Modeling postpartum depression in rats: theoretic and methodological issues

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ABSTRACT

The postpartum period is when a host of changes occur at molecular, cellular, physiological and behavioral levels to prepare female humans for the challenge of maternity. Alteration or prevention of these normal adaptions is thought to contribute to disruptions of emotion regulation, motivation and cognitive abilities that underlie postpartum mental disorders, such as postpartum depression. Despite the high incidence of this disorder, and the detrimental consequences for both mother and child, its etiology and related neurobiological mechanisms remain poorly understood, partially due to the lack of appropriate animal models. In recent decades, there have been a number of attempts to model postpartum depression disorder in rats. In the present review, we first describe clinical symptoms of postpartum depression and discuss known risk factors, including both genetic and environmental factors. Thereafter, we discuss various rat models that have been developed to capture various aspects of this disorder and knowledge gained from such attempts. In doing so, we focus on the theories behind each attempt and the methods used to achieve their goals. Finally, we point out several understudied areas in this field and make suggestions for future directions.

Keywords: Postpartum depression; Rat models; HPA axis; Stress; Estrogen

INTRODUCTION

Postpartum depression: the definition and treatments
Pregnancy, parturition and lactation bring about numerous changes in the female's brain, body and behavior which are essential for the survival and health of the offspring and necessary for the female to successfully respond to the new demands of her changed environment (Hillerer et al., 2012). However, disruption of these normal adaptations may underlie various neuropsychiatric disorders that occur in the postpartum period, such as postpartum depression, anxiety and psychosis disorders (Lonstein, 2007). It is estimated that approximately 5%-12% of mothers display postpartum anxiety (Andersson et al., 2006), 5%-25% postpartum depression (Beck, 2006), and 0.1% postpartum psychosis (Jones et al., 2008). Some individuals also show impairments in prospective memory (Henry & Rendell, 2007). Among these mental disorders, postpartum depression receives much more attention than other postpartum mental disorders because of its relatively higher severity, prevalence and greater impact on both children and mothers. A quick search of PubMed (http://www.ncbi.nlm.nih.gov/pubmed) with "postpartum depression" as a keyword on August 28, 2015 yielded 4 363 hits. As can be seen in Figure 1, the increasing trend started around 2000 and shows no sign of slowing down. This finding also suggests that we do not know enough about the pathophysiology of postpartum depression and more work needs to be done in order to find more efficacious treatments.

What is postpartum depression? Postpartum depression is a severe mood disorder that can affect women shortly after childbirth. Mothers with postpartum depression experience negative emotions (e.g., sadness, anxiety, etc.) and have difficulty caring for themselves and their infants. They may also avoid other people and withdraw from social interactions (O'Hara & McCabe, 2013). For diagnostic purposes, such depressed mood or loss of interest or pleasure in activities must be present daily for at least two weeks. Although postpartum depression is defined as an episode of major depression during the first six months postpartum (O'Hara & McCabe, 2013), the depressive episode could occur any time during the first postpartum year. At present, there is no consensus as to what constitutes the postpartum period for the purposes of research on postpartum depression, and the

prevalent rates vary depending on the specific periods that are examined. One meta-analysis reveals that the combined point prevalence estimates for major and minor depression ranged from 6.5% to 12.9% (1.0%-5.6%) at different trimesters of pregnancy and months in the first postpartum year, peaking at two and six months after delivery (Gavin et al., 2005). Many symptoms of postpartum depression are not

different from those seen in major depressive disorder, with one noticeable difference being that the inflicted mothers lose interest in babies, and may find infant stimuli aversive (Bifulco et al., 2004). These reactions to infants may be linked to the dramatic decreases in several steroid hormones, including estradiol, progesterone, and cortisol, at least for some vulnerable women.
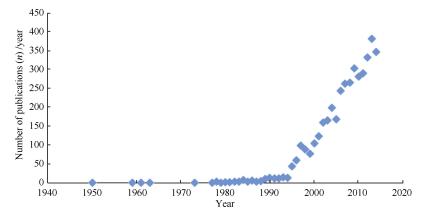

Figure 1 Number of publications from 1950 to 2014 with the keyword "postpartum depression" searched in PubMed on August 28, 2015

Treatments for postpartum depression include psychotherapy and pharmacotherapy (e.g., antidepressants). Systematic reviews have suggested that individual interpersonal psychotherapy (IPT), cognitive-behavior therapy (CBT), and psychodynamic therapy may be effective psychologic treatments for postpartum depression with moderate effect sizes (Pearlstein et al., 2009). Antidepressant medications demonstrate larger effect sizes, but the long-term impacts of prenatal and postnatal drug exposure on the brain and psychological functions of the offspring remain a concern (Pearlstein, 2013). However, because there is little transfer of newer antidepressants to the infant via breastfeeding and they do not appear to be associated with any specific pattern of malformations, it is generally recommended that women remain on their medications (Yonkers et al., 2014).

Risk factors for the development of post-partum depression
Postpartum depression does not have a single cause. Like many neuropsychiatric disorders, postpartum depression has both genetic bases and environmental causes (Kendler et al., 2001). It is well established that, on average, the risk for the development of major depression is approximately one-third genetic and two-thirds environmental (Nemeroff, 2008). Postpartum depression may not be an exception. This conclusion is supported recently by a comprehensive review which examined 214 publications from 2000 through 2013 on biological and psychosocial factors associated with postpartum depressive symptoms (Yim et al., 2015). This large body of literature includes 199 investigations of 151 651 women in the first postpartum year. It reveals that the strongest risk predictors among biological processes for postpartum depression are hypothalamic-pituitary-adrenal (HPA) dysregulation, inflammatory processes, and genetic vulnerabilities. Among psychosocial

factors, the strongest predictors are severe life events, some forms of chronic strain, relationship quality, and support from partner and mother. In this section, we selectively describe the known genetic and broad environmental factors that contribute to this illness.

Genetic factors
Postpartum depression has a strong genetic component. It is often observed that an individual would have an increased risk to develop postpartum depression if she has had symptoms of depression during or after a previous pregnancy; has previous experience with depression or bipolar disorder at another time in her life; or has a family member who has been diagnosed with depression or other mental illnesses. For example, Forty et al. (2006) reported that familial factors play a role in determining vulnerability to postpartum depression (defined as a major depressive episode occurring within four weeks of delivery). They found that among the 90 parous women, 31 had a sister with a history of postpartum depression. In those women, 29% of all deliveries (42% of first deliveries) were followed by an episode of postpartum depression. Of the 59 women whose sister had not suffered an episode of postpartum depression, only 12% of all deliveries (15% of first deliveries) were followed by an episode of postpartum depression. These findings suggest that genes shared by family members may play a role in the etiology of postpartum depression. Although they also support a significant contribution of environmental factors in the development of this complex mental disorder. Couto et al. (2015) conducted a systematic, integrative review that includes 20 studies with different methodologies to answer questions about the relationship between genetic factors and the development of postpartum depression. They reported that postpartum depression shares the same genetic background with major

depression. Thus, several well-known genes implicated in major depression, such as those linked to serotonin transporter (5-HTT), tryptophan hydroxylase 2 (TPH2), monoamine oxidase (MAO), catechol-o-methyl transferase (COMT) are also extensively examined in the context of postpartum depression. The summarized evidence regarding 5HTT gene polymorphisms suggests that the 5HTTLPR long allele might be a risk factor for postpartum depression, especially when it is coupled with other risk factors, such as unfavorable environments; previous psychiatric history; maternity stressors and COMT-Val158Met allele; autumn or winter delivery; and stressful life events, etc. In addition, Lin et al. (2009) examined the role of TPH2, the rate-limiting enzyme of serotonin biosynthesis, in the etiology of peripartum major depression and anxiety disorder in a Han Chinese population in Taiwan. They reported that the TPH2 2755A allele was found only in women with peripartum major depression and anxiety disorder (P=0.043) and exhibited a dominant gene action (P=0.038) with an estimated disease risk of 1.73. Hence, despite its small sample size and ethnic limitation, this study suggests that the TPH2 C2755A polymorphism may represent a population-specific risk factor for postpartum depression and anxiety disorder, perhaps by interacting with hormones. Finally, one large-scale study (n=1 210) used a genome-wide linkage analysis to search for chromosomal regions that contain genetic variants conferring susceptibility for postpartum depressive symptoms and showed modest evidence of an association between postpartum mood symptoms and a single-nucleotide polymorphism on chromosome 1 in the HMCN1 gene (Mahon et al., 2009). HMCN1 contains four estrogen-binding sites and may contribute to a phenotype of postpartum depression. In sum, various studies have suggested that postpartum mood symptoms have a partly genetic etiology, although how different polymorphisms lead to different neurobiological processes that change the vulnerability for postpartum depression remains to be elucidated.

Environmental factors

Here, environmental factors are broadly defined, including any factor that is not biological. Thus, marital problems, low socioecomomic status, lack of social support, obstetric pregnancy-related complications (e.g., Caesarean section or instrumental delivery), and alcohol or other drug abuse problems are all environmental factors that have been implicated in postpartum depression (Giurgescu et al., 2015). One common theme of these factors is that they all exert certain degrees of psychosocial stress upon affected individuals. Thus, it could be concluded that exposure to chronic stress before and/or during pregnancy is one of the most studied risk factors for postpartum depression (Bifulco et al., 1998). Indeed, exposure to chronic stress during pregnancy or shortly after giving birth is cited as a preceding factor for depression (Parker et al., 2003). It is also one of the most convincing, and translational, risk factors that many animal approaches employ to develop postpartum depression models. Accumulating evidence suggests that the way that chronic stress causes postpartum depression is to prevent behavioral,

neuroendocrine, and neuronal adaptations specific to the reproductive status of the female (Hillerer et al., 2012). The readers are encouraged to read Yim et al. (2015) for a detailed analysis of various psychosocial factors.

Behavioral measures for modeling different aspects of clinical symptoms

An ideal animal model of postpartum depression must encompass all of the following important features or components: a genetic risk factor; peripartum stress; altered maternal behavior and associated changes in infants' physiology and behavior and most importantly, various depression-like behaviors. In reality, however, most models only capture some aspects of etiology and risk factors of postpartum depression. As a way to describe various rat models of postpartum depression, we begin with descriptions of some of the tests that have been used to capture various symptoms of postpartum depression and their impacts. One obvious behavioral test of the manifestation of postpartum depression in mother rats is the maternal behavior test. Maternal behavioral test typically consists of a pup retrieval test and an observation test. In the pup retrieval, all pups are first removed from the dam for either a few seconds or several hours, and then re-introduced into the home cage. The number of pup retrievals and pup retrieval latencies are recorded. In the observation test, the frequency and duration of pup licking, nest building and pup nursing are recorded for 10 to 30 minutes. As a validation tool, it should be expected that a rat with depression-like symptoms shows deficits in various maternal responses, such as prolonged pup retrieval, lowered pup licking and reduced high-arched nursing. Slowed body weight increase in postpartum females and rat pups are also being used as a proxy measure of the impact of postpartum depression symptoms (Nephew & Bridges, 2011). However, in reality, this validation criterion (i.e., negative impacts on maternal care) has not always been met.

The forced swim test is a widely used measure of a depression-like state (Englisch et al., 2009). It is also often used to gauge the magnitude of postpartum depression. In a typical study (Slattery & Cryan, 2012), female rats are placed for 15 min in a water-filled cylinder from which they cannot escape. On the next day, they are placed in the same cylinder for 5 min. The time that they spend floating immobile (a measure of "learned helplessness"), swimming or climbing the walls of the cylinder (escape behaviors), and the latency to the first bout of immobility are recorded. Time spent immobile is a measure of passive stress coping (i.e., depression), whereas latency to the first immobility and time spent in escape behaviors are measures of active stress coping.

Another widely used behavioral test of depression is the sucrose preference test. This is a classic test of anhedonia which essentially measures a rat's appetite for a highly palatable, rewarding substance (e.g., 1% sucrose solution) (Hill et al., 2014). A rat is given access to two bottles (water or 1% sucrose) for some time and fluid consumption is measured. The percentage preference for sucrose over water is typically used

as a measure for rats' sensitivity towards reward. A "depressed" rat is expected to show a decreased percentage preference for sucrose than the normal control (Navarre et al., 2010).

The elevated plus maze (EPM) is a canonical rodent test of anxiety-like behavior and has also been used to assess depression-like behaviors in mother rats, given the high-comorbid rate between anxiety and depression. The standard EPM procedure involves placing rats on the EPM for 5 min, and recording the number of entries made into enclosed and open arms and time spent in each. The percentage of testing time subjects spend in the open arms of the maze is an inverse measure of anxiety (or depression).

Various animal models of postpartum depression

In this section, we describe the preclinical approaches that have been taken to model postpartum depression in rats. This list of rat models is not meant to be comprehensive, but rather selective, focusing on those better known models with supporting evidence for their validity. Some models are developed based on the putative changes in parturitional hormones (i.e., the hormone withdrawal model) or stress hormones (i.e., the chronic corticosterone treatment model). Some rely on social stress during the postpartum (i.e., the repeated maternal separation model and the chronic social stress model) or pregnant period (i.e., the gestational stress model). Still others use a traditional depression model (i.e., the learned helplessness model) or a combination of stress and early environmental risk factor (i.e., the maternal immune activation (MIA) potentiated by repeated maternal separation stress model). As is evident, these animal models of postpartum depression all encompass a significant stress component, while the genetic component is missing, partially due to our lack of deeper understanding the determinant genes for this disorder. In terms of various validity, many of these models have certain degrees of face validity, as mother animals subjected to various manipulations exhibit depression-like behaviors during postpartum and occasionally show impaired maternal care. They also have certain degrees of construct validity, as there is a partial match between what is measured at the behavioral (psychological, e.g., depression-like behaviors) and neural levels (e.g., hippocampus) in the animal models of postpartum depression with what is believed to be the behavioral and neural processes underlying this disorder in humans. The *predictive* validity (i.e., demonstrating that antidepressants ameliorate depression-like behaviors in mother animals and improve maternal care), however, has not been well established in most of these models. Unless experimental situations and associated manipulations used to induce postpartum depression in animals are reproducible and consistent within and across laboratories, it is impossible to achieve a high degree of predictive and construct validity. Unfortunately, we are not there yet. With this cautionary note in mind, let us look at some of the commonly studied models.

The hormone withdrawal model

After childbirth, the circulating high levels of estradiol and progesterone achieved during pregnancy decline quickly to pre-pregnancy levels within days. These rapid changes in reproductive hormones immediately following childbirth are believed to contribute to postpartum depression. For example, Bloch et al. (2000) provides direct evidence implicating the reproductive hormones estrogen and progesterone in the development of postpartum depression. They showed that withdrawal from an 8-week treatment of supraphysiologic doses of estradiol and progesterone induced depressive symptoms in women with a history of postpartum depression. Therefore, the hormone withdrawal regimen has been used as a model for examining depression-like behavior in postpartum female rats. In one study (Galea et al., 2001), ovariectomized female rats were injected with a low dose of estradiol benzoate (2.5 μg) and a high dose of progesterone (4 mg) daily for 16 consecutive days. The dose of estradiol was increased to 50 μg from day 17 to 23 to mimic the levels observed in pregnancy. Three days after hormone withdrawal, rats were tested in the forced swim test and open field test (an assessment of general motor activity and anxiety). It was found that female rats undergoing estradiol withdrawal show increased immobility and decreased struggling and swimming behaviors in the forced swim test. These depression-like responses could not be explained by the change in general locomotor activity, as these rats were more active in the open field test. Continual treatment with high levels of estradiol was able to reverse the depression-like behaviors in the forced swim test. For the first time, this study demonstrates that withdrawal from chronic high levels of pregnancy-associated hormones (estradiol and progesterone) can produce depression-like symptoms in female rats and prolonged exposure to high levels of estradiol through the post-partum period might be effective to reverse the effects of hormone withdrawal.

More recently, Schiller et al. (2013) used the intra-cranial (lateral hypothalamus) self-stimulation technique and the forced swim test in an attempt to validate the hormone withdrawal model of postpartum depression in rats. The intra-cranial self-stimulation responding is a test developed to study the brain's reward processing. It is well known that rats implanted chronically with electrodes in the posterior lateral hypothalamus can be trained to press levers in order to self-stimulate this brain region electrically. Anhedonic animals tend to show a decrease in self-stimulation. In this study, they found that ovariectomized rats withdrawn from estradiol treatment showed reduced responding for electrical stimulation and had significantly greater immobility and less swimming than controls in the forced swim test. These results show that withdrawal from estradiol caused anhedonic-like behavior. Navarre et al. (2010) further showed that estradiol withdrawal following estradiol and progesterone treatment causes anhedonia during the early "postpartum" period, as hormonal withdrawal causes animals to display decreased sucrose preference in the sucrose preference test. Overall, the hormonal withdrawal model (especially from estrogen) represents a valid approach for the study of certain aspects of postpartum depression, as it captures the possible negative impacts of hormonal fluctuations associated with pregnancy and lactation on emotion regulation.

The chronic corticosterone treatment model

This model was developed by Brummelte et al. (Brummelte & Galea, 2010; Brummelte et al., 2006) to mimic the hypercortisolism found in patients with major depression. In their studies, rat dams were treated with either a low dose (10 mg/kg) or a high dose of corticosterone (CORT) (40 mg/kg) either during gestation, postpartum, or across both gestation and postpartum. They found that dams exposed to 40 mg/kg CORT during postpartum expressed "depressive-like" behavior compared to controls, with decreased struggling behavior and increased immobility in the forced swim test, reduced body weight, and reduced maternal care (more time off the nest and reduced time spent on nursing). In addition, gestational and/or postpartum treatment with high CORT reduced cell proliferation in the dentate gyrus of postpartum dams compared to oil-treated controls. Therefore, it appears that prolonged treatment with high levels of CORT could be considered as a valid animal model of postpartum depression, due to its negative impacts on maternal care, hippocampal cell proliferation and depressive-like behavior. This approach has an advantage over other physical or social stress models in that it allows for more controllability of the hormone levels in the dams, less individual variability, and avoids maternal separation, which exposes the offspring to the same stressor.

The repeated maternal separation model

The repeated maternal separation model as a possible model of postpartum depression was clearly presented in Boccia et al. (2007). This model is based on the observation that long (>3 h) daily separations of rat pups from their mothers increase dams' stress responses and decrease pup licking. Thus, it was hypothesized that daily long maternal separation would induce learned helplessness, creating a depression-like state in mother rats. In this model, on postpartum days 3-14, mother rats were separated from their litters daily for either 3 h or 15 min and were compared to the control rats that were not separated from their pups or disturbed at all in the forced swim test and maternal behavior tests. They found that dams subjected to repeated, 3 h maternal separation from PND 3-14 developed depression-like behaviors at postpartum week 3, immediately after weaning, with increased immobility in the forced swim test compared to non-separated and 15 min separated dams. This model has an advantage in which it employs a psychological and social stress regimen, rather than physical stressors (e.g., restraining) or pharmacological stress (e.g., corticosterone), which mimics human conditions better, as human depression more often entails loss of, disruption of, or change in significant social relationships.

The chronic social stress model

As mentioned above, chronic exposure to psychosocial stress is a major contributing factor to postpartum depression. Nephew & Bridges (2011) described a novel model that captures this aspect of postpartum depression. In this study, chronic social stress was achieved by using a chronic social defeat paradigm. Previous works show that social defeat of a mother rat is a severe stressor, as acute exposure to a novel male intruder elicits robust stress responses in lactating females (Nephew et al., 2010), and causes a mother to kill her litter (Nephew & Bridges, 2011). Thus, it was hypothesized that chronic daily exposure to a novel male intruder would cause a depression-like state in lactating mothers, reduce the display of maternal behavior (e.g., decreased pup licking and nursing), and increase aggression due to social instigation. In this study (Nephew & Bridges, 2011), postpartum female rats were assigned into the chronic social stress group, which had a novel intruder male placed in their home cage for 1 h each day from days 2-16 of lactation; and the control group, which was exposed to the intruder for 30 min only on days 2, 9, and 16 of lactation - the days when all dams were tested for maternal care and maternal aggression. Maternal care testing consisted of the re-introduction of all eight pups to the home cage after a 30-minute removal, and behavior was then video recorded for 30 min. They reported that on day 9 of lactation, the socially stressed group had longer latency to initiate nursing and lower durations of pup grooming and total maternal care. On maternal aggression, the socially stressed dams also had shorter aggression latencies and longer average aggressive bouts, and their body weight increase and the growth of their pups were both lower than the control dams. This study suggests that chronic social stress during lactation attenuates maternal care and the growth of both dams and pups, and increases the expression of maternal aggression toward a novel male intruder, indicating that this model may be useful to model the social conflict-induced depression-like behaviors in animals.

The gestational stress models

Like other stress-based models, this approach attempts to capture the stress-induced increase in risk to develop postpartum depression by administering chronic stress during pregnancy. One model, developed by Inga Neumann and David Slattery's group (Hillerer et al., 2011) subjected pregnant females alternatively to daily restraint stress and overcrowding (4 unfamiliar pregnant rats housed together for 24 h) from gestation days 4-16. Stressed females showed decreased body-weight gain and increased adrenal weight relative to their nonstressed controls. Chronic stress also prevented a number of peripartum adaptations, including basal plasma hypercorticism, increased oxytocin mRNA expression in the hypothalamic PVN, and anxiolysis (Hillerer et al., 2011). More importantly, none of these parameters were affected in stressed virgins, indicating the specificity of these stress-induced changes to the peripartum period. This model is thought to be more relevant to the human condition than other non-social stress paradigms (e.g. repeated restraint stress) (see below).

In Smith et al. (2004), pregnant rats underwent daily restraint stress (1 h/day, days 10-20 of gestation), or were left undisturbed (control). On post-parturition days 3 and 4, dams were tested in the forced swim test. Gestational stress significantly elevated immobility scores by approximately 25% above control values on the second test day. Maternal behaviors, especially arched-back nursing and nesting/grouping pups, were reduced in the stressed dams. Importantly, their

offspring also showed increased immobility in the forced swim test and hypersecreted stress hormones in response to an acute stress challenge in adulthood. These data show that gestational stress might alter maternal behavior in mother rats by inducing a depression-like state. This state coincides with reduced maternal care, and result in increased stress responses in adult offspring. Overall, applying stress during the gestational period could increase depression-like and anxiety-like behaviors in the postpartum rat, and could be a useful tool to study emotional changes associated with gestation and lactation.

The learned helplessness (LH) model

It has been well documented that exposure to inescapable shock interferes with the subsequent learning of escape responses, in comparison to exposure to equivalent amounts of escapable shock. This effect is known as learned helplessness (LH) and has been used to model major depression (Maier & Watkins, 2005; Malberg & Duman, 2003; Shirayama et al., 2002; Valentine et al., 2008). Williams (1984) conducted the first study that examined the role of controllable versus uncontrollable postpartum stress on subsequent maternal responses towards pups. Specifically, he subjected rat dams to one of three 8-day postpartum treatments on postpartum days 8-15: tail-shock wheel-turn escape training, yoked inescapable shock, or restraint without shock, then conducted maternal behavior observation at 24 h before and 24 h and 72 h after such a treatment. Each shock training session consisted of 80 trials of tail shock ranging from 0.8 mA (Trials 1-19), to 1.0 mA (Trials 20-39), to 1.3 mA (Trials 40-59), and to 1.6 mA (Trials 60-80) presented on a variable-time schedule, with a mean interval of 60 sec and a range of 30-120 sec. Shock terminated when the rat in the escape training group had completed a one-quarter turn of the wheel beyond 0.8-1.6 sec following shock onset. Maternal behavioral observations were conducted after the dams were briefly removed from their pups and the home cage was placed in an observation chamber. Latency and frequency of nest approaching, leaving, pup retrieving and oral contacts were recorded for 15 min. He found that inescapable shock impaired maternal responses, as dams approached the nest slower, spent less time in the vicinity of the nest, and contacted their pups less frequently and for shorter durations. These disruptions in maternal responses were found during both the 24 h and the 72 h posttreatment sessions. Therefore, although the specific mechanisms underlying the effects of learned helplessness on maternal behavior are still not clear, this study demonstrates that the LH paradigm may be a useful model to study postpartum depression.

Recently, Kurata et al. (2009) has provided further support of the usefulness of this paradigm. They also focused on the influence of early postpartum maternal learned helplessness (LH) on subsequent maternal behavior. To induce learned helplessness, dams were given an inescapable shock session (IS-session) on postpartum day 3, and an avoidant test session (AT-session) on postpartum day 4. In the IS-session, each rat was exposed to 80 inescapable foot-shocks (0.8 mA, each duration: 15 sec) from the electrified grid floor in a chamber.

The AT-session was performed 24 h later, in which each rat was placed in the same chamber, and exposed to 15 foot-shock trials. Each foot shock trial could be terminated by pressing a lever. If the escape latency was from 20 sec to 60 sec, the trial was considered a 'failure'. Based on the number of escape failure, rat dams were classified rats as non-LH (<4 failures) or LH (>11 failures). Maternal behavior data collected daily in the first two weeks postpartum showed that the LH dams had reduced levels of active nursing behavior. Once again, this study supports the notion that LH is capable of exerting a robust negative impact on active maternal behavior and could serve as a useful model to study postpartum depression.

The maternal immune activation (MIA) potentiated by stress model

Early life stress is known to induce long term affective dysregulation. As such, most recently our group investigated a potential early life stress-based model termed the maternal immune activation (MIA) model. We injected pregnant female rats with polyinosinic: polycytidylic acid (poly I:C, 4 mg/kg, *iv*) on gestation day 15. Poly I:C is an immunostimulant that is known to induce *in utero* stress in pregnant rats. We then applied the 3-h repeated maternal separation during the first two postnatal weeks and examined the maternal behavior of the adult female offspring when they become mothers. We found that early life-stressed female offspring displayed reduced nest building in the maternal behavior test on postpartum days 2, 4, and 6 compared to dams without a history of early life stress exposure. This preliminary result suggests that early environmental stressors may alter postpartum maternal behaviors and potentially serve as a useful tool to model early life adversity-induced depressive-like behaviors in postpartum rats.

CONCLUSION

Given the detrimental effects of postpartum depression on mothers and their children, understanding the underlying behavioral and neurobiological basis using an animal model would be beneficial. Thus far, we have selectively commented on a few commonly used animal models of postpartum depression and outlined their main findings. These models all encompass a stress component and attempt to capture certain human conditions that posit risks for this disorder; however, they all miss the genetic component. In addition, none of these models is intended to recapitulate all the possible risk factors and the entire symptomology. This might prove to be a more feasible way to reveal the concerted effect of physiological and psychological stress on the brain and psychological functions of the dam.

As pointed out by Hillerer et al. (2012), one major reason that the etiology and neurobiology of postpartum depression remain poorly understood is the lack of appropriate animal models. It is thus urgent to develop and validate an animal model that can simultaneously capture various psychological and physiological processes critical for the normal and disrupted expressions of maternal behavior and mental health of postpartum females.

Additionally, previous work on the psychological processes (e.g., emotion regulation, learning and memory, attention) affected by reproduction (e.g., pregnancy and lactation) and stress often examines them in isolation or in separate tests, precluding the examination of their potential interactions in contributing to postpartum mental disorders. For example, it has been shown that gestational stress often causes a long-lasting suppression of learning and memory ability and can even abolish the cognitive-protective or enhancement effects of maternal experience (Lemaire et al., 2006). However, whether it causes this disruption through disturbing the emotional system or learning and memory mechanisms alone or in combination is not clear, as they are often not assessed concurrently. Further, conflicting findings exist in regards to the effects of reproduction on basic psychological functions. For example, numerous studies report that postpartum rats are less anxious than virgins in behavioral tests of anxiety (Lonstein, 2005). However, many others failed to find similar effects in lactating rats (Lonstein, 2007). Also, how this reduced anxiety interacts with gestational and postpartum stress in giving rise to depression-like and anxiety-like behavior in mother rats is not clear. Additionally, how pup presence and physical contact with pups play a role in modulating the impact of postpartum stress on depression-like and anxiety-like behaviors need to be further examined. For these reasons, one future research direction is to develop innovative animal models that simultaneously capture multiple behavioral and neuroadaptive changes associated with reproductive life and are sensitive to various environmental risk factors. This paradigm could be used to explore the neurobiological correlates of postpartum mental disorders. For example, we could explore the roles of 5-HT and its related receptors, given its known roles in anxiety, depression, affiliation, impulsivity and aggression (Cools et al., 2008; Graeff et al., 1996), and determine how functional disruptions of the bed nucleus of the stria terminalis (BST) contribute to maternal anxiety (Lonstein, 2007).

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