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Effects of early life social stress on maternal behavior and neuroendocrinology

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Summary Maternal mood disorders such as depression and chronic anxiety can negatively affect the lives of both mothers and their adult offspring. An active focus of maternal depression and anxiety research has been the role of chronic social stress in the development of these disorders. Chronic exposure to social stress is common in humans, especially in lactating mothers, and postpartum mood disorders have been correlated with high levels of social conflict and low levels of social support. Recent studies have described an effective and ethologically relevant chronic social stress (CSS) based rodent model for postpartum depression and anxiety. Since CSS attenuates maternal behavior and impairs both dam and offspring growth, it was hypothesized that CSS is an ethologically relevant form of early life stress for the developing female offspring and may have effects on subsequent adult maternal behavior and neuroendocrinology. Dams exposed to early life CSS as infants display substantial increases in pup retrieval and nursing behavior that are specifically associated with attenuated oxytocin, prolactin, and vasopressin gene expression in brain nuclei involved in the control of maternal behavior. Since the growth patterns of both groups were similar despite substantial increases in nursing duration, the early life CSS dams exhibited an attenuated nursing efficiency. It is concluded that early life CSS has long term effects on the neuroendocrinology of maternal care (oxytocin and prolactin) which results in decreased nursing efficiency in the adult dams. The data support the use of early life CSS as an effective model for stress-induced impairments in nursing, such as those associated with postpartum depression and anxiety.

1. Introduction

Exposure to stress is a known predictor of mood disorders, including postpartum depression (Heim et al., 1997; Hammen, 2005; Ross and Dennis, 2009; Murgatroyd et al., 2010). Despite evidence that depression in the mother has negative effects on both parenting (Lovejoy et al., 2000) and psychological development of the offspring (Goodman, 2007), little

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is known about the effects of postpartum depression as an early life stress on adult behavior. Recent rodent studies have been focusing on the use of ethologically relevant stressors, such as chronic social stress (CSS), in the study of the effects of stress on mood disorders (Herzog et al., 2009; Brunton and Russell, 2010; Nephew and Bridges, 2011). It is postulated that CSS may be a relevant and effective form of early life stress to study the transgenerational effects of mood disorders on the offspring.

Chronic social stress (CSS) during lactation can affect maternal behavior and growth of the dam and offspring. The daily presentation of a novel male intruder during lactation decreases maternal care, increases maternal aggression, and inhibits growth in both the dam and her offspring (Nephew and Bridges, 2011). These effects indicate that CSS is an ethologically relevant model for mood disorders that involve impairments in maternal care and attenuated offspring growth, such as postpartum depression. Both the maternal care and offspring growth data suggest that CSS may have enduring effects on the offspring, and research on the effects of chronic stress on maternal behavior support the hypothesis that the effects of chronic stress on maternal behavior are hormonally mediated.

Several neurohormones have been implicated in the etiology of stress-related mood disorders and/or the control of maternal behavior in both rodents and humans, including oxytocin (OXT), prolactin (PRL), arginine vasopressin (AVP), and corticosteroid releasing hormone (CRH). OXT mediates both maternal care (Pedersen and Prange Jr. 1979; Pedersen et al., 1982; Champagne et al., 2001; Pedersen and Boccia, 2003) and maternal aggression (Giovenardi et al., 1998; Elliot et al., 2001; Bosch et al., 2004, 2005; Nephew et al., 2009; Bosch and Neumann, 2011) in rodents. In humans, plasma OXT during pregnancy is negatively associated with postpartum depression, as low plasma OXT suggests an increased risk for PPD (Skrundz et al., 2011). Increased levels of OXT are associated with increased maternal attachment, and serum OXT in mothers with securely attached children is higher during mother–child interactions when compared to insecure mothers (Strathearn et al., 2009). Children raised by their biological parents have higher OXT levels compared to those that were exposed to early neglect (Fries et al., 2005), suggesting that early experience affects the development of central social behavior mechanisms. Several reports have also implicated PRL in the control of rodent maternal behavior (Bridges et al., 1990; Bridges and Ronsheim, 1990; Bridges and Mann, 1994; Bridges et al., 2001), and low plasma levels of PRL are associated with postpartum depression in humans (Abou-Saleh et al., 1998). Central AVP mediates rodent maternal care (Bosch and Neumann, 2008; Nephew and Bridges, 2008a,b) and maternal aggression (Nephew and Bridges, 2008a,b; Gutzler et al., 2010; Nephew et al., 2010), and is elevated in humans suffering from depression and animal models of depression (Goekoop et al., 2006; Surget and Belzung, 2008; Rotzinger et al., 2010). Studies in male mice have identified an epigenetic mechanism for the effects of early life stress on central vasopressin and behavioral alterations associated with depression (Murgatroyd et al., 2009). Corticosteroid releasing hormone (CRH), which increases in response to stress, inhibits maternal care in rats (Pedersen et al., 1991) and primates (Saltzman et al., 2011) and suppresses maternal aggression in mice (Gammie et al., 2004). It has also been a primary target for the development of treatments for stress-induced mood disorders (Heim et al., 1997).

The current investigation compares the maternal behavior and neuroendocrinology of adult female offspring of dams exposed to CSS during infancy to the adult offspring of control dams. Similar studies focusing on the exposure of male rodents to early maternal separation have reported significant depression-associated behavioral and neuroendocrine effects that are mediated by epigenetic mechanisms (Murgatroyd et al., 2009; Der-Avakian and Markou, 2010). Since the pups are left in the cage during the CSS protocol and there were significant effects on dam growth and behavior and offspring growth (Nephew and Bridges, 2011), it was hypothesized that CSS is an ethologically relevant form of early life stress for the female offspring and may have long term effects on subsequent adult maternal behavior and central OXT, PRL, AVP and/or CRH mRNA expression.

2. Methods

2.1. Animals

Animals in this study were maintained in accordance with the guidelines of the Committee of the Care and Use of Laboratory Animals Resources, National Research Council, and the research protocol was approved by the Tufts Institutional Animal Care and Use Committee.

The mothers of the Sprague Dawley rat dams in the current study (Charles River, Wilmington, MA) were subjected to a chronic social stress protocol from days 2 to 16 of lactation as reported in Nephew and Bridges (2011). This procedure consisted of placing a similarly sized (220–300 g) novel male intruder into a lactating female's home cage for one hour from day 2 to 16 of lactation. The pups were left in the cage during the intruder presentation, and the CSS exposure resulted in decreased maternal care and growth of the both the dam and her pups, and increased maternal aggression (Nephew and Bridges, 2011). ''CSS dams'' refers to the adult females exposed to chronic social stress during lactation, and ''early life CCS dams'' refers to the adult female offspring of the CSS dams from Nephew and Bridges (2011) were exposed to CSS when they were 2–16 days old; the focus of the present study.

Three females from eight control and eight chronic social stress dams were housed in groups of three until 70 days of age when they were mated (24 females each for the control and early life CSS groups). Mating consisted of placing a male in each cage for eight days. Three of the control females and five of the early life CSS females failed to give birth. One stressed dam died during parturition, and another early life CSS dam failed to nurse. Two animals from each group did not give birth in time to be included in the study. The final sample sizes were 18 for the control group and 16 for the stressed group. Total pup number and litter weights were recorded on the day of parturition, and litters were then culled to four females and four males. Brains were extracted from the dams on day 21 of lactation, frozen at −80 C and then micropunched to obtain samples of the paraventricular nucleus (PVN), supraoptic nucleus (SON), lateral septum (LS), central amygdala (CeA), and medial amygdala (MeA) for PCR analysis of relative mRNA levels.