of HPA axis activity during lactation has been hypothesized to prevent the development of depression in vulnerable women (Carter et al., 2001). Accordingly, disruption of such normal adaptations is a likely contributory factor in the development of postpartum affective disorders (Zonana and Gorman, 2005).

The postpartum period is a time of increased vulnerability to mood disorders, with 20–30% of women experiencing mood disorders within the first 6 weeks postpartum (O'Hara and Swain, 1996; Llewellyn et al., 1997; Pedersen, 1999; Mastorakos and Ilias, 2000). A number of animal studies have demonstrated that chronic stress during pregnancy can affect maternal behaviour (Pardon et al., 2000; Meek et al., 2001; Patin et al., 2002; Bosch et al., 2006) and increase anxiety in the dam (Maestriperi et al., 1991; Darnaudery et al., 2004). Furthermore, attenuation of the stress responsiveness of the HPA axis can be partially prevented by pregnancy stress; an effect which was dependent on the genetically determined level of anxiety (Neumann et al., 2005). However, due to the lack of knowledge, both from a clinical and preclinical standpoint, the neurobiological mechanisms underlying postpartum mood disorders, including postpartum depression, remain largely unknown.

Adverse effects of early life stress on adult neuroendocrine parameters and stress coping are well documented both in virgin female and male offspring (Suchecki and Palermo Neto, 1991; Weinstock et al., 1992; Neumann et al., 1998, 2005; Levine, 2001; Welberg and Seckl, 2001; Pedersen and Boccia, 2002; Bosch et al., 2006). For example, CRH and arginine vasopressin (AVP) expression were found to be altered after exposure to prenatal stress (PS; Bosch et al., 2006). These two neuropeptides are well documented to be involved in stress coping and to undergo adaptations during pregnancy and lactation (for review see Neumann, 2003). One study has shown that exposure to early life stress (7d intermittent stress during gestation) in rats characterized as high licking/groomers, reduced not only this behaviour but also brain oxytocin receptor expression to the level of those characterized as low licking/groomers (Champagne and Meaney, 2006). Despite this, a possible link to peripartum mood disorders in adult life of female offspring has not been demonstrated to date.

We hypothesized that PS exerts long-lasting effects in female offspring, resulting in impaired adaptations to stress during lactation and as such, may be a contributory factor to postpartum mood disorders.

In order to study this hypothesis, prenatally stressed, adult female rats were mated and tested for their maternal behaviour early in lactation. Moreover, plasma ACTH and corticosterone levels were monitored in order to assess the responsiveness of the HPA axis to an acute stressor. Finally, the activity of CRH and AVP were monitored by quantification of their respective mRNA expressions in the hypothalamic paraventricular nucleus (PVN).

## 2. Methods

### 2.1. Animals

All experiments were carried out in accordance with the Guide for the Care and Use of Laboratory Animals of the Government of Bavaria and the guidelines of the National Institute of Health. All efforts were made to minimize animal suffering and to reduce the number of animals used.

Adult, virgin female Wistar rats purchased from Charles River (Germany; 250–300 g body weight) were mated overnight in groups of three with a sexually experienced male. Pregnancy was confirmed by the presence of semen in vaginal smears the following morning (day 1 of pregnancy). Pregnant rats were exposed daily to a psychosocial stressor or remained unstressed and housed in groups of two to three rats of the same treatment group under standard laboratory conditions (12:12 light–dark cycle, lights on at 0600 h, 22 °C, 55% humidity and free access to water and standard rat chow) and were housed singly from day 20 of gestation until weaning of PS or control female offspring at the age of 22 days.

Female offspring, after weaning, were housed in groups of 3–4 of the same treatment under standard laboratory conditions as defined above.

### 2.2. Pregnancy stress

Between days 4 and 10 of pregnancy, half of the pregnant rats ( $n = 7$ ) were exposed to a psychosocial and restraint stressor daily. The former involved the introduction of the pregnant dams as intruders into a lactating resident dam in its home cage for 45 min (Neumann et al., 2001) whereas the latter comprised of 60 min restraint stress (plexiglas column with ventilation holes; 12 cm diameter; Glavin et al., 1994). The stressors were alternated daily, with one exposure between 0900 h and 1200 h and the other between 1400 h and 1700 h in order to decrease the predictability of the stressor (Anisman and Matheson, 2005). Between days 11 and 18 of pregnancy, dams were only exposed to 60 min daily maternal defeat because of significant weight gain of the pregnant rats. This procedure has been successfully used before (Bosch et al., 2006). Pregnant control rats ( $n = 8$ ) were left undisturbed (change of bedding once a week). Control and pregnancy-stressed rat dams gave birth to  $14.3 \pm 0.5$  and  $12.7 \pm 1.3$  pups, respectively. The litter sizes were adjusted to 8 pups. The day of birth was considered day 0.

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