Neurogenesis in the Maternal Rodent Brain: Impacts of Gestation-Related Hormonal Regulation, Stress, and Obesity

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Keywords

Maternal neurogenesis · Hormones · Pregnancy · Stress · Obesity

Abstract

In order to maintain maternal behavior, it is important that the maternal rodent brain promotes neurogenesis. Maternal neurogenesis is altered by the dynamic shifts in reproductive hormone levels during pregnancy. Thus, lifestyle events such as gestational stress and obesity that can affect hormone production will affect neuroendocrine control of maternal neurogenesis. However, there is a lack of information about the regulation of maternal neurogenesis by placental hormones, which are key components of the reproductive hormonal profile during pregnancy. There is also little known about how maternal neurogenesis can be affected by health concerns such as gestational stress and obesity, and its relationship to peripartum mental health disorders. This review summarizes the changing levels of neurogenesis in mice and rats during gestation and postpartum as well as regulation of neurogenesis by pregnancy-related hormones. The influence of neurogenesis on maternal behavior is also discussed while bringing attention to the effect of health-related concerns during gestation, such as stress and obesity on neuro-

endocrine control of maternal neurogenesis. In doing so, this review identifies the gaps in the literature and specifically emphasizes the importance of further research on maternal brain physiology to address them.

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Introduction

Pregnancy is a transformational experience. It results in the onset of maternal behavior that is of paramount significance in determining the health and quality of life of both the mother and her offspring [1]. According to the World Health Organization, 10–20% of women either in pregnancy or who have just given birth will experience a mental health disorder that impairs maternal behavior [2]. In fact, maternal behavioral disorders are linked to onset of risky behaviors such as addiction and suicidal ideation in the mother, disrupted mother-child bonding, and impaired child development [3]. Maternal behavior is regulated by the brain, which displays exceptional neural plasticity to ensure that responses, unique and specific to pregnancy and the peripartum period, are expressed properly. Neural plasticity in the maternal brain encompasses a diverse set of neurobiological alterations

including neurogenesis [4]. There is evidence that maternal behavior can be affected by maternal neurogenesis [5] and a key regulator of maternal neurogenesis is reproductive hormones [6, 7]. Therefore, it is logical to assume that factors affecting reproductive hormone levels may in turn influence neuroendocrine control of maternal neurogenesis and, by extension, behavior. Recent studies have linked pregnancy-specific hormone production levels with an increased risk for a maternal behavioral disorder, specifically peripartum depression [8, 9], and have implicated a role for lifestyle factors, such as maternal obesity in this relationship [10, 11].

Here, our current understanding of neurogenesis in the maternal rodent brain and its neuroendocrine control by reproductive hormones is reviewed. This review deliberately focuses on the commonly used laboratory rodents: rats and mice. Due to obvious ethical considerations, understanding of human pregnancy and associated physiological changes is largely drawn from experimental models. Hence, in this review, while significant *in vitro* study data are presented, findings from *in vivo* experiments are highlighted to understand the biological processes occurring in rats and mice that might be relevant in humans. For example, while adult neurogenesis is observed in rodents, the existence of adult neurogenesis in human remains controversial [12]. Data from laboratory rodents can only be translated to humans once the debate about adult human neurogenesis is resolved. This has been hampered by the need to use postmortem human brain tissue and the limitations of tissue sensitivity to preservation techniques [13]. The question of whether adult neurogenesis in humans can be perceived the same way as that in laboratory animals has been raised [14]. While the science behind human brain studies is persistently and consistently being improved, the next best representation of human brain physiology is arguably mammals of lower species such as rodents. The aim of this report is to understand where the current scenarios stand with respect to the association between hormones and adult neurogenesis that may affect maternal behavior, particularly during the peripartum period, and to highlight areas for further study.

Before specifically discussing maternal neurogenesis, adult neurogenesis will be considered in general. Neurogenesis is the formation of new neurons. It is composed of a series of events, including neural stem cell proliferation, differentiation into neuronal cell types, migration to target regions, and maturation [15, 16]. Completion of neurogenesis is determined by the survival of the newly generated neurons and their integration into a neural cir-

cuit. Therefore, neurogenesis can be regulated at any of these stages. Neurogenesis persists into adulthood against a once commonly held perception [17]. Two regions of the adult brain that are known to be neurogenic are the subventricular zone (SVZ) along the lateral ventricles and the subgranular zone of the hippocampal dentate gyrus [15, 16]. Neural stem cells in the SVZ travel to the olfactory bulb where they differentiate into mature granule and periglomerular neurons [18, 19], whereas neural stem cells in the subgranular zone differentiate into excitatory neurons at the granule cell layer of the hippocampus [20, 21]. Newborn neurons in the olfactory bulb contribute to the maintenance of neuronal networks in the region and regulate some associated behaviors such as olfactory fear conditioning and perceptual learning [22–25]. In the hippocampus, the newly generated neurons participate in memory formation and can affect behavior including anxiety, memory, and pattern separation [23, 26, 27].

Olfactory bulb and hippocampus are the 2 established target regions of adult neurogenesis in rodents and, even though subject to scientific debate [28], other regions of the adult brain including hypothalamus [29, 30], thalamus [30], striatum [30, 31], neocortex [31, 32], substantia nigra [33], and the amygdala [34] have shown the presence of newborn neurons. However, neural stem cells in the adult brain are not spontaneously active. They reside in a state of quiescence and can be activated by a stimulus after which they may commit to neuronal fate [35]. There are both extrinsic and intrinsic stimuli. Examples of extrinsic influences include exercise [36, 37], diet [38–40], and stress [41–43]. Intrinsic factors include genetic determinants [44, 45], neurotrophic factors [46, 47], neuroinflammation [48, 49], and neuroendocrine control [50–54].

In the context of maternal neurogenesis, the neuroendocrine control of adult neurogenesis is an important factor since it is reflected strongly in the maternal brain during pregnancy. The maternal brain exhibits remarkable plasticity that is unique to pregnancy and the accompanying maternal experience. One of the features of plasticity in maternal brain is maternal neurogenesis. The distinctive neurogenesis in a maternal brain can be attributed to the dramatic changes in hormonal profile during and after pregnancy [7, 55, 56]. However, their relationship does not follow a linear trend and is poorly understood.

In this review, 2 external factors, gestational stress and obesity, are discussed in particular because of their severity as maternal health concerns and their association with

Fig. 1. Schematic diagram to distinguish between what is known and not known about the neurogenic niches of maternal neurogenesis, the regulation of maternal neurogenesis by maternal hormones, and the effect of gestation stress and obesity on the neuroendocrine control on maternal neurogenesis.

impaired maternal response and paripartum depression [57–61]. Gestational stress and obesity are also closely associated with the neuroendocrine system. While there is more knowledge about the effect of gestational stress on the neuroendocrine regulation of maternal neurogenesis [62], the involvement of gestational obesity in this mechanism has received little or no attention as of yet even though there are reasons to believe that there is a potential for it [discussed in Effect of Environmental Disruptions on Maternal Neurogenesis and Behavior] [8, 11]. As presented schematically in Figure 1, the following sections review what is known about the events of maternal neurogenesis in the hippocampus and SVZ of rodent brain, its regulation by maternal hormones, and the effect of gestational stress and obesity on the neuroendocrine regulation of maternal neurogenesis. In addition, the relationship between maternal neurogenesis and maternal behavior, one that is complex and poorly understood, in rodents is briefly discussed.

Maternal Neurogenesis in the Hippocampus

The hippocampus is typically known to regulate spatial and cognitive performances [63, 64]. It is not an intrinsic component of the “maternal circuit” [56, 65], but it is connected with multiple regions of this circuitry by means of the limbic system [66]. Therefore, hippocampal plasticity can affect maternal behavior through its reciprocity with the maternal neural network. This association has sparked interest in the neuroendocrine research community as discussed below.

Most studies involving rodents have examined maternal neurogenesis in the hippocampus at different stages of gestation and the postpartum period (shown in Fig. 2). This has been achieved by using a combination of markers for cell division with those for different stages of neurogenesis. The nuclear protein Ki67 is a commonly used endogenous proliferative cell marker, while 5-bromo-2'-deoxyuridine (BrdU), a synthetic nucleoside that is an analogue of thymidine, has served as an exogenous mark-

Fig. 2. Cell proliferation, neuronal differentiation, and cell survival in the hippocampus of maternal rat and mouse brain at different stages of gestation (early, mid, and late) and postpartum (early and late). Gestation days are numbered by assigning GD 0 to the day at which a vaginal plug was detected. Unidirectional arrows pointing downward indicate a decrease, and bidirectional arrows indicate no change in the level of the respective parameters. The timeline bar is not to scale. Superscripts represent the sources corresponding to the data. GD, gestation day.

er of both cell proliferation and survival as well as in the birthdating of newborn neurons [67]. In terms of neuronal cell markers, doublecortin is often used to assess differentiation of neural progenitor cells into the neuronal fate and quantify immature neurons. Doublecortin is a microtubule-associated protein expressed by neuronal precursor cells and immature neurons that require further development to attain full functional capacity [68]. A trusted marker for fully functional or mature neurons is neuronal nuclei (NeuN) protein, which is localized in nuclei and perinuclear cytoplasm of most of the neurons in the central nervous system of mammals [69].

Rats: During Gestation

In rats, the gestational period is commonly 21–22 days long and changes in hippocampal neurogenesis are observed near to the end of pregnancy. On gestation day (GD) 1, GD 6, and GD 18, hippocampal cell/neural stem cell proliferation remains unchanged [70–72]. However, gestation-induced effects on hippocampal cell proliferation are observed later in pregnancy; specifically, a significant reduction in Ki67-positive cells in pregnant rats on GD 19 [73]. This is consistent with a prior reported tendency of reduced cell proliferation on GD 21 [74]. However, there are also results suggesting a lack of gesta-

tional effect on hippocampal cell proliferation on GD 20 [71] and GD 21 [62]. These discrepancies may be related to different methodological approaches, including the use of BrdU [71] versus Ki67 to identify and quantify cell proliferation [73, 74]. BrdU is only incorporated in newly dividing cells when they are in the S-phase, and Ki67 is expressed in proliferating cells during most of the cell cycle until they enter cell cycle arrest [75]. BrdU labeling is also dependent on BrdU's ability to enter into the proliferating cell's DNA, frequency, and number of times it was administered, as well as the time between administration and assessment. Hence, when comparing Ki67 cell counts from 1 study with BrdU-positive cells from another, multiple factors need to be considered since Ki67 labeling will likely be different than BrdU labeling. This apparent lack of consistency in the data supports the need for further investigation of hippocampal neurogenesis to clarify effects in late gestation. During mid-gestation, on GD 12 [76], and late gestation, GD 19 [73], the population of immature neurons was reduced compared to that in non-pregnant females. The reduced immature neuron numbers during late pregnancy can be a result of less cell proliferation at this time. During mid-gestation, however, decreased number of immature neurons may be a case of slower rate of differentiation since survival of proliferative cells early on in pregnancy (GD 1) remained unchanged toward the end (GD 22) [70].

Rats: Postpartum

Postpartum effects on hippocampal cell proliferation are more profound and consistent. Compared to a non-pregnant state, a decrease in cell proliferation has been recorded in early postpartum (PD) at days PD 1 [77], PD 2 [78, 79], PD 8 [76, 78], and PD 13 [80]. These timepoints are in line with the lactating period in a rat dam. It has been suggested that the negative correlation between cell proliferation and lactation in the first week of the postpartum period is due to utilization of metabolic resources for successful lactation and optimum neonatal growth [78, 80]. This is understandable since both cell proliferation and lactation are highly energy-demanding processes [81, 82]. Thus, converging and conserving the metabolic reserves in favor of neonatal nourishment through lactation would be a prudent physiological development. Concurrently, the proliferative cells in early postpartum (PD 2) show poor survival a week after proliferation (PD 9), giving rise to fewer immature neurons than nulliparous rats [78]. By the second week (PD 16), the number of mature neurons was unaffected, which suggests that neuronal maturation is hastened to match the basal levels

as in nulliparous rats by this time [78]. This also means that the survival of cells proliferating at PD 2 decreases 1 week after proliferation (PD 9) but returns to normal in the following week, that is, 2 weeks after proliferation (PD 16) [78]. However, the latter result was contradicted in another study that reported reduced cell survival, about 2 weeks after cell proliferation, at PD 20 [80]. This raises the possibility that cell survival is determined by the stage of postpartum period and not the life span of proliferated cells. Alternatively, this dissimilarity may be species-dependent, since 1 study used Sprague-Dawley rats and the other employed Wistar rats. Another difference was between the BrdU dose regimen. In the study with Sprague-Dawley rats, a single BrdU injection on PD 2 was used [78], while 4 daily (PD 1–4) BrdU injections were administered in Wistar rats, which is expected to label the sum of proliferative cells over all 4 days [80]. Independently, cell survival was also not different between postpartum and virgin animals on PD 15 [77]. The decline in hippocampal neurogenesis during postpartum period is further supported by fewer immature neurons on PD 22 [83], PD 24 [84], and PD 30 [76]. Cell proliferation on PD 28 is similar to that in virgin animals [78]. Based on these observations, the detection of fewer doublecortin-positive immature neurons seen in late postpartum or after weaning might be explained by poor survival of the newly proliferated cells and their reduced ability to differentiate into immature neurons, rather than changes in the rate of cell proliferation since this parameter remains unchanged at this time. However, there is no report on hippocampal cell proliferation between PD 13 and PD 28. This absence of data opens the possibility that lower cell proliferation at PD 13 may also influence the immature neuron population during late postpartum or postweaning.

Hippocampal neurogenesis is also regulated by other factors associated with maternal experience including parity [79]. Stimuli from pup exposure have a differential effect on hippocampal neurogenesis between nulliparous and primiparous rats. Cell proliferation increased significantly in nulliparous rats when they were exposed to foster pups [79]. On the other hand, postpartum suppression of cell proliferation in dams was reversed upon removal of pups [78]. The increased cell proliferation in nulliparous rats in response to pup exposure can be explained by the absence of pregnancy and postpartum hormonal state, whose negative effect on cell proliferation in the postpartum period may be dominating the neurogenic effect of pup exposure. For postpartum dams, pup exposure increases basal corticosterone, which can cause the suppression of cell proliferation that is normally observed

during this period [78]. Early postpartum cell proliferation is the same in both primiparous and multiparous rats, but the former group shows greater cell survival. This can be due to some behavioral and hormonal differences between multiparous and primiparous animals: since multiparous mothers are already reactive to the pups, the time taken to express maternal behavior is shorter for them than for primiparous mothers [85]; maternally experienced mothers are also more aggressive than the inexperienced ones [86]; and prolactin levels are lower in multiparous mothers [87]. However, while the above are presented as possible justifications for parity and pup-induced change in hippocampal neurogenesis, this list is likely incomplete reflecting the limitation of the few studies that have assessed these relationships. Hence, further investigations are required to establish the mechanisms behind these effects.

Mice: During Gestation and Postpartum

Mice usually have gestations lasting between 19 and 21 days [88]. Consistent with reports in rats, cell proliferation in the dentate gyrus is independent of gestational effects on GD 6.5 in mice [7]. However, cell proliferation decreases in the pregnant cohort by mid-gestation (GD 14.5, 16.5, and 18.5) when compared to age-matched virgin animals [89]. Newborn cells on GD 11–12 also face a poor chance of survival 14 days later (PD 4–5). This is accompanied by a decrease in immature neurons in the pregnant mice. By PD 21, hippocampal neurogenesis in dams is comparable to the levels in virgin mice [90].

It is evident from the amount of information available to review here that very few studies have focused on hippocampal neurogenesis in the maternal mouse brain. Considering the variation between different strains within the same mouse species more research is required to better distinguish between mechanistic and species-specific features of maternal neurogenesis in the hippocampus.

Maternal Neurogenesis in the SVZ

The SVZ runs along the lateral ventricles and retains embryonic features in the adult brain such that its resident neural stem cells have the potential of developing into adult-born neurons [91, 92]. These neural stem cells migrate a long distance, also known as the rostral migratory stream, to the olfactory bulb where they mature into new olfactory neurons [18, 19, 93]. Research has shown that newborn interneurons are necessary for expression

of some olfactory behaviors [22]. More generally, the olfactory bulb is crucial for the mother to exhibit maternal behavior [94, 95].

Rats: During Gestation and Postpartum

Only a few sets of data are available on pregnancy-regulated neurogenesis in the SVZ of rodent brains (shown in Fig. 3). In the SVZ of rats, brain cell proliferation is unchanged on GD 6 [71] and increased on GD 20 [96]. No change in cell proliferation is seen again on PD 8 [78]. In the context of neurogenesis in the postpartum period, it may be possible that changes to maternal neurogenesis are favored in the rostral and not the caudal SVZ. This is because the increase in BrdU-positive cells that is seen on PD 7 in CD-1 mice is in the rostral SVZ region [7], and the lack of postpartum effect on cell proliferation that was noted on PD 8 was in the caudal regions of the SVZ of rats [78]. Of course, it is possible that this difference in cell proliferation in the postpartum period is species-specific, but it also suggests a possibility that even within the SVZ, there are regions more suited than others for maternal experience and, hence, there are varying levels of maternal neurogenesis along the rostrocaudal plane of the SVZ.

Mice: During Gestation and Postpartum

Changes in neurogenesis are first detected in the mouse brain on GD 6.5 when cell proliferation increases by 65% [7]. Mitotic activity then returns to baseline until PD 7 when a 35% elevation from baseline is observed [7]. Neurogenesis levels return to normal on PD 14 and PD 21 [7]. Following proliferation, cells have a high capacity for survival as a doubling of olfactory bulb neurons was noted 4 weeks after GD 6.5 and PD 7 in CD-1 mice [7]. This observation of increased cell proliferation on GD 6 has been confirmed by others [5]. In addition, overall SVZ proliferation in pregnant mice on GD 14 was similar to ovulating mice; however, there was a significant decrease in the posterior component of the SVZ, defined by Bregma 0.5 mm, in the pregnant group [97].

The existing literature on maternal neurogenesis indicates that the contrasting cases between the 2 neurogenic niches, hippocampus and SVZ, may be by virtue of their endogenous differences such as their progenitor cells, microenvironment, and route of migration. Dissimilar results are also observed between the 2 laboratory animal species and their strains. Hence, the neurogenic feature may be species-dependent owing to their genetic, hormonal, physiological, and behavioral variabilities. Another determinant of neurogenesis is the stage of maternal/reproductive episode. Therefore, future investigations

Fig. 3. Cell proliferation and survival in the SVZ of maternal rat and mouse brain at different stages of gestation (early, mid, and late) and postpartum (early and late). Gestation days are numbered by assigning GD 0 to the day at which a vaginal plug was detected. Unidirectional arrows pointing upward indicate an increase and bidirectional arrows indicate no change in the level of the respective parameters. The timeline bar is not to scale. Superscripts represent the sources corresponding to the data. GD, gestation day; SVZ, subventricular zone.

may benefit from simplifying the peripartum period into more frequent intervals to get a comprehensive timeline of maternal neurogenesis.

Functional Implications of Maternal Neurogenesis

Like any behavioral performance, maternal behavior is primarily an outcome of the synchronized and coordinated activity within the maternal neural network. This coordination entails wide-ranging mechanisms of neural plasticity such as dendritic morphology and spine density, remodeling of the synaptic communications, glial

density, and neurogenesis that have been reviewed elsewhere [98]. Therefore, to establish a linear connection between maternal neurogenesis and behavior is unlikely to be successful. Here, studies that investigated the contribution of neurogenesis in regulating maternal behavior and associated high-order functions such as cognition and memory are reviewed.

Functional Implications of Maternal Neurogenesis in the Hippocampus

Lower hippocampal cell survival in primiparous rats, relative to multiparous rats, was linked to more time spent nursing pups [79]. This suggests a negative correla-

tion between postpartum hippocampal cell survival and nursing in primiparous rats [79]. Spatial memory retention is also negatively affected by greater immature neuron density in maternal experienced dams as opposed to nulliparae [99]. In lactating dams, the typical postpartum reduction of hippocampal neurogenesis was observed, but these animals also showed the least depressive-like behavior when compared to control and thelectomized rats [100]. It appears that reduced hippocampal neurogenesis in rodents is beneficial for certain functional outcomes. This may explain why increased hippocampal neurogenesis is not generally observed in the maternal rodent brain as depicted by Figure 2. However, the link between maternal neurogenesis and maternal behavior can be altered by other factors such as stress. For example, reduced levels of neurogenesis caused by stress led to poor maternal behavior expression as represented by less time spent nursing pups and in the nest [84, 101]. This counters the previously perceived negative correlation between hippocampal neurogenesis and maternal behavior. Surprisingly, the negative effect of the stress hormone corticosterone on neurogenesis did not correspond to maternal mood deficit during the lactation period [100]. In fact, lactating dams experienced reduced hippocampal neurogenesis but displayed the least depressive behavior when compared to control and thelectomized animals [100]. Here, the expected maternal mood deficit may have been missing because the elevated corticosterone was a result of suckling and not stress [100]. In addition, sex hormones can also affect the maternal neurogenesis-maternal behavior relationship. In a hormone-stimulated mouse model mimicking the postpartum estradiol withdrawal state, there was an increase in depressive and anxiety-like behavior with decreased newborn neuronal survival [55]. Here, estradiol administration increased cell survival more than the hormone-stimulated pregnant group and normalized the behavioral deficits [55]. As expected, estradiol withdrawal had a decreasing effect on rat hippocampal neurogenesis [102]. In brief, these data suggest that the link between maternal neurogenesis and maternal behavior and/or mood disorders depends on confounding factors.

Association between Maternal Neurogenesis and Mood Disorders

The neurogenesis theory of depression [103] that was proposed a couple of decades ago is now a debatable hypothesis [104, 105]. A major finding against the neurogenesis hypothesis of depression is that anxiety/depression-related behaviors were unaffected by ablation of

hippocampal neurogenesis in mice [106]. However, there is evidence to suggest that neurogenesis is involved in the pharmacological effect of antidepressants. For instance, fluoxetine, which belongs to the selective serotonin reuptake inhibitor (SSRI) class of antidepressants, reverses stress-induced decrease of hippocampal neurogenesis and decreases stress-induced anxiogenic and depressive behavior in male rodents [42, 107]. Similarly, in female mice, fluoxetine's positive influence on hippocampal neurogenesis was accompanied by fluoxetine's relieving effects on anxiety and depressive-like behaviors [108]. Furthermore, the neurogenic and antidepressant effects of fluoxetine were most prominent during the diestrus and estrus phases of the mouse estrous cycle, suggesting that the phase of estrous cycle determines the drug's efficacy. By contrast, sertraline, which is another SSRI, was not associated with an effect on hippocampal neurogenesis in nonpregnant female rats [73]. These data supporting different possible neurogenic effects of SSRIs are correlative in nature. However, if the results were to indicate causative effects, then any disparity between possible neurogenic effects of fluoxetine and sertraline might be due to differences in the tested animal species and the type of SSRI administered. In the case of maternal hippocampal neurogenesis, sertraline also had no effect on the immature cell density in pregnant rats [109], but chronic fluoxetine treatment (for ≥ 20 days) in the postpartum period led to an increased population of immature neurons after weaning in dams exposed to gestational stress [110] but had no effect on the immature hippocampal neuron numbers at or before weaning [84, 111]. It has been suggested that this differential effect of fluoxetine at different times within the postpartum phase is because of the limiting effects of postpartum hormones on fluoxetine's actions and latency in drug action [111]. The latter notion is further supported by an increase in hippocampal immature neurons upon fluoxetine treatment starting from mid-gestation until after weaning [112]. Consistent with studies in male rodents [42, 107], the alteration of hippocampal neurogenesis by fluoxetine in the maternal brain might be considered stress-dependent as well [110, 112], but fluoxetine administration starting at pregnancy was independent of stress [112]. Therefore, fluoxetine's effects on hippocampal neurogenesis in the maternal brain can also be influenced by the time at which the drug is administered. Gestational fluoxetine treatment failed to rescue stress-induced maternal behavior deficits, but in nonstressed dams, fluoxetine did increase nursing behavior compared to untreated dams [112].

To summarize, it has been shown that adult neurogenesis is involved in the pharmacological effects of antidepressants in the maternal brain as well as in male and female rodents. However, the extent of involvement is dependent on several factors including stress, the time and duration of drug administration, and the type of drug used. Therefore, even though the role of neurogenesis in depression is widely argued and the link between maternal neurogenesis and maternal behavior is not well established, neurogenesis is involved in the mechanism of action of antidepressants. In addition, further research is required to understand the role of neurogenesis in treating behavioral disorders.

Functional Implications of Maternal Neurogenesis in the SVZ

Neural progenitors originating from the SVZ mature into granular and periglomerular neurons in the olfactory bulb [18]. Olfactory neurogenesis is involved in maintaining pregnancy to parturition and affecting nursing and pup-retrieving behaviors [113]. The hormone shown to exert a profound effect on SVZ neurogenesis in rodents is prolactin. Likewise, it is responsible for the modulation of maternal behavior. Low prolactin levels reduced SVZ neurogenesis as expected, and this corresponded to anxiogenic behavior in postpartum mice. As a result, the quality of maternal care, but not basic behaviors, was compromised. This was indicated by the tendency of the mothers to frequently leave the pup-bearing nest or not to prioritize nursing their pups [5]. In addition, SVZ irradiation, and hence, inhibition of olfactory neurogenesis, did not influence maternal behavior [114]. Instead, social interaction with a male mouse was impaired. This appears to undermine the importance of olfactory bulb in mediating maternal responses [115]. Even though this study does not focus on neurogenesis specifically, the discrepancy in the conclusions can be attributed to the type of behavioral tests performed and the procedures employed. In fact, early postpartum mice that spend an extended period of time with males are quick to retrieve pups and crouch over them compared to isolated dams [116]. Even in nulliparous mice, the presence of male pheromones induced maternal instincts [116]. The mechanism behind this is proposed to be prolactin-dependent SVZ neurogenesis [116]. Apart from prolactin's influence on the maternal circuit, the influence of male pheromones suggests that olfactory neurogenesis is necessary for this response. While prolactin is hailed as the prime mediator here, null mutation of the prolactin receptor gene impaired pup-retrieving performance by pri-

miparous mice [117]. Thus, the prolactin receptor is important for the expression of maternal behavior and, as such, ligands other than prolactin may mediate or contribute to this response. Placental lactogen infusion into the medial preoptic area reduced the time of onset of maternal behavior in steroid-primed nulliparous rats [118]. This reiterates the importance of examining the role of lactogenic receptors and their other ligands in influencing maternal behavior through neuroplasticity and, in relevance to this review, maternal neurogenesis.

Neuroendocrine Control of Maternal Neurogenesis

Neuroendocrine mechanisms lie at the heart of the peripartum scheme. The neuroendocrine system governs plasticity in the brain and has an integral role in determining maternal behavior [119]. The reproductive hormone levels go through dramatic changes in the maternal system (reviewed here: [56]), and these changes affect neurogenesis. The regulation of maternal neurogenesis by the characteristic hormones in the maternal system is reviewed here.

Estradiol and Progesterone

The serum levels of the sex steroids, estradiol and progesterone, change across different stages of the estrous cycle and pregnancy in rodents. This is illustrated in Figure 4. Knowledge of the changing levels of estradiol and progesterone helps in the understanding of their effects on neurogenesis in the female adult brain at distinct reproductive stages.

Progenitor cell proliferation in the hippocampus is highest in the proestrus phase of the estrous cycle compared to the estrus and diestrus stages [120]. This is attributed to the high levels of the estrogen hormone during the proestrus phase [120]. Further support was provided by a reduction in cell proliferation upon estrogen removal by ovariectomy, which was later normalized by estradiol administration [120]. In subsequent studies, estradiol's inductive effect on cell proliferation was established [121–123]. In addition, estradiol promotes new cell survival [120, 123]. However, estradiol's effect on neurogenesis can be influenced by adrenal steroids. Adrenal steroids exert an opposite response by decreasing cell proliferation after chronic estradiol treatment [121]. This also explains a part of why chronic estradiol administration does not just lack an effect but reverses the outcome of acute estradiol [121]. Estradiol stimulates adrenal activity [124], and the resulting corticosteroids de-

Fig. 4. Serum levels of estradiol (a) and progesterone in cycling and pregnant rats and mice (b). Values for serum estradiol and progesterone in cycling mice were obtained by gas chromatography-mass spectrometry and adapted from Nilsson et al. [194]; values for serum estradiol and progesterone in cycling rats were obtained by radioimmunoassay and adapted from Smith et al. [195] and Fillingim and Ness [196]; values for serum estradiol in pregnant rats and mice were obtained by radioimmunoassay and adapted from McCormack and Greenwald [197] and Paris and Frye [198], respectively; values for serum progesterone in pregnant rats and mice were obtained by competitive binding assay and adapted from Virgo and Bellward [199] and Morishige et al. [200], respectively. Due to insufficient data on the hormone levels during postpartum period, this figure only shows serum hormone levels during estrous cycle and pregnancy in rodents. In general, there is a sharp drop in both estradiol and progesterone levels at parturition in female rats and mice [6, 155]. In the latter species, progesterone is barely detected at parturition [155].

crease cell proliferation in the hippocampus [125]. However, other mechanisms are likely involved in regulating estradiol's chronic effects, since the absence of adrenal activity eliminates estradiol-linked suppression of cell proliferation but does not reverse it [121]. Moreover, the stress-estradiol link is not fixed. It is dependent on the duration, time, and type of stress as well as the course of estradiol exposure and its cross-interaction with other hormones [122]. As expected, 3 days after stress expo-

sure, there was an increase in cell proliferation in virgin rats [62], whereas a 10-day lapse between stress and analysis revealed reduced cell proliferation [74]. That being said, both these intervals had the same effect on late-gestation cell proliferation: an increase. In a separate study, chronic stress had no effect on cell proliferation in females [126].

In another study on the differential effects of acute and chronic estradiol exposure, elevated cell proliferation was

also reported to decline with the acute-chronic estradiol transition [123]. Moreover, the acute effects were dose-dependent, where only moderate doses exert a response. The fading responses with chronic estrogen exposure can be attributed to the hormone-mediated downregulation of its own receptors [127], since it has been shown that estradiol acts through estrogen receptors α and β in the dentate gyrus to impart its actions on cell proliferation [128, 129]. Even more convincing for the relationship between estradiol and cell proliferation is the coexpression of both estrogen receptor- α and - β on neural stem cells and immature neurons in the dentate gyrus [130]. This is only suggestive of a part of the estradiol-mediated response on neurogenesis. There has been mention of estrogens' homeostatic mechanism, secondary messenger pathways, and different cell signaling intermediates, which has been reviewed by others [131].

In hormone-stimulated pregnancies designed to mimic the withdrawal of estradiol in the postpartum period, cell proliferation decreased in both rats and mice [55, 102], consistent with studies that found postpartum decreases in cell proliferation [76–80]. However, this does not necessarily represent the situation in natural pregnancy, since other hormones are also critically involved in this period [132].

The other sex steroid progesterone elicits a modulatory effect on estradiol action with respect to hippocampal neurogenesis [123, 133]. Studies found that progesterone decreases the estrogen-mediated increase in cell proliferation [123, 134, 135]. However, a 21-day or a chronic hormone injection regimen showed that progesterone, when used in combination with estradiol, did not have an effect on cell proliferation or neuronal differentiation in the hippocampus [133]. Another facet of progesterone's action is that the hormone alone induces cell proliferation and at least one mechanism is receptor-mediated [134, 135]. Progesterone receptors are expressed in the majority of hippocampal neurons and involved in hippocampal neurogenesis [134]. Their distribution does vary across different regions of the hippocampus and in the presence of progesterone [134]. For instance, chronic versus acute progesterone administration decreases progesterone receptor mRNA levels in the CA1 region of the hippocampus [134]. Collectively, these findings suggest differential actions of progesterone under different circumstances such as presence of another hormone and length of exposure. However, the limited literature on progesterone's effect on adult neurogenesis warrants further investigation in the context of pregnancy.

Lactogens

Pregnancy-stimulated neurogenesis in the early gestation period was first reported in CD-1 mice that showed increased neural stem cell proliferation in the SVZ at GD 7 and PD 7 when prolactin secretion is high [7, 136]. However, hippocampal proliferation of neural stem cells remained unchanged at GD 7. This shift in maternal neurogenesis was attributed to the lactogenic hormone, prolactin. Prolactin infusions led to twice the number of mature interneurons in the olfactory bulb without affecting cell death in either the SVZ or olfactory bulb [5, 7]. On PD 2, low prolactin levels decreased cell survival in the olfactory bulb [5]. Newly proliferated cell numbers in the SVZ also decreased upon blockade of prolactin secretion by the dopamine agonist, bromocriptine [116]. In contrast, prolactin had no effect on neural stem cell proliferation or differentiation in mouse hippocampus [5, 7, 137]. This was true in both pregnant and nonpregnant states. These results support a region-specific role of prolactin on adult maternal neurogenesis.

Prolactin signals its action through binding a type 1 cytokine receptor at the cell surface [138]. The prolactin receptor has 2 main isoforms in the rodent brain: long and short forms. They primarily mediate the janus kinase/signal transducer and activator of transcription and mitogen-activated protein kinase/extracellular signal-regulated kinase signaling pathways [50, 139, 140]. The prolactin receptor is widely spread out in the brain with a dense distribution in the maternal brain circuit and more importantly, in the maternal behavior centric region of the hypothalamus, medial preoptic area [141, 142]. In fact, the density of the receptor distribution changes with time in pregnancy [141]. Distribution patterns of prolactin receptor show light labeling in the hippocampus and dense labeling in the choroid plexus, the region adjacent to SVZ [142]. The short form of prolactin receptor is also present in the SVZ itself [7, 143]. A more relevant finding is that gestation-stimulated neurogenesis decreased by 50% in mice heterozygous for the prolactin receptor gene [7]. Thus, the selective action of prolactin on SVZ neurogenesis is understandable and suggests that it is, in fact, prolactin receptor signaling that regulates neurogenesis. It is also likely that prolactin receptor-induced SVZ neurogenesis directly involves newly proliferating cells and immature neurons since cells labeled with BrdU and doublecortin were colocalized with the prolactin receptor [143].

The choroid plexus may also represent a site for facilitating the neurogenic action of the prolactin receptor since the choroid plexus synthesizes prolactin receptor

mRNA [144], secretes cerebrospinal fluid, and is in close proximity to the cerebral vasculature [145]. The involvement of the choroid plexus in transporting prolactin into the brain is debatable and therefore, an avenue worth further investigation [146, 147]. Also, the presence of prolactin can affect the expression of different variants of prolactin receptor by the choroid plexus [148]. Hence, serum and cerebrospinal fluid concentrations of prolactin and its exchange between the 2 media also pose as important determinants of lactogen-mediated SVZ neurogenesis.

There are also other lactogenic hormones, including placental lactogens, which are produced at higher levels than prolactin during some stages of pregnancy and are capable of binding and signaling through the prolactin receptor [149]. Thus, consideration of a role for placental lactogens as well as prolactin on gestation-induced neurogenesis is warranted. There are 2 major forms of rodent placental lactogen: I (prolactin-3d1) and II (prolactin-3b1). Mouse placental lactogen-I is detectable first at GD 5, while the biphasic prolactin surges associated with early pregnancy are still present, and peaks at around GD 10 to values greater than the highest serum prolactin level in early gestation [150]. The levels fall beyond this point and disappear after GD 18 [150]. Mouse placental lactogen-II appears at mid-gestation and begins to rise until term when prolactin is again detected in the circulation [151]. The absence of prolactin during mid-gestation is a result of negative feedback by placental lactogens through effects on tuberoinfundibular dopamine neurons [152]. At this time, rodent placental lactogen-I is detected in the lateral ventricles which is topographically close to the neurogenic niche, SVZ [152]. Additional support for placental lactogen as a potential neurogenic molecule comes from studies in humans, where placental lactogen is also known as chorionic somatomammotropin hormone. Human placental lactogen binds to the prolactin receptor with higher affinity than prolactin itself and its concentration in the serum surpass that of prolactin by 50-fold [149, 153]. Together, these reports from humans suggest that placental lactogen is an important ligand for the prolactin receptor and by extension, important for prolactin receptor-mediated signaling during pregnancy such as in maternal neurogenesis. However, while the data support the possibility that human placental lactogen is the major ligand for prolactin receptor in pregnancy, this is yet to be determined in rodent species as the relative affinity of placental lactogens and prolactin for the prolactin receptor is not reported.

Early pregnancy surge in SVZ neurogenesis has also been detected in a study including pseudopregnant mice

[7]. As a result, it was suggested that embryo implantation may not be necessary for maternal SVZ neurogenesis at GD 7 [7]. Here, the increase in neurogenesis may be copulation-induced and studies have shown that male pheromones themselves have the capacity to stimulate forebrain neurogenesis in the female brain [116, 154]. While these studies have shown that prolactin mediates this response, effects of other hormones such as luteinizing hormone and ovarian hormones may also be present. Assuming similar hormonal profiles in inbred and outbred mouse strains, it is worth noting here that the dose at which estradiol (0.2 µg/day for 6 days) and progesterone (0.4 µg/day for 6 days) were infused through the intracerebroventricular route was significantly higher than the physiological values [7, 155]. Thus, the reported failure to induce neurogenesis by these exogenous hormones [7] may be because of their dose-dependent action. In addition, since elevated SVZ neural stem cell proliferation has been recorded in pseudopregnant mice [7], placental hormones, like placental lactogens, might not be an absolute requirement for the neurogenic effect in early pregnancy. However, this does not rule out a role for these other hormones in natural pregnancy. Placental lactogen, for example, is present abundantly in maternal rodent circulation during pregnancy [150, 151]. Drawing from human studies, placental lactogen shows a greater affinity for the prolactin receptor than prolactin itself and serum concentrations of placental lactogen can be 50-times higher than prolactin during pregnancy [153]. Variation in placental lactogen RNA and protein levels has also been associated with pathological conditions; for example, they are negatively correlated with clinical depression in some pregnant women [8, 9]. Hence, placental lactogen has both mechanistic and potential diagnostic or therapeutic significance and, thus, poses as an important lactogen receptor ligand. The question remains if placental lactogen has an equally important role in rodent physiology as in humans. If true, it is likely that placental lactogen may still affect neurogenesis in natural rodent pregnancy, at least in a coordinated fashion with prolactin, during the early phase of pregnancy. Neurogenesis is not solely determined by cell proliferation; hence, placental lactogen may also play a role in cell survival, death, differentiation, and/or maturation in pregnancy. More insights on receptor-ligand interactions, dominance of placental hormones in the maternal system, differences between the 2 major rodent placental lactogens in the brain, and comparison of the lactogens between species will be valuable for understanding lactogen-stimulated neurogenesis and maternal brain plasticity and warrant further investigation.

Oxytocin

Relative to the aforementioned hormones, oxytocin is a fairly newly discovered candidate in the regulation of adult neurogenesis. As such, little is known about its role in the 2 classic neurogenic niches in the female brain.

In adult male rats, oxytocin injections through the intraperitoneal route showed a dose-dependent increase in hippocampal proliferative cells [156, 157]. More chronic oxytocin treatment sustained the survival of the newborn cells [156]. Oxytocin also increased doublecortin-positive cells in the hippocampus of socially disrupted adult rats [158]. One way this is mediated is by the oxytocin receptors in the CA2 and CA3 regions of the hippocampus. Neural progenitors do not express the oxytocin receptors, so the hormone-induced cell proliferation may not be a direct effect on the neural stem cell [159]. It is possible that this is propagated through the CA3 region, which regulates adult neurogenesis [160]. Important here, oxytocin emerges as a potent inducer of neurogenesis since it can exert its effects even in the presence of stress and high glucocorticoids, which are common downregulators of neurogenesis [156]. This is perhaps not surprising since the hypothalamo-pituitary-adrenal axis activity is suppressed by oxytocin [161, 162].

Most studies have looked at oxytocin-mediated neurogenic responses in male animals. While this informs us about the biological functions of the hormone, it does not necessarily represent the situation in females. More specifically, factors influencing oxytocin response, such as activation of brain regions and neural connections, receptor binding, and effect of stress have been shown to differ between the 2 sexes [163–166]. Moreover, gestation in itself is distinct from intact female physiology.

Potential sex differences were recently examined in adult hippocampal neurogenesis, in a study that is perhaps the first study to consider a role for oxytocin in adult neurogenesis in the female brain [167]. Hippocampal neurogenesis, represented by a doublecortin-positive cell count, was reduced upon treatment with multitargeted biopolymer encapsulated oxytocin injections. In contrast to previous studies, oxytocin decreased hippocampal neurogenesis in males as well [167]. This difference in the effect of oxytocin on males could reflect variations in the hormone treatment regimen used in these studies. The findings in the recent study using males and females also showed that oxytocin negatively affects estradiol levels [167]. This could be a mechanism behind the reduced neurogenesis, but there was no strong correlation. Thus, based on current knowledge, investigations into oxytocin

as a regulator of adult neurogenesis, particularly in the female and during pregnancy, warrants further investigation.

Effect of Environmental Disruptions on Maternal Neurogenesis and Behavior

Gestational Stress and Maternal Neurogenesis and Behavior

Stress during pregnancy, including related to lifestyle and/or environmental disruptions, can make a mother vulnerable to adverse health conditions such as postpartum depression [168]. Rodent studies showed that maternal stress by restraint during early (GD 5–11) and mid-late gestation (GD 11–17) caused an increase in cell proliferation at GD 21 compared to nonstressed pregnant animals [62, 74]. The case is different for maternal neurogenesis in the postpartum phase. Hippocampal neurogenesis, marked by Ki67 and doublecortin-positive cells, at PD 21/weaning and PD 28 was unaffected by gestational [110, 111] and pregestational stress [112]. In the SVZ of mouse brain, cell proliferation at GD 7 was the same in both stressed and control pregnant mice and the same was true for mature neuron count at PD 14 [169]. This suggests that stress affects hippocampal and SVZ neurogenesis in the maternal brain differently between gestation and postpartum phases.

Corticosterone-related stress studies have also revealed more about the stress-neurogenesis relationship in mothers. A low dose (25 µg/mL) of corticosterone administered orally followed by adrenalectomy significantly decreased basal corticosterone levels in the blood during postpartum period and this was accompanied by an absence of reduced cell proliferation that is typically observed during this period [78]. This implies that the elevated postpartum levels of corticosterone play a role in pulling down cell proliferation levels. Corticosterone elicits a dose-dependent action on newly proliferated cells in the hippocampus of mothers [101]. A prolonged corticosterone injection regimen at a dose of 10 mg/kg during the second half of rat pregnancy does not change BrdU cell density after weaning, but a 40 mg/kg dose brings a significant decline compared to control pregnant rats [101]. Both of these doses, however, decrease the BrdU cell density in corticosterone-injected dams versus control pregnant rats when administered in the postpartum period [101]. The higher dose during both gestation and postpartum also decreases to a greater extent, although, not significantly, the BrdU cell density in the corticoste-

rone injected pregnant group as opposed to the control pregnant group [101]. Here, it is worth noting that the duration of corticosterone injections in the postpartum period was significantly longer (~50%) than during gestation. Hence, the effects may be a culmination of both dose and length of exposure to corticosterone.

The mechanism behind the effect of stress on maternal neurogenesis may include the neuroendocrine system. It is known that estradiol increases serum corticosterone levels by enhancing adrenal activity [124, 170]. Four hours after a subcutaneous injection of estradiol benzoate, BrdU cells increased but then decreased after 48 h of estradiol treatment in ovariectomized rats [121]. Each of these times was accompanied by a 100% and 175% increase in serum corticosterone values, respectively, compared to control [121]. This suggests that estradiol's neurogenic effect was dominated by the raising level of corticosterone such that BrdU cell count was lower than the control group [121]. Prolactin, the lactogen that is known to stimulate neurogenesis in the mouse SVZ, is abundant during the postpartum/lactation phase [171]. In male mice, this hormone is proposed to oppose the nonneurogenic effects of corticosterone as a subcutaneous injection of prolactin to stressed animals markedly promotes cell proliferation and neuronal maturation [172]. Assuming that this principle is true in the case of lactating females, the absence of a gestational stress effect on postpartum neurogenesis, as discussed above, may be explained. Thus, inclusion of lactating females in future studies aimed at understanding the neuroendocrine pathway involved in stress-linked maternal neurogenesis is justified. Certain evidences indicate that stress-induced functional effects in the mother are mediated through changes in neurogenesis. With high corticosterone exposure in the postpartum period, there was a negative correlation between neurogenesis and depressive behavior [101]. The effect of stress on depressive symptoms was reduced with maternal experience when compared to nulliparous rats [84]. Hence, the effect of neurogenesis on depression is dependent on the hypothalamo-pituitary-adrenal axis as is widely accepted [173]. Nonetheless, the role of neurogenesis in the etiology of depression remains to be elucidated. After exposure to stress, increased cell proliferation was linked to alleviation of depressive-like symptoms. Indeed, virgin rats showed a more pronounced effect, but there was a similar trend among the pregnant group as stressed pregnant rats, in their late gestation, spent slightly less time being immobile in forced swim test than pregnant control cohort [62]. In another study, stress during early gestation (GD 5–11) did not have any

effect on depressive behavior, but it did increase anxiety in pregnant rats as opposed to virgin animals [74]. With respect to neurogenesis, there was a tendency toward an increase in cell proliferation [74]. Therefore, dissimilar results may be arising from the differences in the neurophysiology between virgin and pregnant rats.

Drawing from the above, gestational stress affects hippocampal neurogenesis at late gestation, but the effect wears off in the late postpartum phase of rats. Despite the innate hyporesponsiveness to stress postpartum, this is also the time when there is increased vulnerability to developing mental health disorders, which in turn challenge maternal responses [174, 175]. Neurogenesis appears to reduce the negative effects of stress on maternal behavior. Hence, maternal neurogenesis, if not direct, is likely an indirect mechanism in maternal behavioral disorders.

There is certainly a lack of information regarding the effect of stress on SVZ neurogenesis. Therefore, further investigations on species differences as well as the origin of neurogenesis are called for. In this context, nature of the stress and the method of administration are important variables in understanding the relationship between gestational stress and neurogenesis in the mothers.

Gestational Obesity and Maternal Neurogenesis and Behavior

The prevalence of obesity (BMI ≥ 30.0) during pregnancy is alarmingly high [176] and is strongly associated with maternal mental health disorders including peripartum depression [61, 177, 178]. With increasing preference in lifestyle choices that promote a reduction in physical activity and high caloric food intake, the number of obese pregnant individuals is expected to trend upward in the absence of any wide-scale and strict interventions [179]. Quite clearly, understanding the effect of gestational obesity on a mother's brain physiology will provide valuable insights for the development of targeted therapy for maternal brain health. However, there remains a lack of information available on this matter.

Neurogenesis is implicated in the pathogenesis of depressive disorder even though they may be indirectly linked [105]. Most studies investigating the effect of high-fat diet linked obesity on adult neurogenesis have used male subjects. Male mice fed with a high-fat diet for 7 weeks have reduced neurogenesis in the hippocampus compared to those fed a normal diet [180]. These data are consistent with a strain-specific study where high-fat diet consumption for 4 and 12 weeks also decreased proliferative cell and immature neuron populations in the hippocampus of male mice of the C57BL/6N and C3H/HeN

strains [181]. Similar effects of high-fat diet on hippocampal neurogenesis were also recorded in male rats, raising the possibility that this effect is consistent across rodent species [182, 183]. However, outcomes may vary depending on multiple factors. For example, a recent study reported that hippocampal neurogenesis in male mice is unaffected by an 18-week high-fat diet administration [38]. This stark contrast may be attributed to the different high-fat diet models pursued in these studies, which varied in terms of the age of animal at diet initiation, length of diet consumption, and metabolic changes determined by glucose tolerance. In rats, there is also a sex-specific effect. Hippocampal BrdU cells, 2 weeks after BrdU injection, remained unchanged in females rats [182]. In female mice, whole hippocampal neurogenesis is uninterrupted by diet, but there is a significant diet-induced reduction in proliferative cell count and immature neuron population in the dorsal hippocampus [38]. This finding may explain the impact of high-fat diet on cognition (a function related to the dorsal hippocampus) as reported by other studies [184]. Hippocampal neurogenesis fluctuates in a cycling female across different phases of the estrous cycle [120]. Hence, future studies should include the estrous phase-dependent changes to obtain a more comprehensive understanding of the influence of diet on neurogenesis. The role of diet on maternal neurogenesis is poorly understood. Existing literature, as mentioned, involves studies on males and nonpregnant females, and hence, animal models pertaining to pregnant female subjects will be of critical importance in the field. There are some data from human studies; however, that supports a series of hypotheses and urges the inception of such animal research. Maternal obesity is associated with decreased placental maturity and placental lactogen RNA levels in human term placenta samples [10, 185]. Reduced human placental lactogen RNA and serum protein levels are also associated with increased risk of peripartum depression and are biomarkers of peripartum depression [9]. In addition, risk of developing peripartum depression increases with maternal obesity [61, 177, 178]. Together, these observations raise the possibility that placental lactogen may not only act as a marker, potentially reflecting the negative effect of obesity on placenta development and thus function, but also as a mediator of obesity-induced depressive disorder in mothers.

The significance of human placental lactogen in the pathogenesis of peripartum depression is further supported by the facts that human placental lactogen is (i) produced at high levels during pregnancy [153], (ii) detected in the cerebrospinal fluid [56, 186], and (iii) a high

affinity ligand for the prolactin (lactogenic) receptor [187]. Recent data suggest that a high-fat diet for several weeks has a negative effect on maternal behaviors in pregnant mice including nest building and pup retrieval as well as a modest effect on anhedonia postpartum [188]. Interference with prolactin receptor signaling during pregnancy [189], lower levels of prolactin receptor ligand (prolactin), and reduced SVZ neurogenesis [190] are linked to impaired maternal behavior. Furthermore, both prolactin and placental lactogens are implicated in these effects, as knockout of prolactin alone [117] was not sufficient to explain the negative effects seen with lactogen receptor knockout in mice [189]. Together, these findings raise the questions whether a high-fat diet affects (i) lactogen levels (placental lactogens as well as prolactin), (ii) lactogenic signaling, and/or (iii) neurogenesis during pregnancy.

In addition, obesity increased hypothalamic cell proliferation and neuronal maturation [191]. Hypothalamic neurogenesis is important for energy balance [192] and is also implicated in oxytocin-mediated social behavior [167]. More importantly, the hypothalamus is at the epicenter of maternal neurobehavioral anatomy. The medial preoptic area in the hypothalamus is rich in prolactin receptors and responsible for nursing behavior [193]. The amygdala, which is part of both maternal and limbic network, has also shown evidence of adult neurogenesis [34]. Therefore, alongside the classical neurogenic targets, SVZ and hippocampus, the neurogenesis in the core maternal network is deserving of equal attention.

Conclusion

Neurogenesis is a multistep process and its progression depends on the success and completion of each phase. More specifically, the newly generated neuronal count depends on the rate of neural progenitors that differentiated into neurons, which, in turn, depends on the overall turnover of proliferated neural stem cells. Ultimately, a functionally mature neuron can integrate into a neural circuit whose relevance to maternal behavior also needs to be taken into account. Therefore, any functional outcome exerted by neurogenesis is likely a culmination of all events and not an immediate result. Knowledge of the temporal and anatomical changes of maternal neurogenesis will lay the foundation for more targeted cellular research including the role of relevant genetic and epigenetic machineries.

Reproductive hormones affect different parameters of neurogenesis. In pregnancy and postpartum, where hormonal levels change rapidly and frequently, the cumulative effect on neurogenesis also changes accordingly. Hence, it may not be possible to fully understand the neuroendocrine physiology involved in maternal neurogenesis without considering effects on neurogenesis at each day of the peripartum period along with the corresponding levels of hormones. Finally, while the functional implications may become clearer by specifically targeting endocrine-controlled maternal neurogenesis at different stages, separating 1 component from the other in the maternal neuroendocrine multisystem network is not without its challenges. However, existing literature provides sufficient evidence endorsing the potential therapeutic properties of the reproductive hormones to mitigate mental behavioral disorders in mothers around the time of pregnancy and parturition. This is a step toward tackling major maternal health crises such as peripartum depression and anxiety, which can be worsened by comorbidities during gestation including obesity and stress.

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Acknowledgment

We thank Dr. Jeremy Chopek for comments that greatly improved the quality of this article. All figures have been created with BioRender.com.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This work was supported by the Canadian Institutes of Health Research (Funding Reference No. PJ9 – 166215). N.N. is the recipient of a Research Manitoba Master's Studentship.

Author Contributions

Both N.N. and P.A.C. made contributions to the literature review. N.N. drafted the original manuscript and P.A.C. provided editorial additions and comments.

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