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REVIEW ARTICLE

Plasticity of the Parental Brain: A Case for Neurogenesis

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Profound behavioural changes occur in the mother at parturition, together with extensive remodelling of neural circuits. These changes include neurochemical, morphological and functional plasticity. The continuous generation of new neurones in the hippocampus and the olfactory system is an additional form of neuroplasticity that contributes to motherhood. This review describes the reciprocal relationships between hippocampal and olfactory neurogenesis and parental behaviour. Studies in rodents demonstrate that parturition and interactions with the young affect both cell proliferation and survival in a different manner across neurogenic zones. Species in which an individual recognition of the offspring is formed, such as sheep, show a down-regulation of neurogenesis during the perinatal period. This would function to decrease cell competition, favouring the selection of newborn neurones involved in olfactory recognition of the young. Also, in biparental species, increases in olfactory neurogenesis occur in the father in response to pup exposure during the early postpartum period. Oestradiol, corticosterone and prolactin changes associated with parturition are the main physiological factors involved in the regulation of neurogenesis that have been determined so far. In the father, prolactin mediates an enhancement of olfactory neurogenesis. Contradictory evidence indicates a functional link between neurogenesis and parenting behaviour. Mice receiving focal irradiation of the olfactory neurogenic subventricular zone show few disturbances in the expression of maternal behaviour, whereas a reduction of both hippocampal and olfactory neurogenesis as a result of the infusion of an anti-mitotic agent induces behavioural deficits. Disrupting prolactin signalling abolished increased paternal neurogenesis and offspring recognition by the father, and rescuing this neurogenesis restored recognition behaviour. More studies that selectively suppress the changes of neurogenesis are needed to confirm the role of new neurones in regulating parenting behaviour.

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Introduction

In the majority of mammalian species, females usually display a typical avoidance response to young. However, at the very end of gestation and at parturition, females suddenly change their behaviour, showing a very rapid interest to the newborn. Cleaning of the neonate and consuming amniotic fluids and placenta are widespread behaviours among mammalian orders. Mothers of many mammals also emit characteristic vocalisations in response to their young and show behaviours that protect the young from predation and, often, keep the young in close proximity to the mother. Nursing, the most important and common pattern of maternal behaviour in mammals, occurs shortly after the young are born (1).

There is now substantial evidence that the behavioural changes that the mother undergoes are a consequence of dramatic hormonal changes that occur during pregnancy and parturition. These fluctuations generate changes in the brain that induce a high state of maternal responsiveness. These neural changes, or neural

plasticity, defined as dynamic shifts in the strength of pre-existing connections across distributed neural networks and the establishment of new connections through dendritic growth and arborisation (2), could result in morphological and neurochemical plasticity. For example, profound alterations were demonstrated in astrocytic morphology and neural connectivity in the paraventricular and supraoptic nuclei in late pregnant rats, which contributes to a greater efficiency of the oxytocin system (3). A dramatic increase in the electrophysiological and neurochemical activity of the olfactory bulb in response to young odours was reported in ewes at the time of parturition (4–6). As early as 3 h postpartum, glial plasticity is up-regulated in the cingular cortex of mother rats (7). Changes in cell volume in the medial preoptic area, a key region for induction of maternal behaviour, were reported during lactation (8). Lactating females have elevated spine densities in the hippocampus (9) and show significant dendritic remodelling in pyramidal neurones (10).

Another form of brain plasticity which refers to the capacity of the brain to manufacture new neurones has been discovered in two regions of the adult brain, the sub-ventricular zone (SVZ)-main olfactory bulb (MOB) continuum and the dentate gyrus of the hippocampus (11–13). Over the past few decades, adult neurogenesis has been described in several additional regions, such as the neocortex, the piriform cortex, the amygdala, the striatum, the substantia nigra, the dorsal vagal complex and the hypothalamus (14). However, reports of the changes in neurogenesis observed in these 'nonclassical' structures, as well as indications of their functional role, are still debated and are not discussed in the present review.

Addition of adult-born neurones in the olfactory system and in the hippocampus contributes to various forms of learning (11,13). Thus, adult neurogenesis, in addition to others forms of brain plasticity, may constitute an adaptative response to motherhood by favouring learning ability. The present review highlights an emerging body of literature showing that neurogenesis in the olfactory system and in the hippocampus is regulated by parenting and, more specifically, by parturition and interactions with young (Table 1). In addition, we consider recent evidence indicating a possible functional link between this form of neuroplasticity and parenting, including kin recognition.

Neurogenesis in the adult brain

Continuing neurogenesis mainly occurs within two areas of the adult mammalian brain: the SVZ and the sub-granular zone (SGZ) (Fig. 1) (11,12,15,16). The SVZ lies adjacent to the wall of the lateral ventricle and gives rise to neuroblasts that migrate over a great distance through the rostral migratory stream and differentiate into granule neurones and periglomerular neurones in the olfactory bulb. The SGZ, which is located in the granule cell layer of the dentate gyrus, generates neurones that migrate over a short distance and become dentate granule cells.

Adult neurogenesis includes the proliferation, migration, survival, differentiation and integration of newborn neurones. All of these successive steps are regulated by a host of intrinsic and extrinsic factors reflecting physiological and/or pathological states (17). The germinative zones contain neural stem cells that have the potential for self-renewal and the generation of all three main cell lineages of the brain: neurones, astrocytes and oligodendrocytes (18). In the SGZ, two populations of neural stem cells likely co-exist. Among the two types, type 2 progenitors, which may arise from type 1 cells, generate astrocytes and neuroblasts (19). Among the different cell types identified in the SVZ, type B cells have been identified as slowly-dividing cells with neural stem cell properties (i.e. the ability of self-renewal and multipotency) (16). Using acute anti-mitotic administration, it has been shown that type B cells give rise to type C progenitors, which divide rapidly and, in turn, generate neuroblasts (type A cells).

Heterotopic transplantation experiments have demonstrated the pivotal role played by the local microenvironment in the fate determination of the neural stem cells in the SGZ and SVZ (20,21). The term 'niche' is used to designate such a unique microenvironment that supports and regulates stem cell behaviours. The neurogenic niche refers to all the molecular and cellular components that determine the properties of the neural stem cells and control adult neurogenesis. This includes neurotrophic factors released from blood vessels and astrocytes and neurotransmitters from nerve terminals (19). Altogether, these extrinsic signals provide permissive and instructive cues that determine, in combination with intrinsic factors, the potency of neural stem cells. By contrast to neuroblasts originating from the SGZ, those in the SVZ migrate over a long distance through the rostral migratory stream en route to the olfactory bulb. Tangential migration requires the presence of polysialated neural cell adhesion molecule (PSA-NCAM) and chemical signals (22,23). Once in the core of the olfactory bulb, newborn neurones turn radially toward the granule cell layer and to the periglomerular cell layer (15).

In rodents, almost one-half of the newborn neurones from the SGZ and SVZ die within a few weeks after their birth (24,25). Evidence indicates that neuronal activity is critical in determining survival. From 2–4 weeks after their birth, newborn neurones in the dentate gyrus exhibit lower thresholds for long-term potentiation (26). This enhanced plasticity occurring during a particular period may provide a fundamental mechanism for adult neurogenesis-dependent learning. In the SGZ, the survival of newly-generated neurones is strongly influenced by spatial learning, enrichment and exercise (27,28). The period of elimination of adult-born olfactory neurones coincides with a time window during which odour deprivation, olfactory enrichment or odour training have the most influence on the survival of the newborn neurones (24,29–32). Furthermore, it has recently been shown that, during this time, newborn neurones show a transient expression of long-term potentiation, providing a possible substrate for adult neurogenesis-dependent olfactory learning (33).

The functional impact of the integration of newborn neurones into mature circuits is still a matter of debate; however, taken together, the observations noted above illustrate that neuronal activity plays a key role in the selection of newborn neurones and that adult-born neurones may contribute to distinct forms of learning.

A growing body of literature using various methods to impair adult neurogenesis shows the role of hippocampal neurogenesis in some forms of hippocampus-dependent learning tasks in rat and

Table 1. Various Regulations of Cell Proliferation and Survival in the Hippocampal (A) and in the Subventricular Zone/Olfactory Bulb (B) Systems by Pregnancy, Parturition, Postpartum Period and Exposure to Pups in Mono- and Biparental Species.

			Hippocampal neurogenesis		
Context	Conditions	Species	Proliferation	Survival	Reference
(A)					
Pregnancy	Day 1	Rat	0		65
	Day 7	Rat	0		66
	Day 18	Rat	0	↑	67
	Day 21	Rat	0		68
	Day 7	Mice		0	56
Parturition/postpartum	Day 1	Rat	↓		69
	Day 2	Rat	↓		70,71
	Day 8	Rat	↓		70
	Day 14	Rat		↓	69
	Day 21	Rat		↓	71
	Day 28	Rat	0		70
	First week	Mice		↓	72
	Second week	Mice		↓	72
	Day 2	Sheep	↓		73
	Day 3 pup removal	Rat	0		70
	Day 2 lamb removal	Sheep	↓		73
	Sensitisation	Rat	↑		71
	Sensitisation	Vole	↑	↑	75
Paternal behaviour	Exposure to pups 2 days	Mice	↑		82
	Exposure to pups 3 weeks			↓	78
	Exposure to pups 20 min/3 days	Vole	↑		75

			SVZ/MOB neurogenesis		
Context	Conditions	Species	Proliferation	Survival	Reference
(B)					
Pregnancy	Day 7	Rat	0		66
	Day 21	Rat	↑		66
	Day 7	Mice	↑		56,57
	Day 14	Mice	0		56
	Day 21	Mice	0		56
Parturition/postpartum	Day 0	Mice	0		56
	Day 7	Mice	↑		56
	Day 14	Mice		↑	56
	Day 2	Sheep	↓		73
	Day 2 lamb removal	Sheep	0		73
Paternal behaviour	Exposure to pups 2 days	Mice	↑		82
	Exposure to pups 5 days	California mice	↑		95

SVZ, subventricular zone; MOB, main olfactory bulb; 0, no change; ↑ increase, ↓ decrease

mice, despite inconsistent results (34). Many studies showed impairment in long-term but not in short-term memory when spatial navigation learning of rats and mice were tested in the Morris water maze. However, other studies reported no effects on long-term term retention of spatial learning (35). Similarly, controversial studies have been reported in contextual fear conditioning, with some studies showing deficits in short- and long-term memory, whereas others report no defect (34). These contradictory findings could arise from the various experimental designs used, the methodology for ablating neurogenesis and the behavioural paradigm for testing memory (34).

Similarly, conflicting results are reported from the growing collection of studies examining the effects of reducing olfactory neurogenesis in mice on olfactory-guided behaviour (36,37). Odour discrimination is not impaired in animals in which olfactory neurogenesis has been altered during adulthood (38–40). By contrast,

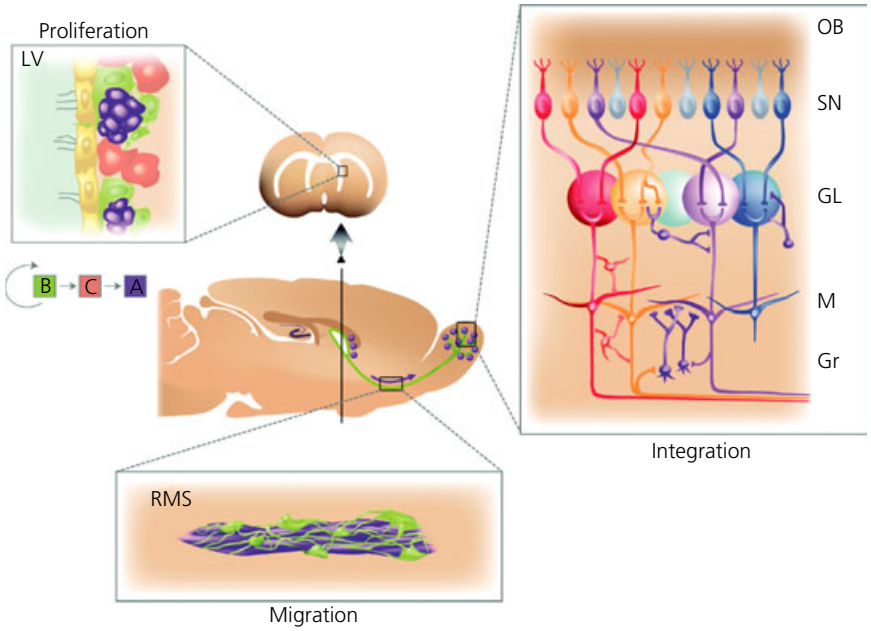

Fig. 1. Hippocampal neurogenesis: stem cells in the subgranular zone of the dentate gyrus give rise to transit ampliflying cells that differentiate into immature neurones, which migrate into the granule cell layer of the dentate gyrus. Immature neurones mature into new granule neurones. Olfactory neurogenesis: proliferation in the subventricular zone takes place in the medial wall of the lateral ventricle (LV), where stem cells (B) divide to generate transit amplifying cells (C), which, in turn, give rise to neuroblasts (A) that migrate in chains in the rostral migratory stream to their final destination in the olfactory bulb (OB). After reaching the OB, neuroblasts migrate radially and adult-born cells mature into olfactory inhibitory interneurones of two mains types (i.e. granule cells and periglomerular cells) in their respective olfactory bulb layers [i.e. the granule cell layer (Gr) and the glomerular layer (GL)]. RMS, rostral migratory stream; SN, sensory neurones; M, mitral cell layer.

olfactory neurogenesis is more involved in the cognitive processing of olfactory cues. Mice in which neurogenesis was blocked did not discriminate two perceptually similar odourants after having been exposed to these odourants for 10 days, suggesting an involvement of olfactory neurogenesis in olfactory perceptual learning (41). Blocking neurogenesis impairs short-term memory using a habituation/dishabituation task (38) and long-term memory using an associative olfactory task (32,39). However, studies from Breton-Provencher *et al.* (38) and Imayoshi *et al.* (40) reported that long-term memory was not affected after ablation of olfactory neurogenesis, although similar associative olfactory tasks have been used.

It should be noted that studies designated to examine the contribution of adult neurogenesis to social behaviours are still scarce (42). Only one study has explored the possible involvement of hippocampal neurogenesis in the context of social behaviour and reported no deficit in social transmission of food preference, which is a behavioural test that depends on hippocampal function (43). However, the demonstration of a causal link between adult olfactory neurogenesis and social behaviour has recently been demonstrated (42). In mice, the female prefers to mate with dominant males (44). A 7-day period of exposure to dominant-male odour induces a preference for a dominant male over a subordinate male (45). Suppression of neurogenesis by an anti-mitotic agent prevents the display of preference for the dominant male. However, anti-mitotic treatment also blocks hippocampal neurogenesis. Ablation of neurogenesis more specific to the olfactory system, such as irradiation of the SVZ, results in disturbed social interaction of the female with males: irradiated females showed longer behavioural interactions with a familiar male compared to controls and this alteration was not observed with females (46). Thus, newly-born olfactory interneurones in a female could support the processing of male odours involved in mate recognition. However, a previous study reported that SVZ-irradiated and control males spent a similar amount of time investigating an intruder male (39). Whether social impairments observed in irradiated females are restricted to opposite sex-interactions or are specific to the female is not known. Another functional approach of neurogenesis consists of evaluating whether newly-generated neurones might partly integrate the olfactory network that processes olfactory information. In male hamsters, double immunohistochemistry labelling for Fos and NeuN showed that olfactory bulb cells born in adulthood are activated by socio-sexual stimuli such as oestrous females or an aggressive male (47), suggesting that newly-born neurones participate in the olfactory processing of conspecific odours.

Below, we particularly focus on how parental behaviour can regulate the birth, fate and integration of neuronal precursors into the adult brain, and how this adult neurogenesis contributes to the ability of individuals to respond in an appropriate way to the need of their progeny.

Regulation of neurogenesis by parenting

Pregnancy and parturition are associated with dramatic hormonal changes. As a rule, late pregnancy and the peri-parturitional period

are generally characterised by a decrease in progesterone levels that have been high throughout pregnancy, especially in the late period, followed by an increase in levels of oestradiol. In addition to oestradiol and progesterone, across pregnancy, a rise in the activation of the foetal and maternal hypothalamic-pituitary-adrenal occurs, with the glucocorticoids, in particular cortisol, peaking at parturition (48). The change of oestradiol and progesterone steroid balance induces a rise in levels of the pituitary hormone, prolactin, which occurs in most species 24–48 h before parturition; this high level is maintained during lactation as a result of suckling stimulation (49,50).

Interestingly, the majority of the hormones listed above are regulators of adult neurogenesis (51). Oestradiol affects both proliferation and survival in the dentate gyrus in female rodents, mainly resulting in an increase in cell proliferation and a decrease in cell survival (52). By contrast, oestradiol actually down-regulates cell proliferation in the SVZ, leading to a decreased number of newborn cells in the olfactory bulb (53). Neuroactive metabolites of progesterone, dihydroprogesterone and tetrahydroprogesterone, drastically decrease the number of newly-formed cells (54) and progesterone modulates the effects of oestradiol on hippocampal neurogenesis (51,55). Prolactin increases cell proliferation in the SVZ and, consequently, cell survival in the olfactory bulb, although it does not affect hippocampal neurogenesis (56). In the same vein, the reduction of serum prolactin levels by bromocriptine treatment during pregnancy decreases cell proliferation in the SVZ and cell survival in the olfactory bulb but does not affect hippocampal neurogenesis (57). Although little direct evidence for a regulation of neurogenesis by corticosterone in female is found in the literature, prolonged treatment with high levels of corticosterone either during 21 days in the adult female rat or during pregnancy and/or the postpartum down-regulates hippocampal cell proliferation (58,59). However, high levels of this hormone induced by an intense stressor have no effect on cell proliferation in the hippocampus [predator odour: (60); foot shock: (61)]. By contrast, a long-lasting stress induces opposite effects depending on the different processes involved in neurogenesis: a reduction in cell proliferation (51), a decrease in differentiation/migration (62) and an increase in cell survival (63). By contrast, no regulation of olfactory neurogenesis by corticosteroids has been reported, despite the presence of glucocorticoid receptors in the olfactory bulb (64).

Because pregnancy and parturition are accompanied by hormonal changes that can act as possible regulators of neurogenesis, it is not surprising that both periods result in alterations of neurogenesis but differentially according to the neurogenic zone.

Hippocampal neurogenesis

Pregnancy

No changes in cell proliferation have been reported either during early (56,65,66) or late gestation (66–68) in rodents. Differentiation/migration of the granule cells in the dentate gyrus of rats, as revealed by expression of PSA-NCAM, are enhanced during late gestation (67). Only two studies in rats have examined fluctuations of cell survival during pregnancy, reporting no change at the very end of gestation (65,68).

Thus, there is little evidence that pregnancy is associated with changes in hippocampal neurogenesis. However, there is a clear lack of experimental data particularly during the last days of gestation, during which dramatic hormonal changes occur. In addition, the studies were focused on mice and rats and different pictures can be expected when considering species differences in the hormonal regulation of pregnancy.

Parturition and early postpartum period

In all of the species studied so far, parturition and the early postpartum period are accompanied by a significant decrease in cell proliferation in the hippocampus. In primiparous mother rats, this was reported at postpartum days 1, 2 and 8 (69–71), although no effect was observed later, at postpartum day 28 and after weaning (70). In mice, there was a decrease in newly-surviving cells during the first and the second weeks of lactation (72). Similarly, in sheep, a down-regulation of cell proliferation was observed in primiparous mothers in contact with their lambs for the first 2 days postpartum (73). Surprisingly, whether cell survival is altered during parturition and early postpartum period at the onset of maternal behaviour is not known. Rather, cell survival was assessed either at postpartum days 14 (69) or 21 (71) and both studies reported a significant decrease compared to virgin rats in dioestrous.

The down-regulation of cell proliferation during early postpartum could be under the influence of endocrine and/or social changes occurring at that time. However, the specific contribution of each factor is not clear. Female rats receiving oestradiol and progesterone injections for 23 days to simulate pregnancy had lower levels of cell proliferation compared to control animals 3 days later after the end of steroid treatment, suggesting that the down-regulation of cell proliferation during early postpartum is under steroid control (74). However, mother rats that had pups removed at birth showed no change in cell proliferation at postpartum day 3 compared to dioestrous virgins (70). This suggests that parturition by itself would have a positive influence on neurogenesis, which may appear to be paradoxical because corticosterone levels are elevated at parturition. It is possible that, if cell proliferation had been examined closer to the time of pup removal, a decrease in cell proliferation would have been observed. In sheep, however, when first-time mothers were immediately separated from their lambs at parturition, a down-regulation of cell proliferation was reported at postpartum day 2, indicating that parturition and associated hormonal changes could be involved (73). Oestradiol and cortisol show a rise in plasma levels at parturition and these variations could account for the changes in cell proliferation in the hippocampus. It appears that glucocorticoid changes are primary to the steroid effects because oestradiol increases or has little or no effect on cell proliferation in rats (51). In addition, several neuropeptides, such as oxytocin, are released in the brain during the expulsion of the neonate at parturition and further studies are needed to determine the regulation of hippocampal neurogenesis by these peptides.

By taking advantage of maternal sensitisation (i.e. the induction of maternal behaviour in naïve female rodents by pup exposure), a few studies have investigated the importance of stimuli provided by neonatal pups outside the context of parturition. Nulliparous rats exposed to pups showed increased cell proliferation in the granule cell layer of the dentate gyrus compared to nulliparous females, regardless of their parental response (71). Similarly, virgin female prairie voles exposed to pups exhibit increased hippocampal cell proliferation (75). Although an increase in cell survival was reported in virgin females 21 days after pup exposure (71), the influence on survival of the newborn neurones at the time of pup exposure is not known. Overall, it appears that the decrease in cell proliferation observed during the first postpartum days is mainly driven by the actual physiological conditions associated with parturition.

It is well-known that the first parturition and interactions with the offspring facilitate the long-term expression of maternal responsiveness. Studies in rodents and sheep indicate that maternal experience induces changes in receptors and/or in neural reorganisation that could mediate the enhanced maternal responsiveness to hormones and pup stimulation (1,76,77). Adult neurogenesis is also influenced by maternal experience. Primiparous and multiparous female rats had lower levels of cell proliferation at postpartum day 2 than nulliparous females, although no difference was observed between primiparous and multiparous mothers (71). However, when the ratio of surviving cells at postpartum day 21 versus the number of proliferating cells was examined, multiparous mothers had more new cells surviving than primiparous females. Whether the effect of parity on cell survival can be observed just after parturition is not known and it would be critical to relate theses changes to the enhanced maternal responsiveness occurring at parturition in experienced mothers.

Paternal behaviour

Few mammalian species display biparental care, and interaction with the offspring and the associated hormonal changes could produce neurogenesis variations in fathers. For example, virgin male prairie voles, a biparental species, exhibit an increase in cell proliferation when exposed to pups for a 20-min period, similar to virgin females (75). By contrast, in another biparental species, the California mice, fathers show reduced hippocampal cell survival after 3 weeks of pup exposure (78).

In laboratory mice, males are usually aggressive towards pups, even showing infanticide behaviour (79). However, mated males cohabitating with their mates engage in paternal behaviour (80,81). Recently, the activation of cell proliferation has been reported in male mice kept for the duration of pregnancy and for 2 days with their pups (82). More studies are needed to determine whether the activation of hippocampal neurogenesis in male can be observed in other biparental species and whether it could be linked to neuroendocrine changes such as vasopressin activation, which facilitates paternal care in virgin prairie voles (83), and/or to interactions with pups.

Olfactory neurogenesis

Pregnancy

In rodents, the production of neuroblasts within the SVZ is activated during pregnancy. Female mice exhibit an increase in cell proliferation in the SVZ at gestational day 7 compared to virgin females but not at gestational days 14 and 21 (56,57). The dynamics of cell proliferation appear to be quite different in female rats because the increase was observed on day 21 of pregnancy, although not on day 7 of pregnancy, compared to virgins (66). This species difference is quite surprising in light of the role of prolactin in stimulating cell proliferation in the SVZ. Systemic or central administration of prolactin induces cell proliferation in ovariectomised mice (56) and a reduction in prolactin levels by bromocriptine prevents this increase in early pregnant mice (57). Because, both in mice and rats, prolactin is released phasically during early pregnancy, a similar increase in cell proliferation can be expected in both species. Similarly, the lack of increased cell proliferation at postpartum day 21 observed in mice but not in rats is somewhat puzzling because, in both species, serum prolactin levels rise dramatically at that time (50). These differences could be a result of methodological differences, such as the use of bromodeoxyuridine (BrdU) (51,84). For example, the amount of BrdU injected and the number of BrdU injections differ between mice studies and rat studies. It is also possible that prolactin differently regulates neurogenesis in mice and rats. In addition, placental lactogens levels rise during the second half of gestation in rats but not in mice (85) and these differences could account for the different fluctuations of cell proliferation found between mice and rat at the end of pregnancy.

To date, no study has examined the variation of newly-born neurones within the olfactory bulb across pregnancy. However, in mice, adult-born olfactory interneurones are fully responsive to novel odourant stimulation at 2 weeks of age (86). It is possible that the wave of increased cell proliferation observed at gestational day 7 leads to the integration of a greater number of functional newly-generated interneurones at parturition, which is a time of high olfactory demands associated with the onset of maternal behaviour. Accordingly, reducing cell proliferation in the SVZ on gestational day 7 by bromocriptine treatment induces a down-regulation of newborn neurones in the MOB on postpartum day 2 (57).

Parturition and the early postpartum period

Parturition and the early postpartum period do not stimulate cell proliferation in the SVZ of mice, although an increase is observed at 7 days postpartum (56). Olfactory cues coming from conspecifics can prevent this increase. Exposure to female pheromones during pregnancy reduced levels of cell proliferation on day 7 of pregnancy to that of a virgin nonpregnant mouse (87). In sheep, a down-regulation is observed in mothers in contact with their lambs for 2 days but not in ewes separated from their lambs at birth (73). These species differences could be related to methodological issues and/or to the difference in mothering styles between rodents and

ungulates for which olfactory demand differs (77,88,89). Although, in both mice and sheep, odours from the young become very potent stimuli allowing the normal development of maternal care, in sheep, they also provide a basis for the individual recognition of the offspring. After parturition, the ewe learns the olfactory signature of her young within a few hours. Once this learning has been performed, the female will only take care of her young, rejecting any other young trying to nurse (90). This olfactory learning could contribute to the negative effect exerted on olfactory cell proliferation in the SVZ. Unexpectedly, the presence of neural precursors within the MOB was found in sheep, and ewes separated from their lamb immediately after birth significantly expressed less cell proliferation compared to nonpregnant females (73). This inhibition of cell proliferation in the MOB is likely the consequence of interplay between oestradiol and cortisol during pregnancy and parturition. Interestingly, oestrogen and glucocorticoid receptors are present in the MOB (64,91–93). Such a change was not found in the SVZ of ewes separated from their lambs and this could be related to a lack of evidence for oestrogen and glucocorticoid receptors in this area (93,94).

No indication is available in the literature indicating a change in the number of newly-born interneurones in the MOB at parturition, which is surprising given the possibility that changes in neurogenesis at that period could have some functional role in the onset of maternal behaviour.

Paternal behaviour

Adult neurogenesis in the olfactory system has been examined in the process of fatherhood in the monogamous, biparental California mouse. Five days of pup exposure induces an increase in cell proliferation in the SVZ (95). Similarly, male mice kept for the duration of pregnancy (18 days) with their partners and pups for 2 days after birth show 20% more proliferating cells in the SVZ than males separated from their pups or from their lactating female partners and pups at parturition (82). This enhanced cell proliferation in the SVZ is maintained for up to 8 days after parturition. The sensory factors involved have been examined extensively. Surprisingly, it appears that odours from their lactating female partners and pups are not sufficient by themselves. Rather, physical interactions with own pups but not with unrelated pups for 2 days stimulate proliferation in the SVZ (82). These early postnatal interactions also lead to a greater number of newly-born interneurones in the olfactory bulb, 3 weeks after parturition. In a series of elegant experiments, Mak and Weiss (82) further show that prolactin mediates enhanced olfactory neurogenesis in the paternal brain. Blocking prolactin mediation within the brain prevents enhanced cell proliferation in males interacting with pups. Similar results were obtained in males with a disruption in the prolactin receptor gene (82). The endocrine and social regulation of male neurogenesis is not specific to the olfactory system and comparable results were found for hippocampal neurogenesis (82). This contrasts with the female for which hippocampal and olfactory neurogenesis are differently regulated during pregnancy and early postpartum period.

Regulation of parenting by hippocampal and olfactory neurogenesis

As noted above, hippocampal and olfactory neurogenesis are regulated by factors associated with pregnancy, parturition and early interactions with offspring. Nevertheless, these studies are correlative and, to allow a better understanding of the function of neurogenesis, a common strategy is to examine the consequences of its ablation.

Although pregnancy, parturition and interactions with offspring are all accompanied by variations in the rate of production of new neurones in the hippocampus and in the olfactory system, a few studies have investigated their functional importance in the onset of maternal behaviour and recognition of the progeny. Mice with focal irradiation of the SVZ performed 2.5 months before parturition showed little disturbance with respect to the expression of maternal behaviour during the first week postpartum: they spent a longer time at the nest and, consequently, more time nursing their litter (46). Neither retrieval behaviour, nor the ability of mothers to discriminate their own pups from alien pups was affected by reduced olfactory neurogenesis. Similarly, a reduction of both hippocampal and olfactory neurogenesis by infusion of an anti-mitotic agent during pregnancy or a reduction of olfactory neurogenesis by suppression of prolactin secretion did not induce deficits in the expression of maternal behaviour when mice were tested in the home cage (57). Nevertheless, treated mothers were more anxious, in contrast to the SVZ-irradiated females in the study by Feierstein *et al.* (46), and, when they were tested in a novel environment, they had impaired maternal behaviour. The anxiolytic effects of prolactin have been recognised in lactating rats (96) and low-prolactin postpartum mice displayed high levels of anxiety compared to postpartum controls (57). Thus, the possibility exists that the impaired maternal behaviour observed at least in low-prolactin mothers with reduced neurogenesis is a consequence of increased anxiety.

Strong evidence showing an involvement of olfactory neurogenesis in parenting comes from the study of paternal behaviour in mice (82). When males interacted with their pups for 2 days, new olfactory interneurones preferentially respond to odours of their adult offspring compared to non-offspring odours, supporting the view that the adult born neurones make a unique contribution to processing of pup odours (82). Furthermore, paternal mice with a targeted disruption in the prolactin receptor gene did not exhibit the enhanced neurogenesis normally observed after 2 days of interactions with pups and they were unable to recognise their own adult offspring. However, rescuing this olfactory neurogenesis in $Prlr^{-/-}$ mice restored recognition (82). These data indicate that newly olfactory interneurones could be necessary for adult offspring recognition. They also raise a number of additional questions: although male laboratory mice do not show spontaneous paternal behaviour, what is the contribution of olfactory neurogenesis in biparental species? Does olfactory neurogenesis play a similar role in mothers for whom it is crucial to recognise their offspring? For example, in sheep, do newly-born olfactory interneurones provide a substantial support for the formation of olfactory memory for offspring immediately after parturition?

Conclusions

There are multiple mechanisms of plasticity that occur when a mother interacts with her offspring and neurogenesis is only one example of these. We still need to understand what determines which plasticity mechanism is functional and under what conditions. However, determining the functional significance of newly-generated neurones on the adult MOB and dentate gyrus is an important challenge in the field of behavioural neuroscience. To date, studies on adult neurogenesis have failed to clearly delineate specific functions of newborn neurones. Most of them have focused on the role of newly-generated cells with respect to learning and memory using precise psychophysical approaches. Progress calls for complementary approaches based on ethologically-relevant experiments. Behavioural domains such as parenting represent more naturalistic contexts and an important challenge for future work aiming to elucidate the functional contribution of adult neurogenesis. Hippocampal neurogenesis may support the enhancement of spatial memory employed during foraging behaviours in lactating females (69,97,98). Similarly, the integration of new neurones into the MOB could contribute to the high olfactory perceptual and memory demands associated with maternal behaviour, such as attraction to offspring odours and recognition of the individual olfactory signature of young (90). Surprisingly, this hypothesis has recently received support from studies on paternal recognition in mice. However, the present review describes a field that is still in its infancy. There is a need for more functional studies aiming to make sense of the variations observed in neurogenesis around the final stage of parturition and during parenting. Disentangling the role played by the various hormonal factors acting to promote parenting will be a challenging task because the elucidation of the role played by some of them in the process of neurogenesis (e.g. oxytocin) has not yet started. Finally, recent evidence suggests that neurogenesis also occurs in other regions than the MOB and the dentate gyrus, although at a much lower rate (14). Interestingly, the bed nucleus of the stria terminalis and the amygdala show changes in cell survival in mothers at 4 weeks postpartum (99). These changes in new cells after a maternal experience are likely to have functional consequences because these areas are critical for the expression of maternal behaviour, and new cells may be added to these areas for the purpose of maternal circuit function.

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