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Transgenerational effects of social stress on social behavior, corticosterone, oxytocin, and prolactin in rats

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ABSTRACT

Social stressors such as depressed maternal care and family conflict are robust challenges which can have long-term physiological and behavioral effects on offspring and future generations. The current study investigates the transgenerational effects of an ethologically relevant chronic social stress on the behavior and endocrinology of juvenile and adult rats. Exposure to chronic social stress during lactation impairs maternal care in F0 lactating dams and the maternal care of the F1 offspring of those stressed F0 dams. The overall hypothesis was that the male and female F2 offspring of stressed F1 dams would display decreased social behavior as both juveniles and adults and that these behavioral effects would be accompanied by changes in plasma corticosterone, prolactin, and oxytocin. Both the female and male F2 offspring of dams exposed to chronic social stress displayed decreased social behavior as juveniles and adults, and these behavioral effects were accompanied by decreases in basal concentrations of corticosterone in both sexes, as well as elevated juvenile oxytocin and decreased adult prolactin in the female offspring. The data support the conclusion that social stress has transgenerational effects on the social behavior of the female and male offspring which are mediated by changes in the hypothalamic–pituitary–adrenal axis and hypothalamic–pituitary–gonadal axis. Social stress models are valuable resources in the study of the transgenerational effects of stress on the behavioral endocrinology of disorders such as depression, anxiety, autism, and other disorders involving disrupted social behavior.

Introduction

Social stressors such as impaired maternal care and family conflict are robust challenges which can have long-term physiological and behavioral effects on the offspring. Disruptions in social behavior are particularly common in children exposed to maternal depression and/or family conflict (Davalos et al., 2012; Goodman, 2007; Hay et al., 2008; Josefsson and Sydsjo, 2007; Moehler et al., 2007; Verbeek et al., 2012). Furthermore, prior exposure to life stress confers susceptibility to stress-related psychopathologies including postpartum depression (Heim and Binder, 2011; Heim and Nemeroff, 2001). The current study investigated the transgenerational effects of an ethologically relevant social stress on the social behavior and endocrinology of juvenile and adult rats.

In the present model of chronic social stress (CSS), lactating dams (F0 generation) are exposed to intruder male rats for 1 hour daily. F0 dams receiving CSS exhibit deficits in the duration of pup grooming and nursing and increased maternal aggression (Nephew and Bridges, 2011), and thus the female offspring (F1 generation) receive both direct (through decreased maternal care) and indirect (through exposure to aggressive conflict between the dam and intruder males) early life stress. Adult F1 dams exposed to early life CSS also display decreases in maternal care (reduced pup grooming and nursing), impaired lactation through decreased milk intake by the pups, decreased saccharine intake (a measure of anhedonia), decreased maternal aggression, and increased restlessness/anxiety through increases in non-maternal care behaviors such as nesting, self grooming, and activity. On day 2 of lactation, F1 dams exposed to early life CSS exhibit a 60% decrease in the duration of maternal care that is driven by a 79% decrease in nursing and a 60% increase in non-maternal care behaviors. These behavioral effects are associated with decreases in hypothalamic oxytocin (OXT), vasopressin (AVP), and prolactin (PRL) gene expression (Murgatroyd and Nephew, 2013) as well as decreases in basal plasma concentrations of estradiol and prolactin and increased corticosterone during lactation (Carini and Nephew, 2013). Additional developmental elements of the model include the effects of potential hormonal changes in the F0 dams on developing F1 offspring and germ line exposure of the F2 generation during early life stress exposure in the F1 animals. Both the F0 and F1 dams represent ethologically relevant models of postpartum depression and anxiety, and the current study investigated the transgenerational effects of CSS on the F2 generation. In addition to assessing ethologically relevant changes in social behavior to compare

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with previous studies using maternal care as a measure of anhedonia, saccharin preference was included as a standard abstract measure of anhedonia. Based on previous studies on the transgenerational impact of differences in maternal care and related data from the F1 dams, it was hypothesized that the F2 male and female offspring of CSS dams would exhibit decreases in social behavior which would be accompanied by decreased basal concentrations of plasma corticosterone, oxytocin and prolactin.

Several studies have concluded that the hypothalamic–pituitary–adrenal (HPA) axis plays a central role in mediating the behavioral and physiological effects of early life stress in both animals (Bosch et al., 2007; Catalani et al., 2011; Murgatroyd and Spengler, 2011; Veenema, 2009) and humans (Essex et al., 2002, 2011; Francis et al., 1999; Meaney and Szyf, 2005; Tu et al., 2007). Children exposed to the early life stress of maternal depression exhibit disturbances in HPA activity which may include stressor specific changes in the pattern of basal plasma cortisol (Essex et al., 2002, 2011). Previous studies of the CSS model have reported elevated basal corticosterone levels in the CSS F1 females as nulliparous adults and dams (Carini and Nephew, 2013), which parallels data in adolescents exposed to both maternal depression and family anger (Essex et al., 2011), as the F1 females are exposed to decreased maternal care and the conflict between the dam and the novel male intruder. Several studies in rodents have observed decreased basal corticosterone in adult offspring of dams administered exogenous corticosterone in drinking water (see Catalani et al., 2011 for review). It has been suggested that the level of corticosterone exhibited in these lactating dams is similar to corticosterone levels after maternal stressors (Catalani et al., 2011). It was hypothesized that CSS F2 offspring would have lower basal corticosterone, similar to adolescents exposed primarily to maternal depression during early life and the adult offspring of dams treated with corticosterone during lactation (Catalani et al., 2011; Essex et al., 2011).

The importance of OXT as a mediator of social behavior is well known (Feldman, 2012; Nephew, 2012; Veenema, 2012; Young et al., 2008), and previous data indicate that OXT is a potential mediator of the adverse effects of early life CSS on maternal behavior in lactating dams and their adult offspring (Murgatroyd and Nephew, 2013). While there are numerous reports in animals and humans which indicate that impairments in social behavior are associated with a decrease in OXT (Feldman, 2012; Nephew, 2012), recent clinical work suggests that both high and low levels of OXT can indicate a disruption in typical social interaction, depending on gender and social context (Miller et al., 2013; Parker et al., 2010). The effects of OXT on social behavior can be transgenerational (Champagne, 2008; Curley et al., 2012), which is specifically relevant to the current study of the social behavior of the F2 offspring of socially stressed dams. Based on the decreased hypothalamic OXT gene expression in the F1 generation (Murgatroyd and Nephew, 2013), it was hypothesized that the F2 offspring of CSS dams would have decreased plasma concentrations of OXT.

Prolactin is a key mediator of both mammalian lactation (Freeman et al., 2000; McNeilly et al., 1983; Powe et al., 2010) and maternal care (Bridges, 1994; Bridges et al., 1997; Grattan, 2002; Grattan et al., 2001), although less is known about its role in non-maternal social behavior. PRL also has inhibitory actions on HPA activity following stress exposure which may be related to its role in maternal care (Torner and Neumann, 2002). Study of early life CSS exposed females indicates that plasma PRL concentrations are decreased in both juvenile and maternal early life CSS exposed females, and in maternal dams this decrease in peripheral PRL is associated with impaired maternal care and lactation and decreased expression of the long form of the PRL receptor in the PVN (Carini and Nephew, 2013; Murgatroyd and Nephew, 2013). Since many endocrine mediators of maternal care are also known to affect other forms of social behavior, it was hypothesized that the female F2 offspring would exhibit lower levels of social behavior accompanied by decreased plasma PRL.

The current study investigated the social behavior of the male and female F2 offspring of dams exposed to early life stress as both juveniles and adults and whether these behaviors would be accompanied by changes in plasma corticosterone, PRL, and OXT. The current investigation extends the transgenerational value and application of the CSS model of postpartum mood disorders to early life stress associated disorders in both males and females such as depression, anxiety, and autism. The overall hypothesis was that the male and female F2 offspring of social stressed dams would display decreased social behavior as both juveniles and adults and that these behavioral effects would be accompanied by changes in plasma corticosterone, PRL, and OXT.

Methods

Animals

Sprague-Dawley rats (Charles River Inc., Kingston, NY) 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. “CSS dams” refers to the adult females exposed to chronic social stress during lactation (F0), “early life CCS F1 dams” refers to the adult female offspring of the CSS dams, and their F2 offspring are the focus of the present study.

CSS model: Creation of F0 dams

The CSS dams were subjected to a chronic social stress protocol from days 2 to 16 of lactation as reported (Carini et al., 2013; 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 1 hour from days 2 to 16 of lactation. Control dams were not exposed to the CSS protocol; they were only tested for maternal care and maternal aggression on days 2, 9, and 16 of lactation. The pups are left in the cage during the intruder presentation, and the CSS exposure results in reduced maternal care (pup grooming and nursing) and increased anxiety-related behavior and maternal aggression (Nephew and Bridges, 2011).

Early life CSS: Creation of F1 females and their F2 offspring

The control and early life CSS F1 females were the offspring of the F0 control and CSS dams; the differences between the treatments of the control and early life CSS F1 females were limited to the exposure of the early life CSS F1 females to attenuated maternal care and conflict between their F0 mothers and the male intruders during age 2 to 16 days. The F1 control and early life CSS animals were treated identically after the age of 16 days. After weaning all F1 pups on day 23, the female offspring from the twelve control and twelve CSS dams were housed in groups of four until 70 days of age when two from each litter were mated with 6 proven breeder males (24 F1 females for the control and early life CSS groups). Successful mating was determined by body weight gain. Behavioral and endocrine data from those F1 females have been previously reported (Carini and Nephew, 2013). Total F2 pup number and litter weights were recorded on the day of parturition, and litters were then culled to four females and four males. The F2 control and early life CSS animals were treated identically throughout the study; the only difference between the two groups was the attenuated maternal care (including deficits in pup grooming, nursing, and milk intake by pups) and increased restlessness and anxiety-related behavior (nesting, self-grooming, locomotor activity) expressed by the early life CSS F1 dams towards their F2 offspring. In addition, the F2 animals were exposed to the decreased prolactin and increased corticosterone levels of their F1 mothers during lactation (Carini and Nephew, 2013). The early life stress behavioral experience of the F1 generation included decreased maternal care from the F0 dams and the conflict between the