



Maternal exercise increases but concurrent maternal fluoxetine prevents the increase in hippocampal neurogenesis of adult offspring

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ABSTRACT

Treating postpartum depression (PPD) with pharmacological antidepressants like fluoxetine (FLX) is complicated because these drugs can remain active in breast milk and potentially affect infant development. Alternatively, non-pharmacological treatments such as exercise are associated with beneficial effects on infant development but its potential ability to counter the effects of PPD are largely unknown. To investigate this, we treated dams with corticosterone (CORT) or vehicle (sesame oil) from postpartum days 2–25 to model PPD. Within oil and CORT treatments, dams were also assigned to one of these treatments: 1) exercise (voluntary running wheel) + FLX (10 mg/kg, i.p.), 2) exercise + saline (vehicle for FLX), 3) no exercise + FLX, 4) no exercise + saline. Both male and female offspring were analyzed, and this generated a total of 16 experimental groups for this study. Adult male and female offspring (125 d old) of these dams were tested for anxiety-like behavior in the novelty suppressed feeding test and stress reactivity in the dexamethasone suppression test. Hippocampal tissue was processed for doublecortin, a protein expressed in immature neurons. Regardless of sex, maternal exercise increased neurogenesis in the dorsal hippocampus of adult offspring, but concurrent exposure to maternal fluoxetine prevented this effect. Exposure to either maternal exercise or maternal FLX facilitated HPA negative feedback in adult males but not females. Maternal postpartum CORT also facilitated HPA feedback in adult offspring of both sexes. Collectively, these data indicate that maternal exercise increased dorsal hippocampal neurogenesis in both sexes but differentially affected offspring HPA axis based on sex. Alternatively, maternal postpartum FLX facilitated HPA axis negative feedback only in males. These findings indicate that different types of maternal interventions bear long-term effects on offspring outcome with implications for treating PPD.

1. Introduction

Quality of maternal care is a crucial factor in the neurodevelopmental outcome of children (Kaffman and Meaney, 2007). Maternal mood disorders, such as postpartum depression (PPD), are not only devastating for maternal mental health, but can also perturb maternal caregiving (Lovejoy et al., 2000). PPD is associated with disengaged or withdrawal of maternal care and can manifest as hostility towards the infant (Lovejoy et al., 2000). Altered patterns of maternal behavior can influence child development and increase risk for adverse behavioral outcomes (Brummelte and Galea, 2016). Prescription antidepressants such as selective serotonin reuptake inhibitors (SSRIs) like fluoxetine (FLX; Prozac) can be prescribed for PPD. However, FLX remains active

in breast milk and can directly reach the developing infant (Weissman et al., 2004). Moreover, it is uncertain if FLX is efficacious in alleviating mood disturbances and restoring maternal caregiving behaviors in women (Sharma and Sommerdyk, 2013). For these reasons, it is unclear whether risking neonatal FLX exposure outweighs potential therapeutic effects of FLX. Regardless, it is estimated that 6% of mothers utilize prescription antidepressants after birth (Smolina et al., 2015). Given the potential risks of pharmacological antidepressants on infant health, mothers may be more inclined to use non-pharmacological interventions such as exercise. However, whether maternal exercise interacts or prevents the long-term effects of PPD on offspring development remains unknown. The goal of the present study is to use a rodent model of PPD and compare how different types of maternal treatments (FLX vs.

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exercise) affect long-term outcomes of adult male and female offspring

Research attempting to ascertain whether risks of neonatal exposure to SSRIs outweigh the adverse effects of untreated PPD on child outcome is inconclusive. This ambiguity may be explained by methodological considerations because the effects of neonatal SSRI exposure depend on whether sex differences, timing of exposure, and concurrent maternal depression were analyzed. PPD is associated with increased risk for depression particularly in girls (LeMoult et al., 2015) and lower IQ particularly in boys (Azak, 2012). Given the sex differences in outcome following maternal untreated PPD, it is reasonable to predict that sex differences may persist after treatments for PPD in offspring. For example, maternal FLX exposure can impair the negative feedback system of the hypothalamic-pituitary-adrenal (HPA) axis in response to dexamethasone administration in adult offspring depending on both sex and concurrent depression modelling. For example, maternal FLX treatment throughout gestation and postpartum impaired HPA axis negative feedback in both adult male and female mice offspring (Avitsur et al., 2016; Avitsur, 2017). However, those studies did not use a concurrent model of maternal depression. When using a rat model of PPD, maternal FLX treatment in the postpartum impaired HPA axis negatively feedback only in adult male but not female offspring (Gobinath et al., 2016). Impaired HPA axis negative feedback is biomarker of depression (Ising et al., 2007). Therefore, the translational implications of maternal SSRI use on risk for depression in offspring based on these preclinical findings may be sex-specific and more related to postpartum exposure. In clinical studies, maternal SSRI use has been associated with increased risk for autism (Brown et al., 2017). However, this effect is also moderated by concurrent maternal depression (Viktorin et al., 2017) and is particularly linked to exposure during the first trimester (Brown et al., 2017; Suján et al., 2017). Collectively, these studies underscore the importance of sex, timing, and concurrent maternal adversity as factors in evaluating the conflict between risk of neonatal SSRI exposure versus untreated PPD on offspring behavioral outcome. The following study will compare whether maternal postpartum FLX exposure within a model of PPD can differentially impact adult male and female offspring outcomes.

Unlike maternal FLX exposure, maternal exercise is relatively less controversial with generally beneficial effects reported on offspring outcome. For example, maternal exercise mitigates the risk for obesity and metabolic measures on offspring outcome (Blaize et al., 2015; Vega et al., 2015; Wasinski et al., 2015). Further, as in the case of maternal SSRI exposure, maternal exercise can affect offspring in a sex-specific manner. For example, maternal exercise prevented insulin resistance in male, but not female, offspring in response to a maternal high-fat diet (Fernandez-Twinn et al., 2017). These beneficial effects of maternal exercise also include reduced anxiety-like behavior in rat pups (both sexes; Aksu et al., 2012), increased hippocampal cell proliferation in adolescent rats (only females studied; postnatal day 36; Bick-Sander et al., 2006), and increased number of neurons in the CA1 and CA3 subfields of the hippocampus in adult rats (both sexes; postnatal day 120; Dayi et al., 2012). However, these studies did not challenge the dams with a concurrent model of maternal depression. This point is particularly important because it remains unclear whether the beneficial effects of maternal exercise persist in the context of maternal depression. In dams exposed to prenatal stress, maternal forced treadmill exercise did not prevent prenatal stress-induced anxiety-like behavior in adult male offspring (Lee et al., 2016). This could indicate limitations of exercise to offset the effects of prenatal stress (Griesbach et al., 2012). Moreover, forced exercise is considered more stressful than a voluntary running intervention which may also explain its limited effects in a model of prenatal stress (Ke et al., 2011; Lee et al., 2016). Recently, we used a voluntary exercise intervention over the course of pre-conception, gestation, and postpartum in a CORT-induced rat model of PPD. We found that voluntary running did not prevent reductions in quality of maternal care, but it reduced passive coping or maternal depressive-like behaviour in the forced swim test and

increased neurogenesis in the dam with concurrent FLX treatment (Gobinath et al., 2018). To further expand on the developmental effects of exercise we compared the effects of maternal postpartum FLX and/or maternal voluntary exercise to impact adult male and female outcomes.

To address whether the effects of maternal postpartum FLX and/or maternal exercise exposure would counter the effects of PPD, we used a rat model of corticosterone (CORT)-induced PPD and observed adult male and female offspring for anxiety-like behavior in the novelty suppressed feeding test, HPA axis negative feedback in the dexamethasone suppression test, and hippocampal neurogenesis (density of doublecortin (DCX)-expressing immature neurons). In this model of PPD, dams are treated daily with high levels of CORT from postpartum days 2–25 to induce a depressive-like phenotype. This methodology models index episode of depression occurring after parturition, which is characteristic of 40% of women with PPD (Fisher et al., 2016). Our laboratory has shown that maternal postpartum CORT treatment reduces voluntary engagement with the litter and increases maternal passive coping behavior in the forced swim test (Brummelte and Galea, 2010; Brummelte et al., 2006; Workman et al., 2016; Workman et al., 2013; Gobinath et al., 2018). We have also shown that concurrent FLX treatment prevented CORT-induced disruptions in maternal care but also increased anxiety-like behavior, HPA axis activity, and hippocampal neurogenesis after a battery of behavioral tests in adult male but not female offspring (Gobinath et al., 2016). The present study will expand on these findings by comparison how maternal exercise (i.e. access to voluntary running wheel from pre-conception through weaning) affected adult male and female offspring neurodevelopmental outcome. Because exercise is generally associated with beneficial effects for maternal mental and physical health, we hypothesized that maternal exercise alone or in conjunction with FLX would offset the developmental effects of maternal postpartum CORT exposure on offspring outcome. Further, we hypothesized that overall males would be more sensitive to these maternal treatments than females. More specifically, we hypothesized that maternal FLX exposure would bear sex-specific effects on HPA axis negative feedback and neurogenesis selectively in males given our previous findings (Gobinath et al., 2016). Furthermore, developmental CORT, FLX, and exercise exposure has been linked to altered hippocampal neurogenesis (Brummelte et al., 2006; Dayi et al., 2012; Gobinath et al., 2016, 2017a, 2018), and we predicted that the sex-specific effects would also be present in the hippocampus.

2. Methods

2.1. Animals

Sixty-two adult female Sprague-Dawley rats (2–3 months old, Charles River) and 16 adult male Sprague-Dawley rats (2–3 months old, Charles River) were initially housed in same-sex pairs in opaque polyurethane bins (24 × 16 × 46 cm) with aspen chip bedding. Rats were maintained in a 12 h: 12 h light/dark cycle (lights on at 7:00 a.m) and given rat chow (Jamieson's Pet Food Distributors Ltd, Delta, BC, Canada) and tap water ad libitum. For an overview of experimental procedures, refer to Fig. 1. All protocols were in accordance with ethical guidelines set by Canada Council for Animal Care and were approved by the University of British Columbia Animal Care Committee.

2.2. Exercise treatment

Upon arrival in the conventional facility, female rats were randomly assigned to either standard housing conditions with no running wheel (“non-exercise;” n = 32) or housing with voluntary access to running wheels (“exercise;” n = 30; Med Associates Inc., VT, USA). Female rats in the exercise and non-exercise conditions were housed in separate colony rooms. Running wheel activity was recorded daily via an external electronic LCD counter. Dams could voluntarily run from arrival

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