Behavioural Brain Research 339 (2018) 222–231

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Perinatal fluoxetine increases hippocampal neurogenesis and reverses the lasting effects of pre-gestational stress on serum corticosterone, but not on maternal behavior, in the rat dam

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ARTICLE INFO

Keywords:
Depression
Neuroplasticity
SSRI
Anxiety
Reproduction
Corticosteroid binding globulin

ABSTRACT

There is increasing evidence that mental health concerns, stress-related mental illnesses, and parental stress prior to conception have long-term effects on offspring outcomes. However, more work is needed to understand how pre-gestational stress might affect neurobehavioral outcomes in the mother. We investigated how chronic stress prior to gestation affects maternal behavior and related physiology, and aimed to determine the role that perinatal SSRIs have in altering these stress effects. To do this, female Sprague-Dawley rats were subject to chronic unpredictable stress (CUS) prior to breeding. During the perinatal period they were administered fluoxetine (10 mg/kg/day). Four groups of dams were studied: Control + Vehicle, Pre-gestational Stress + Vehicle, Control + Fluoxetine and Pre-gestational Stress + Fluoxetine. Maternal weight, breeding success, and maternal caregiving behaviors were recorded. Measures of serum corticosterone and corticosteroid-binging globulin (CBG) and the number of immature neurons in the dorsal hippocampus were also assessed in the late postpartum. Main findings show pre-gestational stress resulted in poor reproductive success and maintenance of pregnancy. Pre-gestationally stressed dams also showed higher levels of nursing and fewer bouts of licking/grooming offspring in the first week postpartum – behaviors that were not reversed by perinatal fluoxetine treatment. In the dam, perinatal fluoxetine treatment reversed the effect of pre-gestational maternal stress on serum corticosterone levels and increased serum CBG levels as well as neurogenesis in the dorsal hippocampus. Maternal corticosterone levels significantly correlated with blanket and passive nursing. This work provides evidence for a long-term impact of stress prior to gestation in the mother, and shows that perinatal SSRI medications can prevent some of these effects.

1. Introduction

Up to 20% of women experience a stress-related disorder, such as depression or anxiety, during the perinatal period, yet our understanding of how maternal stress and mental illness affect the maternal brain and maternal behavior is far from complete. Importantly, there is a need to determine how maternal outcomes are affected by stress prior to gestation as stress is an associated risk factor for maternal mental illness during the perinatal period [1]. We know that maternal stress effects are transmitted across generations, particularly when stress occurs during the perinatal period [2,3]. However, little is known about how pre-gestational stress affects neurobehavioral outcomes in the mother. One study has shown that pre-gestational stress can increase anhedonia as well as serum corticosterone and corticosterone-releasing hormone levels during late pregnancy [4]. Assessment of additional maternal outcomes, such as maternal care, as well as central measures of neuroplasticity, are needed to further understand the long-term effect of pre-gestational stress on the mother.

Of particular importance is the effect of maternal stress on maternal caregiving behaviors that may have a long-term effect on offspring outcomes. Stressed, depressed, and anxious mothers respond more negatively to their infants compared with healthy mothers [5–7].

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https://doi.org/10.1016/j.bbr.2017.11.038
Received 26 September 2017; Received in revised form 16 November 2017; Accepted 29 November 2017
Available online 05 December 2017
0166-4328/

Perinatal depression and anxiety also reduces synchrony between mother and infant by reducing vocal and visual communications, touching, and smiling [5,6]. Alterations in maternal caregiving behaviors after repeated maternal stress, or exogenous administration of glucocorticoids, occur in rodent models. Dams stressed during gestation spend less time licking and grooming offspring and often more time nursing offspring [8–12] and dams receiving postpartum corticosterone treatment spend less time nursing offspring [8]. However, the effects of pre-gestational stress on maternal-caregiving remain to be explored.

Maternal stress and stress-related disorders can also affect the neurobiology of the mother. Clinical work shows changes in many brain areas of women with affective symptoms and postpartum depression [13], and these changes are often unique from depression outside of the perinatal period [1]. Animal models are beginning to show that maternal stress can remodel the maternal brain. Repeated restraint stress during pregnancy, or exogenous corticosterone administration, alters hippocampal neurogenesis, dendritic morphology, and other measures of plasticity in the maternal rodent brain during pregnancy and the postpartum period [11,14–20]. Gestational stress can also abolish the enduring increase in hippocampal LTP months after giving birth, suggesting a long-term impact of stress exposure on the maternal brain [21]. More work is needed to understand how maternal stress, prior to conception, influences hippocampal outcomes; as the hippocampus, and neurogenesis in this brain area, plays a critical role in emotion, stress, anxiety, and depression [22–24], as well as maternal experience [25–28].

Many women are prescribed selective serotonin reuptake inhibitor medications (SSRIs) during the perinatal period to treat stress-related affective disorders. Prescription estimates for treatment of perinatal affective disorders with SSRIs range from 4 to 10% of pregnant women in developed countries [2,29–32]. These drugs act to alleviate depressive symptoms in adults by normalizing serotonin function, regulating the HPA axis [33], and altering hippocampal plasticity [34,35]. During the perinatal period, SSRIs may also affect maternal care-giving behaviors and maternal brain plasticity. Clinical work shows that when controlling for the effects of maternal depression, mothers treated with an SSRI during pregnancy interrupt their child more during play [36]. Others show that effective antidepressant treatment improves gratification in the maternal role but not maternal-infant interaction in women with Postpartum Depression (PPD) [37], while others show no effects of antidepressant medications on maternal feelings of attachment [38]. In rodent models, gestational SSRI treatment increases the frequency of maternal licking of offspring, and in low doses, increases the duration of crouching over offspring [39]. This is also evident with postpartum SSRI treatment which increases arch-back nursing behaviors, reduces maternal self-grooming, and reverses the effects of high corticosterone levels on maternal care-giving behaviors [40,41]. Recent work also shows significant changes in hippocampal plasticity in the maternal brain in response to SSRI treatment; SSRIs increase neurogenesis in the maternal hippocampus [41] and decrease both global measures of methylation in the dentate gyrus and serotonin metabolism in the hippocampus of the mother [42]. Thus, emerging evidence points to potential long-term effects of SSRIs on the brain and behavior of the mother.

Our aim was to investigate how chronic stress prior to gestation affects maternal behavior, related physiology, and neuroplasticity, and to determine how perinatal SSRI treatment with fluoxetine, one of the most popular SSRIs, might alter these stress effects in the mother. It was expected that both pre-gestational stress and perinatal SSRI treatment would have enduring effects on neurobehavioral outcomes in the mother, particularly those of maternal care-giving behaviors and neurogenesis, with SSRIs preventing the effects of maternal stress on these measures in the mother.

2. Material and methods

2.1. Animals

Thirty-four adult female Sprague-Dawley rats (175–199 g, approximately 60 days of age) and 9 adult male Sprague-Dawley rats (275–299 g) were purchased from Harlan Laboratories Inc. (Indianapolis, Indiana). Animals were kept under standard laboratory conditions in a 12:12-h light/dark schedule and rats were initially housed in same-sex pairs in clear polyurethane bins with basic enrichment and ad libitum access to rat chow and tap water. Experiments were approved by the Institutional Animal Care and Use Committee (IACUC, 12-H-053, 14-H-011).

As maternal stress in rodents can induce aspects of anxiety and depressive-like behavior, a model of chronic unpredictable stress (CUS) was utilized in the present study based on previous work [4,43]. Prior to breeding, females were randomly assigned to stress or control groups (16 control, 18 stress). Female rats in the control group were pair-housed and those in the stress group were individually housed and subjected to CUS for 3 weeks. Single housing was part of the stress procedure as single housing alone can induce depressive-like behavior in female mice [44]. The CUS consisted of 0–2 stressors per day for 3 weeks prior to breeding. Stressors included restraint under bright light for 1 h; 24 h overcrowding; overnight exposure to damp bedding; 12 h food deprivation; 5 min of forced swimming or cage rotation for 12 h. Females were weighed weekly during the stressing procedure, and percent weight gain was calculated. After CUS, all females were subject to behavioral testing to assess the effects of stress on anxiety and working memory (both of which are associated with depressive-like behavior). Fluoxetine or vehicle treatment began during gestation and lasted until sacrifice, resulting in 4 groups of dams: Control + Vehicle (CV, n = 8), Pre-gestational Stress + Vehicle (PGSV, n = 9), Control + Fluoxetine (CF, n = 8) and Pre-gestational Stress + Fluoxetine (PGSF, n = 9). See Fig. 1 for a timeline of the study. Unfortunately, due to unexpected pregnancy loss (see below and Fig. 2), particularly in the stressed females, group sizes were lower with n = 5–8/group (CV = 6, CF = 7, PGSV = 5, PGSF = 5).

2.2. CUS effects on weight, exploration, and memory in females prior to breeding

Female weight across CUS, activity in an open field, as an indicator of anxiety-like behavior and working memory performance after stress, as a measure of working memory deficits associated with depression [45] were measured prior to breading as described [46–48]. The day prior to testing, each female was habituated to a darkened polyurethane apparatus (50 cm × 50 cm × 50 cm), which served as an open field test, for 15 min. Anymaze Behavioral Tracking Software (Stoelting Europe, Ireland) was used to calculate freezing episodes as an indicator of anxiety-like behaviors as well as distance moved in the periphery and center of the arena.

Twenty-four hours later, the ORT test began, and each female was put into the arena with two identical objects that were placed in opposite corners of the arena floor. Each female was allowed to explore the objects for a 10 min familiarization period. After a one hour delay, each female was again placed in the same arena for 5 min but one object was replaced with a novel object in the same location. Twenty-four hours later females were tested again in the same way with one original object and one novel object. Time spent investigating each object and time with the novel, versus familiar, object was calculated as a percent. For object novel recognition memory, novel object exploration time was calculated as novel exploration/(novel + familiar exploration)*100 at the 1 h and 24 h period. Percentage of total time