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Franco Rafael Mir, Antonella Pollano, María Angélica Rivarola

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TITLE

ANIMAL MODELS OF POSTPARTUM DEPRESSION REVISITED

AUTHOR NAMES and AFFILIATIONS

Franco Rafael Mir [1,3]

Antonella Pollano [2,3]

María Angélica Rivarola [2,3]

1-Departamento de Ciencias Exactas Físicas y Naturales, Universidad Nacional de La Rioja

Av. Luis M. de la Fuente S/N, Ciudad Universitaria de la Ciencia y de la Técnica, F5300 La Rioja - Argentina

2-Instituto de Investigaciones en Ciencias de la Salud (INICSA), Consejo Nacional de Investigaciones Científicas y Tecnológicas, Universidad Nacional de Córdoba.

Enrique Barros esq. Enfermera Gordillo. Ciudad Universitaria. X5016 - Córdoba - Argentina

3-Facultad de Ciencias Exactas Físicas y Naturales, Universidad Nacional de Córdoba

Av. Velez Sasfield 299. X5000JJC – Córdoba - Argentina

CORRESPONDING AUTHOR

María Angélica Rivarola arivarola@unc.edu.ar

SUMMARY

Postpartum depression (PPD) is a heterogeneous mood disorder and the most frequent psychiatric complication of the postnatal period. Given its potential long-lasting repercussions on the well-being of the mother and the infants, it should be a priority in public health. In spite of efforts devoted to clinical investigation and preclinical studies, the underlying neurobiological mechanisms of this disorder remain unknown in detail. Much of the progress in the area has been made from animal models, especially rodent models. The aim of this mini-

review is to update the current rodent models in PPD research and their main contributions to the field. Animal models are critical tools to advance understanding of the pathophysiological basis of this disorder and to help the development of new therapeutic strategies. Here, we group PPD models into 2 main categories (Models based on hormone manipulations, Models based on stress exposure), each of which includes different paradigms that reflect risk factors or physiological conditions associated with this disease. Finally, we provide an overview of emerging models that provide new perspectives on the study of possible pathophysiological factors related to PPD, to contribute to tackling potential therapeutic targets.

KEYWORDS Postpartum depression; animal models; female mental health

1. INTRODUCTION

The reproductive experience (pregnancy, childbirth, and lactation) induces profound physiological, neuroendocrine, and behavioral changes in all mammal species. These changes prepare the female to ensure the survival of her young and herself in the face of the new environmental exigencies of motherhood. It also promotes changes in nerve circuits and behavior that are not directly related to the care of the offspring (but do, indirectly, contribute to it) and involve cognitive, affective, and stress responses (Barba-Müller et al., 2019; Bridges, 2016; Hillerer et al., 2014, 2012). However, the peripartum is also a period of vulnerability for developing mood disorders, especially when risk factors are present that increase susceptibility. Even though the etiology of postpartum affective disorders is not fully known, genetic, psychosocial, environmental and biological risk factors have been proposed (Payne and Maguire, 2019). Among peripartum psychiatric disorders, postpartum depression (PPD) is a serious psychiatric disorder with devastating consequences not only for the well-being of the mother but also for her child and the family. PPD has been estimated to affect 10-20 % of

women (Nguyen et al., 2019). Although the clinical symptomatology of PPD is similar to that of depressive episodes observed in other periods of life (major depressive disorder, MDD), PPD has particular characteristics that justify its consideration as a nosological entity on its own (Brummelte and Galea, 2016).

According to the Diagnostic and Statistical Manual of Mental Disorders, PPD is an episode of major depressive disorder, i.e., the presence of one or more main symptoms (depressed mood, anhedonia) and five or more additional symptoms (weight changes, sleep and eating disorders, agitation or psychomotor retardation, fatigue, feelings of worthlessness or excessive guilt, decreased ability to concentrate, thoughts of death or suicidal ideation) for at least two weeks, occurring either in pregnancy or within 4-6 weeks after delivery. The fifth edition of this manual (DSM-V) specifies the phenomenon as depression "with peripartum onset" with mood symptoms occurring during pregnancy or in the 4 weeks after delivery (Am. Psychiatr. Assoc, 2013). It is worth noting that the definition proposed by the DSM-V remains controversial, principally due to the limited temporal criteria used. The onset of depressive symptoms within six weeks postpartum is accepted by the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) and it is proposed empirically as during the first year after delivery by some authors (Goodman, 2004; O'Hara, 2009).

A common mental health problem that women also experience during the perinatal period is anxiety, which has frequent comorbidity with depression (Dennis et al., 2017). This constitutes peripartum anxiety disorder, and some of the models discussed here can also be used to mimic some of its symptoms. However, models of peripartum anxiety disorder are beyond the scope of this review.

Numerous studies have demonstrated that, if left untreated, PPD can have long-term adverse effects for the mother as well as for the child. There is a general consensus in the evidence that maternal depression constitutes stress for the infant, which in turn can significantly

impact brain development. Adverse effects on the child's cognitive, socioemotional and behavioral development have been widely documented (Bernard-Bonnin, 2004; Fitzgerald et al., 2021; Meaney, 2018; Takács et al., 2020), hence the importance of considering it as a serious public health problem and studying in depth the causes and consequences of this pathology. Despite the large number of epidemiological studies on the prevalence of this pathology and its significant consequences on the progeny, there are several questions about its etiology and a number of gaps in the literature that still need to be addressed.

The use of animal models is essential for studying the biological substrates of disease, understanding etiopathogenesis and pathophysiology, and developing and testing novel treatments. In general, modeling psychiatric illness in animals is a great challenge scientifically (Kokras and Dalla, 2014; Nani et al., 2019; Salgado and Sandner, 2013). Traditionally, three validity criteria are used to determine the ability of a model to provide information on human pathology: predictive validity (whether pharmacological or non-pharmacological treatments used in human patients have the same effect in the animal model), face validity (whether the behavior/phenotype of the model is similar to the human behavior/phenotype of the disease assessed), and construct validity (which refers to the correspondence between the underlying genetic or cellular mechanisms that result in psychological dysfunction in the animal model and in the human population (Belzung and Lemoine, 2011). However, none of the animal models fully meets all the validity criteria. This has led to revisions and redefinitions of the validation criteria of the models (Belzung and Lemoine, 2011; Nestler and Hyman, 2010; Salgado and Sandner, 2013), that are beyond the scope of this review.

Like other psychiatric disorders, PPD is a complex and heterogeneous disease and does not have a single cause. In addition to the psychosocial risk factors associated with PPD (such as stress, lack of social support, marital conflicts, low income, personal and family history of

depression, anxiety, premenstrual dysphoria), several biological factors have been proposed as causes of PPD (Couto et al., 2015)(Bloch et al., 2003; Goodman, 2004; Nguyen et al., 2019; O'Hara, 2009; Payne and Maguire, 2019). Over the last decade, a variety of animal models for studying PPD have been developed and standardized. As it is impossible to reproduce all the complexity of this pathology, animal models developed to study PPD reproduce some specific traits of the disease. Several animal models attempt to mimic depression-like behavior during postpartum, inducing this condition in different ways according to the possible underlying mechanisms that are postulated. Excellent reviews have been previously published (Li and Chou, 2016; Perani and Slattery, 2014).

Considering that it is an area of research that deserves an update, here we review a selection of the classical models and recent literature on relevant animal models used in PPD research over the last 20 years, including approaches emerging in recent years that set new directions in the study of potential strategies for the preclinical investigation of PPD.

2. ANIMAL MODELS OF POSTPARTUM DEPRESSION

Table 1: ANIMAL MODELS OF PPD AND MAJOR FINDINGS

A summary of the pre-clinical studies focused on rodent models of PPD and their main contributions can be found in Table 1.

2.1 Models based on hormone manipulations

2.1.1 Hormone Withdrawal Model

Studies in humans and laboratory animals suggested that the rapid perinatal change in reproductive hormones may contribute to the etiology of PPD qs33 (Schiller et al., 2015). Based on the physiological fact of the abrupt fall in the hormone levels of estrogen and progesterone that occurs after childbirth, PPD has been related to a differential sensitivity to

hormone fluctuations occurring during the postpartum period, giving rise to the hormone withdrawal hypothesis of PPD (S Brummelte and Galea, 2010).

Galea et al. (Galea et al., 2001) provided some of the first experimental evidence using a hormone withdrawal model, developed to investigate depressive-like behavior during the postpartum period in rodents. In this model, hormone-simulated pregnancy (HSP) was induced by daily administration of estradiol and progesterone in ovariectomized female rats for 23 days. After a 2-day period of hormone withdrawal, animals were tested for depressive-like behaviors. Increased depressive-like behaviors were reported in the Forced Swimming test (FST). In later works, Galea also found an increase in anhedonia measured in the sucrose consumption and preference test, not related to alterations in anxiety levels or in general levels of locomotion. At the same time, a decrease was detected in levels of cell proliferation in the hippocampus. This reduction was prevented by estradiol or a selective estrogen receptor β agonist, suggesting an important role of hormone decline in the cellular changes that accompany depressive-like symptomatology during postpartum (Green et al., 2009; Green and Galea, 2008).

In agreement with these findings, Navarre et al. found that estradiol withdrawal induced anhedonia during the postpartum period in the HSP model. However, when comparing with females who had a real pregnancy, this effect was not observed, suggesting that there are other mechanisms during the postpartum period that attenuate the effect of hormone withdrawal (Navarre et al., 2010). Particularly, prolactin and oxytocin levels (known to be increased in the postpartum period) have been shown to possess anxiolytic/anti-stress and antidepressant effects, and could play an important role in regulating neuroendocrine and behavioral characteristics of the peripartum period (see Neumann, 2003). Likewise, other researchers reported that a rapid drop of ovarian hormones induced an increased startle response, and increased anxiety-like behavior in the open field (Doornbos et al., 2009). Using a

different HSP model in rats that mimics human pregnancy and postpartum period, a behavioral phenotype has been reported consistent with PPD, including behavioral despair in the learned helplessness paradigm, increased anxiety in the elevated plus maze and increased aggression. Gene expression analysis revealed transient regulation of several genes (Ca2+/calmodulin-dependent protein kinase IIα, serotonin transporter, myocyte enhancer factor 2A, brain-derived neurotrophic factor, gamma-aminobutyric acid type A receptor α4 and aquaporin 4) in the brain that may contribute to the pathophysiology of PPD (Suda et al., 2008). The peculiarity of this model is that the hormonal doses were administered in such a way as to simulate gestation in humans in which there is a gradual increase in both estrogens and progesterone throughout gestation, as a novel strategy to simulate human PPD. In order to achieve this, ovariectomized rats were given pellet implantation for continuous release of 0.5 mg and 50 mg of progesterone during 21 days, followed by a rapid withdrawal. Similarly, estrogen withdrawal after HSP in mice induced depression-like, anxiety-like behaviors and affected hippocampal neurogenesis (Zhang et al., 2016). The neurobiological and molecular mechanisms underlying this effect indicated a role of hippocampal nNOS-NO-CREB reduction, which may explain the depressive-like phenotype observed in mice (Zhang et al., 2017).

Using the PPD animal model induced by estrogen withdrawal in rats, Wang et al. observed reduced hippocampal expression of the glucocorticoid receptors, GR and Sirtuin 1 (NAD+-dependent histone deacetylase and transcriptional enhancer of GR), suggesting a role of the SIRT1-GR signaling pathway in the neuropathology of PPD (Wang et al., 2020) and indicating the SIRT1 as a promising therapeutic target (Wang et al., 2021). Furthermore, the translocator protein (18 kDa) (TSPO) and related neurosteroids in the hippocampus have also received attention as a potential target for treating PPD in rats (Ren et al., 2020) and mice (Li et al., 2018). In addition to rats and mice, recent studies in Syrian hamsters reported increased anxiety-like behavior but not anhedonia in a model of estrogen withdrawal following HSP, concordant with increased plasticity in the oxytocinergic neural system (Hedges et al., 2021).

Since these are models that simulate a hormonal situation and not a physiological pregnancy (with all the physiological, metabolic, and psychological changes), there are no increases in oxytocin and prolactin, nor does the normal peak of postpartum estrogen (postpartum estrus) occur in the rodents. Some studies reported that HSP-treated rats showed positive nesting behavior within 48 h of the last injection (Stoffel and Craft, 2004), however, not all the range of maternal behavior - such as pup grooming, and nursing - can be assessed using the hormone withdrawal model. Despite these limitations, it has succeeded in reproducing some of the symptoms observed in postpartum depression in different rodents. The studies cited in this section (from Galea et al.,2001 to Wang et al., 2021) highlight the importance of the role of gonadal hormones, particularly estrogen and progesterone, in the etiopathogenesis of PPD and anxiety-like behavior. It is thus a well-established method that has been used in PPD research for 20 years and is currently used in the search for new therapeutic pharmacological strategies (Wang et al., 2021).

2.1.2 Chronic Corticosterone Treatment Model

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and high glucocorticoids during the perinatal period have been postulated as risk factors for developing PPD (Glynn et al., 2013). Thus, perinatal chronic corticosterone administration to rat dams has been proposed as an animal model of PPD. Brummelte et al. demonstrated that chronic corticosterone injections from postpartum days 0-26 induced depressive-like behavior in the FST, reduction in body weight and reduced maternal care (Brummelte et al., 2006). They also showed that dosage (10mg/kg vs. 40 mg/kg) and timing (during pregnancy, postpartum or both periods) of the corticosterone administration differentially affects PPD-like symptoms, with the highest dose administered during the postpartum period being the most efficient experimental paradigm to resemble PPD (Brummelte and Galea, 2010). This experimental model was also successful in

inducing some neuronal markers of depression, such as decreases in dentate gyrus cell proliferation (Brummelte and Galea, 2010), and reductions of dendritic complexity of hippocampal CA3 arbours (Workman et al., 2013). Moreover, chronic corticosterone injections (40mg/kg) for 21 days prior to mating were sufficient to induce a depressive-like phenotype (increased immobility in the FST) and reduced bodyweight in dams during postpartum (Kott et al., 2018). Using the Open Field Test for anxiety measurements, there were no group differences in behavior reported employing this model (Brummelte and Galea, 2010).

The advantage of this model is that the intrinsic and extrinsic variability of different stressors to induce PPD can be avoided, leading to more robust and reproducible results. However, the corticosterone needed to induce some aspects of PPD is very high and raises corticosterone blood to supraphysiological levels that can affect the normal functioning of other systems and the animals' overall health. Besides, it is worth noting that, in human mothers, increased cortisol - as proposed by this model - is not another aspect of PPD. Placental corticotropin-releasing hormone (CRH) and cortisol in maternal plasma increases exponentially during pregnancy, and maternal levels can be 60 to 700 times higher than prior to pregnancy. In response to this high level of cortisol, women with a well-functioning stress response become less responsive to external stressors during pregnancy through reduced activation of CRH neurons in the parvocellular paraventricular nucleus (Kammerer et al., 2002). In women with a dysregulated HPA axis, it is suspected that this attenuation fails to occur and the high levels of cortisol secretion common in pregnancy may then lead to hypercortisolemia. A second possible mechanism is that withdrawal from an excess level of cortisol during pregnancy instigates depression postpartum due to hypocortisolemia (Seth et al., 2016). Thus, more research is needed to determine how changes in cortisol levels are related to perinatal depression.

Pharmacological reversal of depressive-like symptoms by treatment with classical selective serotonin reuptake inhibitors (SSRIs) showed some inconsistent results in this model. Sertraline treatment could not reduce the increased immobility time in the FST (Kott et al., 2018), while paroxetine treatment was effective in blocking the stress-induced corticosterone response but simultaneously increased immobility time in the FST (Overgaard et al., 2018). Fluoxetine treatment prevented corticosterone-induced decreases in maternal care, but this also failed to reverse the increase in immobility time in FST (Qiu et al., 2020). Nevertheless, complex immune, endocrine and drug interactions cause signaling and metabolic alterations that may account for these contradictory results (Qiu et al., 2021, 2020) and may also explain why some women are refractory to classical antidepressant treatment.

2.2 Models based on stress

2.2.1 Gestational Stress Model

Exposure to chronic stress has been successfully used as an animal model to elicit depressive-like behaviors in rodents (Du Preez et al., 2021; Khan et al., 2020; Willner, 2017a, 2017b). In particular, chronic unpredictable stress has proved to be a consistent and effective depression model in terms of generating behavioral, neurochemical, and neuroimmune changes compatible with this disease. However, more than 96% of studies on stress and depression were performed on male rodents (Antoniuk et al., 2019; Gururajan et al., 2019). Among the risk factors for developing peripartum mood disorders is stress during pregnancy. Evidence clearly indicates that stress impacts the plasticity of the mother's brain and affects the adaptive capacity of the HPA axis (Kim, 2020). Given the association between stress and mood disorders it has been proposed as a possible mechanism involved in the development of PPD. For a deep review of the relationship between stress and the maternal brain in laboratory

animals, see (Brummelte and Galea, 2016; Hillerer et al., 2012), and in humans, see (Kim, 2020).

The first studies that investigated the consequences of gestational stress on physiological and emotional parameters of dams date back to 2004, when a study by Smith et al. specifically related gestational stress and the development of depression during the postpartum period in rats. Using a restraint model from gestational day 10 to 20, they found an increase in immobility in FST as well as a decrease in active maternal behaviors toward the offspring, suggesting that stress during pregnancy induces PPD together with a decrease in the quality of maternal behavior (Smith et al., 2004). Darnaudéry et al. reported long-lasting effects of gestational restraint stress (applied 3 times per day for 45 min in the last week of pregnancy) on physiological features and affective-like behavior in mother rats, including anxiety-like and depressive-like behavior (Darnaudéry et al., 2004). In the same line, other authors used the restraint stress paradigm during pregnancy (3 times per day during the last week of gestation) to induce depressive-like behavior during postpartum, which seems to be related to activation of the inflammatory response system (O'Mahony et al., 2006).

Concordant research studies reported that exposure to stress during pregnancy induces depressive-like behavior during the postpartum period, accompanied by structural modifications in brain areas related to mood regulation (Haim et al., 2016, 2014; Hu et al., 2019; Leuner et al., 2014). Furthermore, SSRI antidepressant treatment with citalopram (Haim et al., 2016) or fluoxetine in the postpartum period (Gemmel et al., 2016; Hu et al., 2019) not only reversed the behavioral effects but also the brain modifications observed in mothers stressed during pregnancy. Using a sub-chronic stress protocol during late gestation, however, did not result in a decrease in sucrose preference, indicating that timing is an important factor to consider when analyzing outcomes (Posillico and Schwarz, 2016).

In a recent study, Zoubovsky used a model of “variable psychosocial stress” during pregnancy, applied from gestational day 6.5 to gestational day 16.5 in mice, to study the mechanisms underlying PPD. The stress protocol included foreign object exposure, rat odor exposure, 30° cage tilt, bedding removal, movement on shaker, and frequent bedding changes (2 h each, 2 times per day, separated by at least a 2 h break) during the day, and overnight cage mate change, wet bedding, and lights on. Their findings showed that exposure to psychosocial stress during pregnancy produces adverse effects on neuroendocrine function and on maternal behavior, generating a depressive-like, anhedonic and anxiogenic-like phenotype during the early postpartum period. These changes are correlated with a postpartum maternal HPA axis dysregulation. Psychosocial stress during pregnancy presented as a promising model for dissecting the neuromolecular effects leading to PPD (Zoubovsky et al., 2020).

The gestational stress model, despite differences in the time during which it is applied (early median or late gestation) and in the stress protocols used, resulted in behavioral alterations compatible with postpartum depression-like behavior in the immediate or even long-term puerperium, resulting in an interesting and reliable model to study PPD.

2.2.2 The Chronic Social Stress Model

As mentioned in previous paragraphs, several reviews and works have examined socio-demographic factors, pregnancy-associated psychosocial stress and depression, health risk behaviors, prepregnancy medical and psychiatric illness, pregnancy-related illnesses, and birth outcomes as risk factors for PPD (Hutchens and Kearney, 2020; Katon et al., 2014; Schmied et al., 2013). This literature indicated that women with PPD were significantly younger, more likely to be unemployed, had more pregnancy-associated depressive symptoms and psychosocial stress, were more likely to be smokers, more likely to be taking antidepressants during pregnancy, less likely to drink alcohol during pregnancy, and were more likely to have

pre-pregnancy medical illnesses including diabetes and neurologic conditions than women without significant postpartum depressive symptoms (Katon et al., 2014). In the review by Hutchens et al., the strongest risk factors for PPD were prenatal depression and current aggression (Hutchens and Kearney, 2020).

Nephew and Bridges described and developed a novel animal model that captures at least some of this aspect of PDD. Based on previous research employing a social defeat paradigm (Nephew et al., 2010), the authors reported that acute exposure to a novel male intruder elicits robust behavioral and endocrine stress responses in lactating females (Nephew and Bridges, 2011). Regarding female behavior during the peripartum period, nest defense or maternal aggression is an integral part of the pattern of maternal behavior in the rat, distinguished by being directed at an intruding animal (a male or female rat) that approaches the nest and litter. It consists of various investigatory behaviors, climbing over the intruder, and eventually attacking it with biting and pawing. This differs in many ways from maternal care (i.e., nursing, retrieving pups to the nest, licking their anogenital regions, and general attentiveness to the pups), which is directed at the young, and from nest building. Yet, like maternal care, maternal aggression is dependent upon the young (Rosenblatt et al., 1994).

In this context, it was hypothesized that chronic daily exposure to a novel male intruder would cause a depression-like state in lactating mothers, decrease pup-licking and nursing, and increase aggression due to social instigation. The primary objectives in developing this chronic social stress (CSS) paradigm were to use an ethologically and clinically relevant stressor, induce anhedonia (as measured by maternal care and saccharin preference), increase behavioral measures of anxiety (as measured by self-grooming), and impair pup physiological, behavioral, and/or endocrine development (Carini et al., 2013). The model consists of assigning postpartum female rats into a CSS group, which had a novel intruder male placed in their home cage for 1 h each day from days 2-16 of lactation; and a control group, which was

exposed to the intruder for 30 min only on days 2, 9, and 16 of lactation. On days 2, 9 and 16, all dams were tested for maternal care and maternal aggression. On day 9 of lactation, they reported that exposing a lactating dam to CSS decreased the duration of pup grooming and total maternal care (measured as total duration of nesting, pup grooming, and nursing). Also, the CSS dams had shorter aggression latencies and longer average aggressive bouts (Carini et al., 2013; Nephew and Bridges, 2011). On day 16 of lactation, CSS dams exhibited elevated total aggression, lower saccharin preference and increased self-grooming, but they did not find differences regarding maternal behavior (Carini et al., 2013). Milk intake by the pups from CSS dams was 40 % less than that from control dams on days 9 and 16 of lactation, and pup growth was attenuated on both of these days (Nephew and Bridges, 2011).

In line with the study of the possible consequences of this model, the authors analyzed some neural systems within the amygdala and hypothalamus regions involved in control of the stress response and expression of maternal care that may be mediating the behavioral changes in stressed dams. They found a decrease in oxytocin mRNA expression in the medial amygdala and increases in the expression of corticotrophin-releasing hormone mRNA in the central nucleus of the amygdala, glucocorticoid receptor mRNA in the paraventricular nucleus, and orexin 2 receptor mRNA in the supraoptic nucleus, of stressed compared with control dams. Regarding the hormone profile of the mothers subjected to CSS, there were no significant differences in basal plasma levels of corticosterone, estradiol, prolactin, or oxytocin between the control and CSS dams (Murgatroyd et al., 2015). The same group examined the possible transgenerational influences and effects on social behavior, corticosterone, oxytocin, and prolactin, among other variables (Babb et al., 2014; Murgatroyd et al., 2016; Murgatroyd and Nephew, 2013).

Although this CSS protocol induces certain variations in maternal behavior as well as in the weight of the offspring and dams, it could benefit from using some other tests related to the

evaluation of symptoms of PPD, such as the social interaction test (Lapiz-Bluhm et al., 2008). To cite an example, the decrease in the amount of maternal care can also be interpreted from the point of view of the *tuning hypothesis*: both high and low amounts of maternal care can increase offspring fitness in different circumstances. According to this hypothesis, variation in maternal care may be adaptive for the offspring in addition to the mother if the resulting offspring characteristics are particularly well adapted for the sort of environment in which they will exist. For instance, if the mother spends extensive time foraging for food and provides less maternal care as a result, this may indicate an environment in which greater vigilance and effort will be required by the developing offspring. A key distinguishing characteristic of this hypothesis is that the reproductive fitness of offspring receiving low and high levels of maternal care should differ in different environmental circumstances or contexts, and offspring receiving relatively low maternal care should be relatively more fit in environments that promote low maternal care (Beery and Francis, 2011).

2.2.3 Repeated Pup Separation Stress Model

From the seminal work of Seymur Levine (Levine, 1967), the paradigm of maternal separation (MS) has been used extensively in the scientific literature to study the consequences of early life stress and maternal bond disruption in rodents. There is considerable heterogeneity in experimental manipulations regarding the MS protocol (time and length of separations as well as control groups) and this has sometimes led to inconsistencies in results (Murthy and Gould, 2018; Nishi et al., 2014; Pryce and Feldon, 2003). Despite the methodological differences, the procedure basically involves separating the mothers from their pups for periods that last 3-6 hours daily, during the first 2-3 weeks postpartum. Most of the studies in which the MS paradigm has been used have focused on the effects on the offspring and very few so far on the effects on maternal behavior and physiology.

In earlier studies, alterations of physiological and behavioral responses were demonstrated in mother rats separated from their offspring during the postpartum period (Kalinichev et al., 2003, 2000; Michaels and Holtzman, 2006), leading to the idea that as the mother-pup constitutes a dyad with reciprocal interactions, bonding alteration affects offspring and their mothers in similar way. Boccia (Boccia et al., 2007) proposed the MS paradigm as a model of maternal depression. In this study, prolonged (3h) daily separations of rat mothers from their pups for two weeks postpartum increased immobility in the FST, suggesting a depressive-like response to a social relationship disruption. Similarly, other authors found that separation of pups increased immobility in the FST, along with hippocampal neurochemical alterations related to the depressive-like state in mothers following prolonged pup separations during lactation (Poser Toigo et al., 2012; Sung et al., 2010). In contrast with these results, Eklund (Eklund et al., 2009) found no evidence of stress or anxiety-like behavior following prolonged separation from pups in Wistar dams. In this case, the pup separation protocol consisted of separations of either 4h or 15 min on eight random days during the first two weeks postpartum. Aguggia et al. also assessed the behavioral consequences of early MS in dams (4.5 h/day during the first three weeks postpartum) and found increased anxiety, altered learning and memory processes, but no effect on depressive-like behavior evaluated in the FST (Aguggia et al., 2013).

More recently, a study investigating behavioral and neurobiological consequences of mother-pup separations revealed altered maternal pup-directed behaviors, ultrasonic vocalizations, and neurobiochemical changes following MS, reinforcing the MS paradigm as a model to study postpartum stress and postpartum depression (Bölükbas et al., 2020). In line with these findings, other studies showed that MS produced mild depressive-like and anxiety-like behavior, expanding evidence for the MS paradigm as a model of PPD (Noori et al., 2020).

Despite some contradictory results, the MS paradigm has proven to be a valid model to reproduce PPD, based on psychological stress that involves the disruption of an essential social bond during a critical and vulnerable stage of the reproductive stage, which closely resembles the etiopathogenesis of the disease in humans (Alves et al., 2020).

3. Emerging models

In recent years, other animal models such as pregestational stress have been tested, based on known risk factors, such as a previous personal history of depression or chronic stress that led to increased vulnerability to depression during the postpartum period (Bloch et al., 2003; Gemmel et al., 2018; Payne and Maguire, 2019; Yim et al., 2015). Different pregestational stress protocols have been used, either 5 weeks of chronic mild stress, 3 weeks of chronic unpredictable stress or restraint stress, or a combination of restraint stress and overnight illumination (Czarzasta et al., 2019; Gemmel et al., 2018; Shoji and Miyakawa, 2019; Xia et al., 2016). Overall pregestational stress paradigms resulted in increased depressive-like behavior during the postpartum. Balb/cj female mice, prepregnantly stressed by restraint for 3 weeks, showed a long-lasting PPD-like condition, assessed by the sucrose preference test, FST, and novelty-suppressed feeding test. Additionally, significant neuromolecular alterations in the hippocampus were reported (NR1/Akt/mTOR signaling pathway deficiency and significant reduction of neurogenesis) (Xia et al., 2016). In a study comparing four inbred strains of mice, increased anxiety-like behavior and depressive-like behavior during the postpartum period were reported in Balb/cAJcl females pregestationally exposed to stress (restraint stress for 3 weeks). These females exhibited increased immobility in the FST and lower sucrose preference, suggesting genetic differences in vulnerability to depression-related states during the postpartum period (Shoji and Miyakawa, 2019). Pregestational exposure to chronic mild stress in Sprague Dawley rats for 5 weeks resulted in a depressive-like phenotype during

gestation and postpartum, evidenced by a reduction in self-grooming behavior (splash test) and increased corticosterone levels. Pregestationally stressed dams also presented changes in cardiovascular function and decreased hippocampal BDNF expression (Czarzasta et al., 2019). Exposing female Sprague-Dawley rats to chronic unpredictable stress prior to breeding resulted in poor reproductive success and poor maintenance of pregnancy. Also, these dams showed higher levels of nursing and fewer bouts of licking/grooming offspring in the first week postpartum (Gemmel et al., 2018). The pre-pregnancy stress model has previously been used to determine its consequences in the progeny, but it has only recently begun to be explored in mothers as an animal model of perinatal emotional disorders.

Another recently generated preclinical model in mice consists of loss or reduction in the expression of the $GABA_A$ receptor δ subunit and lack of the K^+/Cl^- co-transporter (KCC2), which is required for effective GABAergic inhibition, specifically in CRH neurons. The CRH neurons of the PVN are fundamental in regulating the HPA axis in response to stress. In this model, the selective deletion of KCC2 specifically in CRH neurons produces a dysregulation of the HPA axis, the expression of depressive-like behavior, and deficits in maternal care during postpartum. The authors propose that the behavioral phenotype observed in these mice restricted to the postpartum period makes it a useful animal model to investigate pathophysiological mechanisms of PPD (Melón et al., 2018). Previous studies reported that alterations in the GABAergic system during pregnancy and postpartum, specifically mice models deficient in GABA-A receptor subunit delta, showed depression-like and anxiety-like behaviors during the postpartum period and also abnormal mothering, with a significant decrease of the pups' survival rate (by cannibalism or neglect) (Maguire and Mody, 2008) (MacKenzie and Maguire, 2014) (Melón et al., 2018). This model suggests that PPD may be linked to an inability to properly regulate the expression of GABA-A receptors during pregnancy via their subunits and reestablish their postpartum functioning (Verbe et al., 2020). $GABA_A$ receptors are a principal target for neurosteroid action and confer neurosteroid

sensitivity. Reliable evidence demonstrated the relationship between dysregulation of the HPA axis and an abnormal postpartum phenotype. The GABA system plays a critical role in inhibiting the HPA, and KCC2 plays a significant role in the GABAergic regulation of CRH neurons in the paraventricular nucleus of the hypothalamus, regulating the response of the HPA axis during pregnancy and the postpartum period (Verbe et al., 2020). These preclinical studies support the hypothesis that differential sensitivity to neurosteroids during periods of hormonal fluctuation may be involved in the development of PPD, and provide a potential functional mechanism for altered maternal postpartum behavior (Schweizer-Schubert et al., 2021).

Less explored, but a still interesting model is high fat diet (HFD)-induced PPD. This model is based on studies suggesting that pre-pregnancy overweight and obesity is associated with increased risk of experiencing PPD (Moazzam et al., 2021). C57BL6/J female mice on HFD for 8-10 weeks developed antenatal obesity and then depressive-like behaviors during the postpartum period, evidenced by increased immobility in the tail suspension test (TST), in addition to HFD-induced cognitive impairment and anxiety-like behavior in the postpartum period. Interestingly, these alterations can be reversed by high fiber dietary intake, possibly by increasing the microbiota metabolite short-chain fatty acids (SCFAs) (Liu et al., 2020). SCFAs are typically produced by the fermentation of non-digestible dietary fiber by the gut microbiota. Although the relationship between the gut-brain microbiota axis and depression is not fully understood, growing evidence suggests that the metabolites of the gut microbiota play a role in the regulation of emotional behavior and the etiopathogenesis of depression (Kelly et al., 2016; Silva et al., 2020; Valles-Colomer et al., 2019; Wu et al., 2020). While the mechanisms are not yet known, the model proposes a new perspective on the role of probiotics as nutritional therapies in psychiatric diseases (Liu et al., 2020). In another study, CD-1 mice were fed a HFD for 5 weeks before pregnancy, continuing during pregnancy and lactation. In the postpartum period, mice on HFD showed anhedonia (a core symptom of

depression) in the sucrose preference test, as well as negative effects in maternal behavior and cognitive function, and increased anxiety-like behavior, supporting a relationship between maternal overweight and postpartum mental illness (Moazzam et al., 2021). Previous studies in rodent animal models associated chronic administration of HFD with depressive-like and anxiety-like behaviors, through different pathways such as the dysregulation of glucocorticoid signaling mechanisms in limbic brain areas (Sivanathan et al., 2015), the activation of the immune system, and disruption of the expression of genes and proteins involved in insulin signaling, synaptic plasticity and corticosterone synthesis (Dutheil et al., 2016), or via decreased serotonin neurotransmission in the hippocampus (Zemdegs et al., 2016). However, the relationship between HFD and PPD has only recently begun to be studied, so further studies are necessary to elucidate the underlying mechanisms.

4. DISCUSSION

Perinatal mood disorders such as postpartum depression are often underestimated, and their etiology and neurobiological substrate are still not fully known. Understanding, diagnosing, and treating PPD adequately is of vital importance, as it compromises not only the health of the mother but also the development of the bond between the mother and the infant, and can lead to alterations in the psychosocial and emotional development of the infant.

Although animal models in the study of psychiatric pathologies continue to generate controversy, for a detailed review see (Gururajan et al., 2019), they represent an opportunity to dissect and analyze the causal or underlying factors of behavioral changes observed in psychiatric diseases. The choice of a model of PPD should consider that there is not yet a model that completely and perfectly mimics the symptomatology presented in human psychiatric disorder, and therefore it is possible to model only some aspects of this. Nonetheless, human studies, together with the results of research in animal models, have

contributed to a better understanding of the underlying mechanisms and possible therapeutic strategies. In order to study and understand the neurobiological basis of PPD, different animal models have been developed covering possible causes or risk factors, among them biological etiology such as hormone withdrawal, HPA axis dysregulation (corticosterone rise), genetic vulnerability, or psychosocial factors, most of which involve stress exposure such as chronic stress, social defeat, and MS.

The present review focused on the animal models most used in the study of PPD and their main findings so far, and animal models that have emerged for the study of PPD in recent years. When testing a depressive-like phenotype in rodents, most of the studies used the FST, a behavioral task that continues to be the gold standard for studying depression-like behavior in rodents and is the most widely used (Bogdanova et al., 2013; Slattery and Cryan, 2012; Yankelevitch-Yahav et al., 2015). Classically, the increase in immobility time is considered a measure of behavioral despair; however, this has been questioned by some authors (Molendijk and de Kloet, 2015) (Molendijk and de Kloet, 2019), who propose that immobility reflects an adaptive coping response to stress rather than behavioral despair. With this in mind, to avoid erroneous conclusions about the results it is best when assessing depression-like states in animal models to include in the experimental design the concomitant evaluation of different dimensions of the depressive state, using various neurobehavioral tools. Other approaches include tail suspension (only in mice) as a measure of behavioral despair, sucrose preference to evaluate anhedonia, grooming behavior as a measure of apathy, open field and plus maze tests to evaluate levels of anxiety-like behavior (which often presents comorbidly with depression), and cognitive function, usually also affected in PPD. Nevertheless, few studies evaluate pup-directed maternal behaviors or multiple behavioral dimensions sequentially in the same experimental research.

In general, animal models of complex, heterogeneous, and multifactorial psychiatric pathologies such as postpartum depression do not cover all aspects of the disease. Therefore, multiple models are necessary to cover all the different aspects. The classical models have provided the biological bases, covering the hormonal aspects and exposure to stress factors, mainly during the postpartum. Emerging models provide new insights to address other possible mechanisms involved, including the genetic aspects, the brain microbiota axis, or pre-pregnancy exposure to stress, generating contributions both for the study of physio pathogenesis and for the investigation of new therapeutic approaches.

Despite being an underexplored research area for many years, there are currently multiple approaches in the design of animal models and also in the behavioral paradigms used to evaluate depressive-like behavior during the postpartum period. This has allowed advances in the knowledge of the underlying etiopathogenesis and the development of new therapeutic tools. It is important, however, to consider and recognize the limitations of each when drawing conclusions, bearing in mind the heterogeneity and complexity of this pathology in humans.

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Table 1: ANIMAL MODELS OF PPD AND MAJOR FINDINGS

A summary of the pre-clinical studies focused on rodent models of PPD and their main contributions can be found in Table 1

Model	Species	Time points of treatment	Time of behavioral testing	Relevant results
Hormone Withdrawal	rat (Long-Evans)	estradiol and progesterone injections to simulate a 23-day gestational period	FST at 2 and 3 days; OF at 4 days after withdrawal	increased immobility, decreased struggling and swiming in the FST, increased area crossings in the OF (Galea et al., 2001)
				decreased cell proliferation in dentate gyrus reverted by an estrogen beta receptor agonist or imipramine treatment (Green and Galea, 2008)
			SPT 2 and 3 days after withdrawal	decreased sucrose consumption and preference (Green et al., 2009)
	rat (Sprague-Dawley)	estradiol and progesterone implanted tubes to simulate a 21-day gestational period	FST at 0, 1, 4 or 7 days; OF at 4 days; EPM at 5 days; LHT or RIT at 28 days after withdrawal	increased escape failure and latency to escape on LHT; decreased immobilty time on day 4 and 7 and increased struggling/climbing on day 7 at FST; decreased time in open arms at EPM; decreased latency to attack at RIT; decreased CAMKIIA, MEF2A, BDNF expression (Suda et al., 2008)

		estradiol and progesterone injections from day 1 to 16, estradiol from day 17 to 22 to simulate a 22-day gestational period	SPT at 1, 2, 4, 7, 14 and 21 days after withdrawal	decreased sucrose preference (Navarre et al., 2010)
		estradiol and progesterone injections from day 1 to 16, estradiol from day 17 to 22 to simulate a 22-day gestational period	OF at 1 day, EPM at 3 days, FST at 4 days, TST at 5 days after withdrawal	increased anxiety- and depression like behavior. GR reduction in a brain region specific pattern (Wang et al., 2020)
				attenuated expression of SIRT1 and GR in the hippocampus (Wang et al., 2021)
			OF, EPM, SPT, FST at 4 days and at 21 days after withdrawal	anxiety and depressive-like behavior in the postpartum period for 3 weeks, realived by YL-IPA08, a new ligand compound of translocator protein 18 kDa (TSPO) poposed to be a potential new target for the treatment of PPD (Ren et al., 2020)
	rat (Wistar)	estradiol and progesterone injections or implanted tubes to simulate a 23-day gestational period	Startle test at 1, 2 and 3 days; OF at 2 days after withdrawal	increased startle response on days 1 and 2; less distance traveled and less time in the inner zone in the OF in rapid hormone withdrawal group (Doornbos et al., 2009)
	mice (ICR)	estradiol and progesterone injections from day 1 to 16, estradiol from day 17 to 22 to simulate a 22-day gestational period	OF at 2 days; EPM at 3 days; FST at 4 days; TST at 5 days after withdrawal	decreased time in open arms at EPM; increased immobility time at FST and TST; decreased 28-day-old BrdU+cells and BrdU+/NeuN+cells; decreased

				density of DCX+fibers per DCX+cell; decreased levels of phospho-NR2B and phospho-Src; decreased levels of BDNF mRNA and protein (Zhang et al., 2016)
			early-EW mice group (evaluated at 2–4 days after withdrawal); late-EW mice group (evaluated at 7–9 days after withdrawal)	increased immobility time at FST and TST in early-EW mice group; decreased nNOS, NO and p-CREB levels in the hippocampus of early-EW mice group, increased StAR and P450scc mRNA and protein levels in the hippocampus of late-EW mice group; reversion of depressive-like phenotype by σ1R activation (Zhang et al., 2017)
	mice (C57BL/6)	estradiol and progesterone injections from day 1 to 16, estradiol from day 17 to 23 to simulate a 23-day gestational period	OF, EPM, SPT and FST at 1-7 days after withdrawal	the TSPO ligand ZBD-2 alleviated depression-like behaviors and enhanced the TSPO brain level by the regulation of the hypothalamic-pituitary-adrenal axis, 5-HT and BDNF secretion, and maintainig expression of the excitatory and inhibitory synaptic protein (Li et al., 2018)
	Syrian hamsters	estradiol and progesterone injections from day 1 to 12, estradiol from day 13 to 17 to simulate a 17-day	EPM, OF and SPT at 3-4 days after withdrawal	increased anxiety-like behavior during the post-partum,increased oxytocin-

		gestational period		immunoreactive cells and oxytocin mRNA in the PVH, and oxytocin receptor density in the DRN (Hedges et al., 2021)
Chronic Corticosterone Treatment	rat (Sprague Dawley)	40 mg/kg corticosterone 26 days from partum	maternal behavior from 2 to 8 days; FST at 24-26 days post-partum	reduced maternal care, reduction in body weight and increased immobility in the FST (Brummelte et al., 2006)
		low (10 mg/kg) or high (40 mg/kg) corticosterone given either during gestation (day 10 to 20), postpartum (day 2 to 24) or across both periods	maternal behavior from 2 to 8 days; FST at 21 and 22 post-partum	reduced maternal care, increased immobility in the FST, decreased hippocampal cell proliferation mainy in the post-partum treated group (Brummelte and Galea, 2010)
		40 mg/kg corticosterone from day 2 to 23 post-partum		reduced maternal care, increased immobility in the FST, reduced the complexity of basal arbours and increased mushroom spines on both apical and basal dendrites (Workman et al., 2013)
		40mg/kg corticosterone for 21 days prior to mating	maternal behavior from 2 to 8 days post-partum; FST at 14-15 days and 22 days after treatment began and 4 days post-partum ; OF at 9 days post-partum	increased immobility in the FST, reduced body weight, dams that received sertraline until the end of gestation spent more time off of the nest compared to corticosterone treated dams that received vehicle or discontinued sertraline during

				gestation (Kott et al., 2018)
		40 mg/kg corticosterone from day 2 to 14 post-partum	FST at 2-3 days and at 12-13 days post-partum	paroxetine blunted the swim stress-induced corticosterone response and increased depressive-like behavior in both FST1 and FST2 (Overgaard et al., 2018)
		40 mg/kg corticosterone from day 2 to 23 post-partum	maternal behavior from 2 to 7 days; FST at 22-23 days post-partum	fluoxetin treatment prevented corticosterone-induced decreases in maternal care, it failed to revert the increase in immobility time in FST of corticosterone treated dams (Qiu et al., 2020)
Gestational Stress Model	rat (Hooded Lister)	from 10 to 20 days of gestation	FST at 3-4 days; maternal behavior at 1-10 days post-partum	icreased immobility in the FST, altered maternal behavior (Smith et al., 2004)
	rat (Fisher)	from 14 to 21 days of gestation	FST at 22, 23 and 24 days post-partum	higher immobility scores in the FST, higher levels of IL-1 in stimulated and unstimulated whole-blood samples (O'Mahony et al. 2006)
	rat (Sprague Dawley)	from 14 to 21 days of gestation	locomotor reactivity to novelty 4 days; EPM 5 days; FST 14-15 days post-partum	increased depressive-like behavior and anxiety-like behavior, altered reactivity to inescapable stress such as novelty (Darnaudéry et al., 2004)

		from 7 to 20 days of gestation	FST at 7 days and 21 days post-partum	increased depressive-like behavior, structural changes in the NAc across the post-partum period (Haim et al., 2016, 2014;)
		from 15 to 21 days of gestation	SPT and OF at the start (before mating), 2 and 4 weeks post-partum	increased depressive-like behavior, decrement of MAP–2 and SYP protein expression in the hippocampus that can be prevented by treatment with progesterone in advanced pregnancy and fluoxetine in the postpartum (Hu et al., 2019)
		from 7 to 13 days of gestation	maternal behavior and EPM at 2 days; FST at 21 days; attentional set shifting test 21-22 days post-partum	maternal care deficits, increased depressive-like behavior, and impaired performance on an attentional set shifting task. Reduced dendritic spine density on mPFC pyramidal neurons and altered spine morphology (Leuner et al., 2014)
		from 16 to 22 days of gestation	SPT at 0-1 days and 7-8 days post-partum	increased anhedonia, altered brian neuroimmune function,changes in microglial density within the the hippocampus (Posillico and Schwarz, 2016)

	mice (C57BL6/J)	from 6.5 to 16.5 days of gestation	maternal behavior 2–5 days; OF at 7 days; FST at 8 days; SPT at 0-6 days; EZM and LDB at 8 days post-partum	abnormal maternal behavior (fragmented and unpredictable maternal care patterns), and the development of depression and anxiety-like phenotypes. Dysregulation in post-partum HPA axis function during post-partum (Zoubovsky et al., 2020)
Chronic Social Stress (CSS)	rat (Sprague Dawley)	intruder male for 1 h each day from 2 to 16 days post-partum	maternal behavior and SPT at 2, 9, and 16 days post-partum	decreased maternal care, increased maternal agression at 9 days post-partum. Increased maternal agression, decreased saccharin preference, but no differences in maternal behavior at 16 days post-partum (Nephew and Bridges, 2011; Carini et al., 2013)
				impaired maternal care and lactation and increased maternal anxiety-like behavior at 9 days post-partum. Increased saccharin preference, maternal aggression and impaired lactation at 16 days post-partum. Decrease in oxytocin mRNA expression in the

				mCeA and increases in the expression of CRH mRNA in the CeA, GR mRNA in the PVH, and orexin 2 receptor mRNA in the SON (Murgatroyd et al., 2015)
Repeated Pup Separation Stress Model	rat (Long Evans)	from 3 to 14 days post-partum	maternal behavior at 2-6 days; FST at 21-22 days post-partum	increased immobility in the FST and reductions in maternal behavior (Boccia et al., 2007)
		from 1 to 10 days post-partum	FST at 35 days post-partum	higher immobility time in the FST. Decreased hippocampal Na, K-ATPase activity, reduced NO levels in the hippocampus (Poser Toigo et al., 2012)
	rat (Wistar)	from 1 to 14 days post-partum (8 random days)	spontaneous motor activity test 3 weeks; defensive withdrawal test at 4.5 weeks after weaning	brief maternal separation increased anxiety-like behavior, resulted stressful for rat mothers, whereas prolonged separations are not (Eklund et al., 2009)
		from 1 to 21 days post-partum	maternal behavior at 3 days; EPM 21 days; FST 22 days; Memory test 24-25 days post-partum	altered maternal care, increased anxiety, negative effect on learning and memory processes, increased c-fos expression in CeA (Aguggia et al., 2013)
	rat (Sprague-Dawley)	from 1 to 14 days post-partum	FST at 22 days; Memory test at 25 days post-partum	decrease in climbing time and an increase in immobility time in the FST (Sung el al., 2010)

		from 2 to 20 days post-partum	maternal behavior at 2, 6, 14, and 20 days; ultrasonic vocalizations at 2, 6, 14, and 21 days; EPM and MBT at 21 days post-partum	increased maternal care towards pups. Increased emission of 50-kHz and 22-kHz. No differences in anxiety-like behavior. Reduced Morc1 but not Nr3c1 expression. Serum GABA but not glutamate levels were significantly increased (Bölükbas et al., 2020)
		from 2 to 15 days post-partum	maternal behavior at 3 days; SPT or EPM at 22 days; FST at 26-27 days postpartum	depressive-like and anxiety-like behavior, no effect on anhedonic behavior, increased care of pups (Noori et al., 2020)
Emerging models: Pregestational stress	mice (BALB/cAJcl)	21 days before maiting	SP at 3-7 days; LDB at 7 days; OF at 8 days; FST at 9-10 days; TST at 11 days post-partumfrom	decreased distance traveled in the OF, increased depression-like behavior in the FST, decreased distance traveled in the light box, decreased time spent in the light box (Shoji and Miyakawa, 2019)
	mice (Balb/cJ)		3 and 12 weeks post-partum	reduced sucrose preference, increased immobility time in FST, increased latency to eat and decreased food consumption in the novelty-suppressed feed test. Additionally, in the hippocampus abnormal GluR1/NR1 expression ratio, deficit in

				Akt/mTOR signaling and reduction in the cell proliferation (Xia et al., 2016)
	rat (Sprague Dawley)	35 days before mating	14 days of gestation; 7 days post-partum	reduced self-grooming in the splash test through pregnancy and post-partum, changes in cardiovascular function, and reduction in hippocampal BDNF (Czarzasta et al., 2019)
		21 days before maiting	1 week post-partum	reduced the maintenance of pregnancy and breeding success in the dam and altered maternal care-giving behavior. Perinatal SSRI treatment ameliorated some of the effects of pre-gestational stress in dams (Gemmel et al., 2018)
Emerging models: High Fat Diet	mice (C57BL/6J)	from 8-10 weeks before maiting untill end of lactation	for 2 weeks post-partum	HFD induced cognitive impairments (MWM), depressive-like (TST), and anxiety-like behaviors (EPM and OF) during the post-partum. HFD affect ultrastructure of hippocampus synapse and monoamine 5HT and NE neurotransmitters. High dietary fiber intake revert antenatal obesity-induced

				PPD (Liu et al., 2020)
	mice (CD1)	5 weeks before maiting	at 15-17 days of gestation; at 6-8, 12-15, 20-22, 21-23 and 23-25 days post-partum;	HFD negatively affected mouse maternal behavior evaluated pre-partum via nest building and post-partum via pup retrieval, affected object recognition memory as assessed by the NOR test and generated anhedonia in the SPF during the post-partum (Moazzam et al., 2021)
Emerging models: GABAergic system	mice KCC2/Crh and Cre -/-		at 2-3 days post-partum	KCC2/Crh mice exhibited depresive-like behavior (FST), anxiety-like behavior (EPM and LDB) and deficits in maternal behaviors. Failed to suppress the stress-induced activation of the HPA axis during pregnancy and post-partum (Melón et al., 2018)
	mouse Gabrd−/− (GABAAR δ subunit deficient)		at 18 days of gestation and at 2 days post-partum	Gabrd-/- mice exhibited depressive-like behavior (FST and SPT) and abnormal maternal behaviors resulting in reduced pup survival (Maguire and Mody, 2008)

FST, Forced Swimming Test; OF, Open Field; EPM, Elevated Plus Maze; SPT, Sucrose Preference Test; LHT, Learned Helplessness Test, RIT, Resident-Intruder Test; TST, Tail Suspension Test; CAMKIIA, Ca2+/calmodulin-dependent protein kinase II Type A; MEF2A, Myocite enhancer factor 2A; BDNF, Brain-derived neurotrophic factor; GR, Glucocorticoid receptor; SIRT1, Sirtuin 1; BrdU, Bromodeoxyuridine; NeuN, Neuronal nuclear protein; DCX, Doublecortin; NR2B, NMDA receptor subunit, Scr, non-receptor tyrosine kinases; nNOS, nitric oxide synthase; NO, nitric oxide; StAR, Steroidogenic acute regulatory protein; CREB, cAMP responsive element binding protein; P450scc, cholesterol side-chain cleavage enzyme; σ1R, sigma-1 receptor; TSPO, Translocator protein; 5-HT, serotonin; DRN, dorsal raphe nucleus; PVH, paraventricular nucleus, IL-1, Interleukin-1; NAc, nucleus accumbens; MAP-2, Microtubule-associated protein 2; SYP, Synaptophysin; mPFC, medial Pre-frontal cortex; HPA, hypothalamic-pituitary-adrenal axis; mCeA, medial central amygdala; CRH, corticotrophin-releasing hormone; SON, supraoptic nucleus; Morc 1, Morc family CW-type zinc finger 1; Nr3C1, neuron-specific glucocorticoid receptor; LDB, Light-Dark Box Test; GluR1, AMPA receptor subunit; NR1, NMDA receptor subunit; Akt, Protein kinase B; mTOR, mammalian target of rapamycin protein; SSRI, selective serotonin reuptake inhibitor; HFD, High Fat Diet; MWM, Morris Water Maze; NE, Norepinephrine; NOR, Novel Object Recognition Test; KCC2, neuron specific K+-Cl− co-transporter; GABAAR, GABA recpetor type A; Gabrd, GABA A receptor δ subunit gene.

Highlights

- Postpartum depression (PPD) has long-lasting negative impact both in mother and infant
- Rodent animal models are useful tools in the study of underlying mechanisms of postpartum depression
- No animal model completely reproduces the symptomatology of such a complex and heterogenous disorder
- Emerging animal models in recent years expanded knowledge about risk factors involved in PPD
- Animal models are necessary to improve the knowledge of PPD etiopathology and guide treatments