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Research report

Fluoxetine normalizes the effects of prenatal maternal stress on depression- and anxiety-like behaviors in mouse dams and male offspring

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HIGHLIGHTS

- Gestational stress increases depression-like behavior in dams.
- Maternal fluoxetine treatment reduces the effects of stress in dams.
- Prenatal stress increases anxiety- and depression-like behavior in male offspring.
- Prenatal stress alters the HPA axis activity in male offspring.
- Developmental fluoxetine treatment reduces the effects of prenatal stress in offspring.

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ABSTRACT

Maternal depression during pregnancy and the postpartum period (lactation) is a common debilitating condition affecting mother-fetus/-infant interactions, which can be a risk factor for cognitive and affective disorders in mothers and their children. Selective-serotonin-reuptake-inhibitor-(SSRI) pharmacotherapy is known as the first-line treatment of maternal depression. However, its use during pregnancy and lactation is a topic of concern. The present study aimed to investigate the effects of prenatal stress alone or in combination with fluoxetine (FLX) on hypothalamic–pituitary–adrenal axis (HPA) activity, anxiety-/depression-like behaviors in dams and in offspring. To do this, gestationally-stressed and non-stressed mouse dams were orally treated with FLX-(8/mg/kg/day) from gestational day 10 to lactation day 20. The behavioral outcomes of prenatal stress and FLX treatment in dams and male offspring were assessed using the sucrose preference, forced swim, zero maze, and light-dark box tests. Stress-induced corticosterone levels were also evaluated as indicative of abnormal HPA-axis function. Our findings indicated that maternal stress resulted in increased depression-like behavior and HPA axis hyperactivity in dams during pregnancy and lactation which were reversed by FLX. Furthermore, prenatal stress increased anxiety/depression-like behaviors and HPA-axis reactivity in male offspring. These effects were reversed by maternal FLX treatment. Developmental FLX exposure, without prenatal stress, did not have any adverse effects on the above measured parameters. Our results suggest that prenatal stress induces maternal depression-like behavior which affects the development of affective symptoms in male offspring, and that remediation of maternal depression-like behavior coincidences with the normalization of anxiety-and depression-like symptoms in male offspring.

Abbreviations: FLX, fluoxetine; HPA, hypothalamic pituitary-adrenal axis; SSRI, selective serotonin reuptake inhibitor; PND, postnatal day; CORT, corticosterone; ANOVA, analysis of variance; SEM, standard error of the mean.

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1. Introduction

Maternal depression during pregnancy and lactation is a common debilitating condition associated with deleterious effects on individuals, families, and society globally [58]. The reported incidence of maternal depression varies widely, from 5% to 25%, depending on the population characteristics, the method of assessment, and the timing of the assessment [29]. Maternal depression is not only highly burdensome for pregnant and lactating women, but also for their children. Maternal depression has been associated with higher rates of poor pregnancy outcomes (such as pre-eclampsia and premature delivery), impaired fetoplacental function, decreased fetal growth, and neonatal complications [24,67]. However, while premature delivery and decreased fetal growth are established outcomes of maternal depression [39], the long-term outcomes are of more interest for offspring. Maternal depression has been associated with developmental delays in 18-month-old children [20], increased behavioral and emotional problems in 4-year-old children [63], and increased anxiety in 6- to 9-year-old children [18]. Furthermore, 42% of maternal depression-exposed girls display emotional disorders during adolescence [37]. Hence, maternal depression may have a somewhat "infectious" nature; when depression during pregnancy and lactation increases the risk for depression in offspring, the offspring may transmit the depressive symptomology to their children [83]. The "infectious" nature of maternal depression may be related to altered hypothalamic-pituitary-adrenal axis (HPA) function in the mother, with circulating stress hormones affecting the development of the child and its neuroendocrine functions [33].

The first-line treatment of maternal depression consists of selective serotonin reuptake inhibitor (SSRI) pharmacotherapy, especially when the mother is suicidal. SSRIs do not cause gross teratogenic alterations and are generally considered safe for use in pregnancy. Yet, while SSRI treatment may decrease maternal depression, and thereby decrease the harmful effects of maternal depression on development of the fetus and newborn, its use during pregnancy and lactation is a topic of concern; multiple studies have reported harmful outcomes in newborns (transient neonatal adaptation syndrome, pulmonary hypertension) and children (increased risk for autism or attention deficit hyperactivity disorder, delayed motor development) [12,16,19,26,30,34,35,41,78,81,86]. These outcomes may be related to changes in the programming of the HPA-axis, since prenatal SSRI exposure was found to significantly increase serum corticosteroid binding globulin levels, but not serum cortisol levels, in neonates, also when controlling for maternal depression. Additionally, neonatal serum corticosteroid binding globulin levels were positively associated with infant salivary levels of evening cortisol [71]. Another study reported that early evening basal cortisol levels were lower in SSRI exposed infants than in non-SSRI exposed infants [66]. Of interest, this effect was related to SSRI exposure during pregnancy, and not breastfeeding [66], suggesting that the prenatal phase is most critical for the programming of the offspring's HPA-axis.

Also in rodents prenatal and/or early postnatal (postnatal day (PND) 2–7; corresponding the third trimester of human pregnancy) [82] SSRI treatment leads to (transient) impaired motor coordination in neonates and decreased social behavior in both juvenile and adult subjects [6,79,90], as well as increased anxiety [28,68,76,88] and (subtle) depression-like phenotypes [57,76]. However, when rat or mouse mothers are exposed to stress and thereby are expected to develop depression-like symptoms, findings are mixed. For instance, it has been reported that simultaneous FLX treatment and prenatal stress exposure in rat offspring was without behavioral alterations [9], whereas another study reported that maternal FLX exposure reversed the reduction in immobility in the forced swim test—that is, reversed depression-like psychomotor retardation—in prenatally stressed adolescent rat offspring [75]. Furthermore, prenatal stress exposure in combination with prenatal and early postnatal SSRI exposure led to a normalization of aggression in mice [44] serum corticosteroid binding globulin levels in rats [45], indicative for adaptive programming of the HPA-axis. It has also been reported that developmental FLX exposure, without prenatal stress, decreased in rats circulating levels of corticosterone (CORT) [70]. Although previous studies have demonstrated that maternal stress during gestation induces depression-like behavior during the postpartum period [31,32,40,48,65,80], maternal stress during gestation was not assessed for its efficacy to induce depression-like phenotypes and HPA axis hyperactivity in the dams during pregnancy in the above described studies. This is not trivial, because stress does not invariably leads to depression; it is dependent on genetic predisposition, early life experiences and more. Furthermore, in humans depression during pregnancy is strongly correlated to depression during the postnatal period [14], raising the possibility that prenatal stress effects continue during the postnatal period. Moreover, because SSRI treatment took place either during [9] or after [45,70,74] prenatal stress exposure in the combined maternally stressed and SSRI treatment rodent studies discussed above, the ability of FLX to remediate depression-like symptoms in offspring may depend on the timing of the treatment. Indeed, FLX was found to affect anxiety- and depression-like behavior specifically when applied during PND 2 and 11 in mice [76]. Treatment timing may also influence the remediation of maternal depression-like behavior, and thereby the combined influence of maternal depression-like behavior and developmental SSRI exposure on behavior of offspring. Given that fostering prenatally stressed pups onto control mothers prevented HPA-axis dysregulation and increased anxiety, postnatal factors may mediate the effect of maternal depression-like behavior on these measures [85]. The aim of this mouse study was to contribute to the research on the consequences of maternal stress for mothers and offspring in terms of affective behavior and the neuroendocrine stress system, and to delineate to what extend these consequences could be remediated by perinatal SSRI treatment. Based on literature findings we hypothesized that stress applied during pregnancy would increase depressive-like behavior and stress responsivity in pregnant dams and that this effect would extend to the postpartum period of the mothers and be transmitted to the offspring. Accordingly, we also hypothesized that perinatal SSRI treatment – covering the pre- and postnatal period – would remediate these affective consequences, but also increase affective phenotypes in offspring without history of maternal stress.

2. Materials and methods

2.1. Subjects

Pregnant NMRI mice were obtained from the animal house of Hayyan Research Institute and all the experiments were performed in this institute. Therefore, there was no animal transportation during the study. The presence of vaginal plug was considered day 0 of pregnancy. Animals were maintained under standard laboratory conditions on a 12:12 h light/dark cycle (lights on at 08:00 AM) and controlled temperature ($23 \pm 1\,^{\circ}C$). Food and water were also available *ad libitum*. All procedures were approved by the Research and Ethics Committee of Hayyan Research Institute.

2.2. Study design

A timeline diagram of the experiments is shown in Fig. 1. In the present study, there were four main experiments: Experiment