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Research report

Brain neurotransmitters in an animal model with postpartum depressive-like behavior

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ABSTRACT

Post-Partum Depression (PPD) occurs in 15% of pregnancies and its patho-physiology is not known. We studied female BALB/c ("depressive") and C57BL/6 (control) mice as a model for PPD and assessed their behavior and correlates with brain neurotransmitters (NTs) – norepinephrine, dopamine, serotonin and intermediates, during the pre-pregnancy (PREP), pregnancy (PREG) and post-partum (PP) periods. Depressive-like behavior was evaluated by the Open Field (OFT), Tail Suspension (TST) and Forced Swim (FST) tests. Neurotransmitters (NTs) were determined in the striatum (care-giving), hippocampus (cognitive function) and hypothalamus (maternal care & eating behavior). In the BALB/c mice, while their performance in all behavioral tests was significantly reduced during pregnancy and P-P indicative of the development of depressive-like responses, no changes were observed in the C57BL/6 mice. Changes in NTs in BALB/C were as follows: PREP, all NTs in the three brain areas were decreased, although an increase in dopamine release was observed in the hippocampus. PREG: No changes were observed in the NTs except for a decrease in 5-HT in the striatum. P-P: striatum, low 5-HT, NE and dopamine; Hippocampus: low 5-HT, NE and high Dopamine; hypothalamus: all NTs increased, especially NE. Following pregnancy and delivery, the BALB/c mice developed depressive-like behavior associated with a significant decrease in 5-HT, dopamine and NE in the striatum and 5-HT and NE in the hippocampus. Dopamine increased in the latter together with a significant increase in all NTs in the hypothalamus. These findings suggest that the development of PPD may be associated with NT changes. Normalization of these alterations may have a role in the treatment of PPD.

1. Introduction

Post-Partum Depression (PPD) is a psychiatric disorder that occurs in 15% of pregnancies and contributes to physical and psychological damage in infant care and bonding. Impaired maternal-infant attachment during the critical stages of early brain development may lead to detrimental effects on infant's socio-emotional and neuro-cognitive development. Thus, these infants may suffer long-term behavioral and emotional problems, including increased susceptibility to mental illness. Moreover, PPD is associated with maternal morbidity and mortality [1].

PPD could result from alterations in hippocampal plasticity during the peri-partum period through the influence of sex steroids, stress, ageing [2] and lactation that may affect hippocampal neurogenesis [3]. The maternal brain is extremely plastic and displays complex neural modifications especially in the hippocampus related to cognition. Consequently, neurogenesis is one of the mechanisms by which the maternal brain exhibits plasticity [4]. Interestingly, repeated stress can alter remodeling of the maternal brain [5].

The monoamine deficiency hypothesis [6] posits that depressive symptoms arise from insufficient levels of the monoamine neurotransmitters 5-HT, NE, DA, or their combinations. The ability of antidepressants to elevate synaptic levels of biogenic amines such as 5-HT, NE, and DA, has been the rationale of therapy by those believing in the monoamine deficiency hypothesis. Maternal depression is also associated with changes in maternal monoamine

Abbreviations: DA, Dopamine; FST, forced swim test; 5-HT, 5-hydroxytryptamine; Hipp, hippocampus; Hypo, hypothalamus; NE, norepinephrine; NTs, neurotransmitters; OFT, open field test; P-P, post-partum; PPD, post-partum depression; PREG, pregnancy; PREP, pre-pregnancy; Str, striatum; TST, tail suspension test.

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neurotransmitters [7,8] which play an important role in maternity [9].

Serotonin (5-hydroxytryptamine or 5-HT) is thought to regulate neuro-developmental processes through maternal–fetal connections that may have long-term mental health implications. It is thought that beyond fetal 5-HT neurons, there are significant maternal contributions to fetal 5-HT during pregnancy [11,12]. Bonnin et al. have shown a new, direct role of placental metabolic pathways regulating fetal brain development and indicated that maternal–placental–fetal interactions could underlie the prominent impact of 5-HT on long-lasting mental health outcomes. Their results proved that serotonin in the fetal brain is derived from endogenous serotonin synthesis in the placenta from the pre-cursor tryptophan [11,13]. Gemmel et al. have investigated neurotransmitters in the maternal brain after repeated exposure to mood-based alterations in order to induce a maternal depressive-like state and have shown that gestational stress increased serotonin metabolism in the prefrontal cortex which was normalized by fluoxetine [14]. However, Although SSRIs trigger a number of intracellular processes that are likely to contribute to their therapeutic effects, early life antidepressant exposure during critical neurodevelopmental periods may elicit lasting negative effects in the offspring [15]. Moreover, pup separation reduces 5-HT1A receptor levels in the hippocampus of mother rats showing a role for the serotonergic system in maternal care and stress [9,10].

Stress experienced during delivery and puerperium is a risk factor for depression [16]. Stress-induced activation of noradrenergic neurons leads to the increased formation of the noradrenaline metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) [17,18]. Doornbos et al. [19], have shown elevated MHPG levels in the circulation of women with PPD symptoms which were associated with a higher stress sensitivity or a decreased stress-coping and was suggested to be involved with the initiation of depression. Oxytocin is important for the onset and progress of birth; it is regulated at the supraoptic nucleus by the release of norepinephrine in part by signals from the uterus [20]. Moreover, interaction between oxytocin genotypes and early experience predicts quality of mothering and postpartum mood [21].

Rats exposed to chronic stress during pregnancy display depressive-like behavior during the postpartum period and this might contribute to alterations in the offspring [22–25]. 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 associated with PPD [4]. As a result, gestational stress was suggested as a translational model for PPD [22].

Spatial memory, anxiety and central monoaminergic activities were measured in non-pregnant (NP) and pregnant females at the beginning and at the end of pregnancy. It was found that pregnancy was beneficial to spatial memory and may have decreased anxiety. Changes in monoamine levels and activity in specific brain regions of Sprague–Dawley rats indicated that the dopamine, norepinephrine and serotonin systems as well as BDNF may have contributed to the observed behavioral differences [26,27].

Increased P-P dopaminergic activity was required for maternal–pup caregiving [28,29]. Higher striatal DA concentrations were detected at 4 days P-P compared with estrous controls [30]. The striatal D2 receptor density was lower in late pregnancy relative to diestrus and early pregnancy [31–33]. The perinatal hormones estradiol, progesterone, cortisol, prolactin and oxytocin are all potential modulators of DA and D2 receptor function [32,33]. Moses- Kolko et al. [31] have shown a rapid attenuation of ventral striatal response to reward receipt in women with PPD. Enhanced responsiveness to selective serotonin reuptake inhibitors during lactation was shown in C57BL/6 mice which has important implications in the treatment of PPD [34]

The hippocampus, amygdala, and prefrontal cortex have been implicated in animal models of PPD [35,1,23]. Likewise, neuroimaging studies in mothers with PPD have demonstrated abnormal activity of the ventral striatum which is characterized by reduced activation in response to rewarding stimuli [31] which provide insight into the neural changes that could contribute to PPD. Hormones are fundamental for both the establishment and maintenance of pregnancy, parturition, and the onset of postpartum maternal behavior, with peptide hormones prolactin and oxytocin, and steroid hormones estrogen and progesterone having key roles. The center of hormone regulation is the hypothalamus, which is the major central nervous system (CNS) component of the hypothalamuspituitary-gonadal axis [36]. Therefore, the hippocampus, hypothalamus and striatum have major role in understanding PPD molecular mechanism.

Since the patho –etiology of PPD is unknown, animal models have been used to mimic the situation in humans. Some use hormonal treatment- ovarian [35] or oxytocin [52,53] – others use behavioral phenotypes. Among the most common of the latter are the differences in mouse strains between C57BL/6 and BALB/c mice. Although these strains differ in their anxiety and maternal phenotype, the majority of the research was focused upon the outcome for the offspring (see) [37]. However, determination of the underlying causes for their differing maternal styles could provide valuable insights into the etiology of the post-partum psychiatric disorder [54]. Two inbred mouse strain models of PPD were selected to study the correlation between NT levels and mood disorders. BALB/c mice are considered an anxious strain in comparison to C57BL/6 mice in behavioral models of anxiety & depression [37]. These strain differences were attributed to genetics, but might also be due to environmental and gene-environmental interactions. BALB/c mice are described as “poor mothers” and C57BL/6 mice as “good mothers” and mothering behavior in rodents affect both anxiety and stress behaviors in the offspring [37]. BALB/c mice showed reduced locomotor activity, less time in unprotected and brightly lit areas in the open field and light: dark assays [38–41], stress-induced increases in corticosterone release [38,42] and ACTH as well as basal differences in CRH, stress-induced differences in CRH receptor immunoreactivity [43], basal and stress-induced differences in expression of GABA A receptor subunits [44,37]. They differed also with respect to emotional reactivity, anxiety-like behavior and general activity with BALB/c mice being more reactive and fearful than C57BL/6 mice [37]. Moreover, they differed with respect to the maternal care: C57BL/6 dams have been found to spend more time licking and grooming their pups than BALB/c mice [45,46]. Moreover, BALB/c mice showed significantly greater anhedonia than C57BL/6 mice following both acute and chronic stress [44], therefore, they are more depressed than C57BL/6 mice.

PPD develops early following delivery. It was shown that the placenta is responsible for the effective serotonin levels during pregnancy in the fetal brain [11–13]. However, the alterations of NT were never before measured in detail in brains of pregnant and PPD mice. We correlated NT brain measurements with the development of PPD. PPD was evaluated by behavioral assays for the detection of depression including the Forced Swim Test (FST), Tail Suspension Test (TST) and Open Field Test (OFT). Two inbred mouse strain models of PPD were selected to study the correlation between NT levels and mood disorders. BALB/c mice are considered an anxious strain in comparison to C57BL/6 mice in behavioral models of anxiety & depression [37]. Characterization of these two mouse inbred strains over the course of pregnancy and in the P-P period for behavioral and intra-brain NT changes in the striatum (care-giving), hippocampus (cognitive function) and hypothalamus