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Intergenerational accumulation of impairments in maternal behavior following postnatal social stress

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ABSTRACT

Early adversity such as depressed maternal care can have long-term physiological and behavioral effects on offspring and future generations. Exposure to chronic social stress (CSS), an ethologically model of postpartum depression and anxiety, during lactation impairs maternal care and exerts similar effects on the F1 dam offspring of the stressed F0 dams. These changes associate with increased corticosterone and neuroendocrine alterations. CSS F2 offspring further display decreased social behavior as juveniles and adults and decreased basal levels of corticosterone. This current study investigates the intergenerational inheritance of alterations in maternal behavior in F2 CSS dams together with neuroendocrine and immune markers to explore whether aspects of maternal behavior are intergenerationally inherited through immune and neuroendocrine mechanisms. We find that defects in maternal care behavior persist into the F2 generation with F2 dams exhibiting a pervasively depressed maternal care and increased restlessness throughout lactation. This occurs together with reduced basal cortisol (in contrast to an increase in F1 dams), a lack of changes in neuroendocrine gene expression, and reduced serum ICAM-1 (intercellular adhesion molecule-1) levels - a marker for inflammation and blood–brain barrier integrity. The data support the hypothesis that the effects of chronic social stress can accumulate across multiple generations to depress maternal care, increase restlessness and alter basal functioning of the immune system and hypothalamic pituitary adrenal axis.

1. Introduction

Social stressors, such as impaired maternal care and maternal depression are associated with adverse behavioral (Lee and Gotlib, 1991) and emotional outcomes (*for review* Beardslee et al. 2011). Children of depressed parents are at risk for developing depressive disorders themselves and other internalizing and externalizing disorders (Lyons-Ruth et al., 1997; National Research Council (US) and Institute of Medicine (US) Committee on Depression et al., 2009). Whether these effects are transmitted beyond 2 generations is not established with few 3-generation studies of major depression (Olino et al., 2008; Pettit et al., 2008). One study of 800 depressed and never-depressed women together with information from their children (at 15 yrs) and grandmothers detected an intergenerational transmission of depression, whereby the grandmother's depression affected the mother's depression and her own stressful life context, and maternal and grandmother depression affected youth depression. This was mediated by interpersonal stress processes, which in turn affected parenting and children's social functioning (Hammen et al., 2004). A further recent study on 251 sets of grandchildren, parents and grandparents found those with 2 previous generations affected with major depression were at highest risk for major depression; though the study was too small to test for sex effects (Weissman et al., 2016).

Intergenerational and transgenerational transmission – defined either by the presence or absence of a direct exposure to the stressor of the parental (F0) and subsequent generations – of parental depression involves environmental risk factors and heritable components of depression, and most likely the interplay of these elements. A challenge in clinical studies is proving that parental depression has true environmental risk effects on offspring outcomes, due to the fact that genetic transmission of depression may confound the environmental effects of parental depression. Mendelian randomization and twin studies are advancing our understanding of genetic and environmental contributions toward depression. However, these techniques are yet to be integrated into a transgenerational study design (Natsuaki et al., 2014). As such, most studies based on clinical samples either represent

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unusually adverse contexts that are difficult to generalize and, for the most part, have not been large enough and/or included multiple collected environmental and biological variables. Animal models allow to control for genetics and the environment. One prenatal stress study in rats, measuring tail chasing behavior as an indicator of postnatal maternal care found a reduction in 3 generations, reflective of intergenerational programming (Ward et al., 2013). Tail chasing is suggested to be indicative of preparations for pup retrieval, where the pregnant female is attempting to retrieve her tail to the nest area. To our knowledge, we are the first to investigate intergenerational inheritance of the effects of postnatal stress on maternal behavior across 3 generations, in clinical or animal studies.

The chronic social stress (CSS) rat model, which has a robust impact on maternal behavior, allows for the intergenerational testing of the effects of maternal social stress across three generations, F0–F2. Exposure of F0 rat dams to chronic stress during lactation impacts maternal behavior including reductions in pup grooming and nursing and increased maternal aggression (Murgatroyd et al., 2015a; Nephew and Bridges, 2011). The female F1 generation of the CSS F0 dams also show decreases in maternal care accompanied by impaired lactation, decreased saccharine intake (a measure of abstract anhedonia), decreased maternal aggression and increased restlessness/anxiety-related behaviors (Carini and Nephew, 2013; Murgatroyd and Nephew, 2013; Murgatroyd et al., 2015a,b). 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 PRL and increased corticosterone during lactation (Carini and Nephew, 2013).

Analysis of the F2 females as juveniles and as adults also reveal altered social behavior, specifically diminished allogrooming during adult social interactions. Allogrooming is a common form of direct mammalian social contact that is necessary for establishing mammalian social bonds at multiple life history stages (Insel, 1997). This was accompanied by decreases in basal corticosterone, elevated juvenile Oxt and decreased adult Prl (Babb et al., 2014) and changes in several immune markers, particularly a significant reduction in inter-cellular adhesion molecule-1 (ICAM-1), a cell-adhesion molecule expressed on macrophages, lymphocytes and endothelial cells which plays an important role in immune-mediated cell–cell adhesive interactions and blood–brain-barrier (BBB) permeability (Murgatroyd et al., 2016). This suggests that the CSS has long-term generational effects on the immune system together with the changes in behavior and the hypothalamic–pituitary–adrenal (HPA) axis.

The behavioral changes in F2 juveniles and adults indicate that F0 CSS effects multiple generations. The developmental elements of the CSS model include the potential effects of behavioral and hormonal or immune changes in the F0 and F1 dams on F2 dams; either through pup-dam interactions, milk constituents, or germline exposure of the F2 generation during early-life stress exposure in the F1 animals. The current study investigated the generational inheritance of alterations in maternal behaviors in F2 CSS dams together with endocrine, immune, gene regulation and epigenetic markers to investigate whether aspects of maternal care are intergenerationally inherited through potential immune and neuroendocrine mechanisms.

2. Methods and materials

2.1. Animals and CSS model

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.

The F0 CSS dams were subjected to a CSS protocol from days 2 to 16 of lactation involving exposure to a novel male intruder for one hour each day (Carini et al., 2013; Nephew and Bridges, 2011). The control and CSS F1 dams 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 2–16 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 old when two from each litter were mated with 6 proven breeder males. 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 CSS animals were treated identically throughout the study; the only difference between the two groups was the attenuated maternal care and increased restlessness and anxiety-related behavior expressed by their respective CSS and control F1 dams (Carini and Nephew, 2013). Importantly, there were no treatment effects on litter size or bodyweights of the F2 pups (day 2 of lactation: F2 litter size, control 15.6 ± 0.5, CSS 15.8 ± 10.4, $p = 0.7$; F2 mean pup bodyweight (g), control 6.8 ± 0.2, CSS 6.9 ± 0.2, $p = 0.7$; F1 dam bodyweight (g), control 340.9 ± 10.4, CSS 345.3 ± 8.0, $p = 0.7$) juvenile or adults (all p's > 0.2) (Carini and Nephew, 2013).

All F2 dams were euthanized on day 23 of lactation; brains were extracted and stored at −80 °C until micropunched, relative to bregma, for PVN (bilateral ∅0.5 mm, −2.0 to −1.5, 0.5 mm lateral to midline, SON (bilateral ∅0.5 mm, −1.5 to −1.0, 1.8 mm lateral to midline) and hippocampus (bilateral ∅1.0 mm, −1.8 to −1.3, 2.5 mm lateral to midline) and trunk blood was collected for serum. The same F2 animals were used for all brain, cytokine and immune assays. Finally, the design of this model ensures that the F1 and F2 generations derive from 10 separate dams each for CSS and control at each generation with only 1–2 pups taken from each litter to avoid litter effects. See Fig. 1 for an overview of the intergenerational model.

2.2. Maternal care and aggression testing

Maternal care and maternal aggression were assessed in all F2 dams between 0800 and 1000 h on days 2 (early), 9 (mid), and 16 (late) of lactation, as previously described for F1 dams (Carini et al., 2013; Murgatroyd and Nephew, 2013). After a 1-h pup removal, maternal care testing was performed, which included reintroduction of all pups

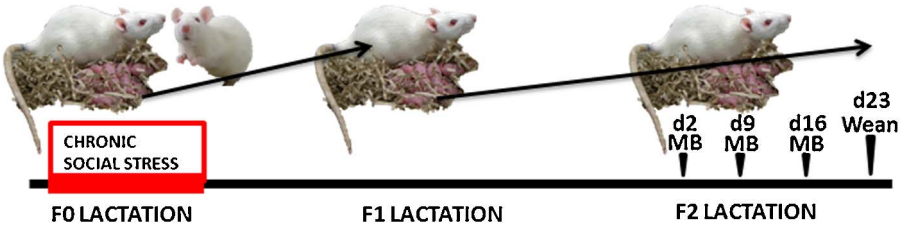

Fig. 1. Schematic of the 3-generational chronic social stress model for maternal behavior. F0 Dams are exposed to stress during lactation (red box). Her offspring (F1) are then allowed to grow and their offspring (F2) are tested for maternal behavior (MB) and endocrine and immune measures. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

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