Hormones and Behavior 77 (2016) 124–131

Contents lists available at ScienceDirect

Hormones and Behavior

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

The effects of gestational stress and Selective Serotonin reuptake inhibitor antidepressant treatment on structural plasticity in the postpartum brain — A translational model for postpartum depression

Achikam Haim [a], Christopher Albin-Brooks [b], Morgan Sherer [b], Emily Mills [b], Benedetta Leuner [a,b,c,*]

[a] Department of Neuroscience, The Ohio State University Wexner Medical Center, Columbus, OH 43210, USA
[b] Department of Psychology, The Ohio State University, Columbus, OH 43210, USA
[c] Behavioral Neuroendocrinology Group, The Ohio State University, Columbus, OH 43210, USA

ARTICLE INFO

Available online 18 May 2015

Keywords:
Amygdala
Dendritic spines
Maternal
Mood
Nucleus accumbens
Prefrontal cortex

ABSTRACT

This article is part of a Special Issue "Parental Care".

Postpartum depression (PPD) is a common complication following childbirth experienced by one in every five new mothers. Although the neural basis of PPD remains unknown, previous research in rats has shown that gestational stress, a risk factor for PPD, induces depressive-like behavior during the postpartum period. Moreover, the effect of gestational stress on postpartum mood is accompanied by structural modifications within the nucleus accumbens (NAc) and the medial prefrontal cortex (mPFC)–limbic regions that have been linked to PPD. Mothers diagnosed with PPD are often prescribed selective serotonin reuptake inhibitor (SSRI) antidepressant medications and yet little is known about their effects in models of PPD. Thus, here we investigated whether postpartum administration of Citalopram, an SSRI commonly used to treat PPD, would ameliorate the behavioral and morphological consequences of gestational stress. In addition, we examined the effects of gestational stress and postpartum administration of Citalopram on structural plasticity within the basolateral amygdala (BLA) which together with the mPFC and NAc forms a circuit that is sensitive to stress and is involved in mood regulation. Our results show that postpartum rats treated with Citalopram do not exhibit gestational stress-induced depressive-like behavior in the forced swim test. In addition, Citalopram was effective in reversing gestational stress-induced structural alterations in the postpartum NAc shell and mPFC. We also found that gestational stress increased spine density within the postpartum BLA, an effect which was not reversed by Citalopram treatment. Overall, these data highlight the usefulness of gestational stress as a valid and informative translational model for PPD. Furthermore, they suggest that structural alterations in the mPFC–NAc pathway may underlie stress-induced depressive-like behavior during the postpartum period and provide much needed information on how SSRIs may act in the maternal brain to treat PPD.

Introduction

Alterations in mood during the postpartum period are reported by approximately 40% of all new mothers with up to one in every five mothers developing the full phenotype of major depression known as postpartum depression (PPD; Gress-Smith et al., 2012; O'Hara, 2009; O'Hara and Wisner, 2014). Although numerous variables enhance vulnerability to PPD, epidemiological studies suggest that pregnancy stress is a major risk factor (Davey et al., 2011; Lancaster et al., 2010). Similar to humans, rats exposed to chronic stress during pregnancy exhibit depressive-like behavior during the postpartum period (Haim et al., 2014; Leuner et al., 2014; O'Mahony et al., 2006; Smith et al., 2004). Recent studies have shown that gestational stress also induces structural modifications within brain areas that have been linked to PPD (Laurent and Ablow, 2012; McEwen et al., 2012; Moses-Kolko et al., 2010, 2011; Sacher et al., 2015) and which are implicated in the regulation of mood and stress including the NAc and mPFC (Price and Drevets, 2012; Russo and Nestler, 2013). Specifically, gestational stress reduces structural complexity and dendritic spine density on medium spiny neurons (MSNs) in the shell of the NAc (Haim et al., 2014), and in addition, diminishes spine density on pyramidal neurons within the mPFC (Leuner et al., 2014).

The negative consequences of PPD on the cognitive, emotional and social development of the offspring are well documented (Grace et al., 2003; Gress-Smith et al., 2012; Letourneau et al., 2012; Verbeek et al., 2012). As such, treatment of depressed mothers is critical and commonly

* Corresponding author at: The Ohio State University, Department of Psychology, 1835 Neil Avenue, Columbus, OH 43210, USA. Fax: +1 614 688 4733.
E-mail address: leuner.1@osu.edu (B. Leuner).

http://dx.doi.org/10.1016/j.yhbeh.2015.05.005
0018-506X/

achieved with administration of selective serotonin reuptake inhibitor (SSRI) antidepressant medications (Berle and Spigset, 2011; Logsdon et al., 2011). Other than one report showing increased neurogenesis in the hippocampus of gestationally stressed mothers following chronic postpartum fluoxetine administration (Pawluski et al., 2012), the ability of SSRI treatment to reverse stress-induced structural and behavioral changes in postpartum females hasn't been assessed.

One of the most common SSRIs prescribed to patients diagnosed with mild to severe depression is Citalopram (Celexa©). Previous work has shown that Citalopram is safe for use in breastfeeding mothers (Rampono et al., 2006). Furthermore, Citalopram was shown to significantly improve mood in mothers diagnosed with PPD (Misri et al., 2012). Here we investigated whether chronic Citalopram administration during the postpartum period would reverse the adverse effects of gestational stress on postpartum mood and structural plasticity in the NAc shell and the mPFC. Given findings demonstrating amygdala dysregulation in PPD (Moses-Kolko et al., 2010; Silverman et al., 2011), we also investigated the effects of gestational stress as well as postpartum administration of Citalopram on structural complexity of neurons within the basolateral amygdala (BLA), another stress sensitive brain region that interconnects with both the NAc and mPFC to form a critical network involved in mood and emotion processing (Mitra et al., 2005; Stevenson and Gratton, 2003; Vialou et al., 2014).

Methods and materials

Animals

Timed pregnant female Sprague–Dawley rats (Taconic, Albany, USA) arrived at our facility on gestation day 4 (GD4) and were individually housed in clear Plexiglas cages with unlimited access to food and water. Rats were kept in a temperature and humidity controlled environment maintained on 12 h/12 h light–dark cycle (lights on at 6 AM). The day of pup delivery was designated as postpartum day 0 (PD0). On PD1, litters were culled to 8–10 pups (4–5 males, 4–5 females) in a randomized manner to minimize the possibility that the effects observed in the stressed mothers are driven by the characteristics of their pups. Pregnant rats were weighed daily from GD7–GD20 to verify the efficacy of the stress protocol since prior studies have reported that gestational stress reduces weight gain during pregnancy (Baker et al., 2008; Haim et al., 2014; Hillerer et al., 2011; Leuner et al., 2014). In addition, both mothers and litters were weighed daily throughout the postpartum period to assess any potential effect of antidepressant treatment or any possible lingering effect of stress as has been reported in some studies (Hillerer et al., 2011; Leuner et al., 2014). All experiments were performed in compliance with The Ohio State University Institutional Animal Care and Use Committee and the U.S. National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Gestational stress protocol

Pregnant rats were randomly assigned to the stressed group or served as unstressed controls. Stressed rats were restrained in ventilated clear Plexiglas cylinders (21 cm long, 6 cm internal diameter) daily from GD7–GD20 in a variable randomized restraint protocol consisting of one of the following: 2 × 30 min, 3 × 45 min, 1 × 1 h and 1 × 2 h. All stress sessions took place between 10 AM and 4 PM. Multiple stress sessions within the same day were always separated by at least 1 h. Although multiple gestational stress paradigms have been used to induce postpartum-depressive like behavior (Haim et al., 2014; Leuner et al., 2014; O'Mahony et al., 2006; Smith et al., 2004), randomized variable restraint stress with different restraint durations is a component of chronic mild stress (CMS) paradigms (Isgor et al., 2004) and was used in this study to reduce stress predictability and potential habituation to the stressor (Grissom and Bhatnagar, 2009). Unstressed controls were handled daily for 5 min.

Minipump implantation and antidepressant administration

Postpartum females were randomly assigned to receive Citalopram hydrobromide (H. Lundbeck, Copenhagen, DK) or saline vehicle resulting in a total of 4 groups: (1) No stress-Saline (n = 8), (2) No stress-Citalopram (n = 8), (3) Stress-Saline (n = 7), (4) Stress-Citalopram (n = 7). The dosage of Citalopram used here (10 mg/kg/day) has been shown to ameliorate mood in women with postpartum depression (Misri et al., 2012) and in addition, has been used in chronic stress rat models to alleviate depressive-like behavior (Chen et al., 2012). Citalopram treatment was administered for 21 days via osmotic minipumps (2ML4, Alzet, Cupertino, CA) which were preloaded with 2 ml of saline or Citalopram and subcutaneously implanted between the scapulae on PD1 under Isoflurane anesthesia. During the surgery, litters remained in their home cages which were kept warm on a heating pad. Following implantation, mothers were placed back in their home cages and provided with ibuprofen (15 mg/kg) via drinking water for 7 days. At the end of the study, fluid from each minipump was aspirated to verify saline/drug delivery.

Forced swim test

The forced swim test (FST) was used to assess depressive-like behavior. Testing was performed during the light phase between 10 AM and 12 PM under 550 lux illumination. Briefly, Plexiglas cylinders (diameter: 30.5 cm, height: 49 cm) were filled to a depth of 30 cm with 25 ± 0.5 °C water. On PD21, postpartum females were individually placed into the FST cylinders for 10 min, towel-dried and returned to their home cage. 24 h later (PD22), rats were returned to the same apparatus for 5 min and the session digitally recorded. The percentage of time spent immobile [(time spent floating in the water only making movements necessary to maintain the head above water/total test time) × 100] was later measured blind by a trained observer using BEST analysis software (Education Consulting Inc., Hobe Sound, FL).

Golgi staining

24 h following the FST, postpartum females (PD23) were deeply anesthetized, rapidly decapitated and brains removed for Golgi impregnation using the FD Rapid Golgi Stain kit (FD Neurotechnologies; Ellicot City, MD). Briefly, small blocks of tissue containing the NAc and mPFC and separate blocks containing the amygdala were placed in plastic scintillation vials filled with 10 ml of a potassium dichromate, mercuric chloride and potassium chromate solution (Solution A + B). Following 2 weeks of incubation in the dark at room temperature, brains were transferred to solution C and stored in the dark at 4 °C for 2 days. Next, coronal sections (150 μm) were cut on a Vibratome, mounted onto gelatin-coated slides and dried at room temperature in the dark. Slides were then rinsed, developed in solutions D + E for 10 min, dehydrated, cleared with xylene and coverslipped with Permount.

Microscopic analyses

MSNs (1.7 mm and 1 mm anterior to Bregma; Paxinos and Watson, 1998) in the shell and core sub-regions of the NAc, pyramidal neurons in layer 2/3 of the prelimbic mPFC (3.7 mm and 2.2 mm anterior to Bregma; Paxinos and Watson, 1998) and principal neurons in the BLA (1.6 mm and 3.3 mm posterior to Bregma; Paxinos and Watson, 1998) were analyzed. Only neurons within these regions that were fully impregnated, not obscured by neighboring neurons and had no obviously truncated dendrites were chosen for analysis. For each animal, five randomly chosen, representative neurons in each region were completely traced. mPFC pyramidal neurons were traced at 10× whereas NAc shell and core MSNs and principal neurons in the BLA were traced at 20× using NIS elements software and a Nikon 90i microscope (Nikon Instruments, Melville, NY). From these traced neurons, total dendritic length