Review

Neural stem cells and the regulation of adult neurogenesis

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Abstract

Presumably, the 'hard-wired' neuronal circuitry of the adult brain dissuades addition of new neurons, which could potentially disrupt existing circuits. This is borne out by the fact that, in general, new neurons are not produced in the mature brain. However, recent studies have established that the adult brain does maintain discrete regions of neurogenesis from which new neurons migrate and become incorporated into the functional circuitry of the brain. These neurogenic zones appear to be vestiges of the original developmental program that initiates brain formation. The largest of these germinal regions in the adult brain is the subventricular zone (SVZ), which lines the lateral walls of the lateral ventricles. Neural stem cells produce neuroblasts that migrate from the SVZ along a discrete pathway, the rostral migratory stream, into the olfactory bulb where they form mature neurons involved in the sense of smell. The subgranular layer (SGL) of the hippocampal dentate gyrus is another neurogenic region; new SGL neurons migrate only a short distance and differentiate into hippocampal granule cells. Here, we discuss the surprising finding of neural stem cells in the adult brain and the molecular mechanisms that regulate adult neurogenesis.

Discovery of Adult Neurogenesis

The concept of neurogenesis in the adult brain has only recently gained wide acceptance, though support had slowly been building over the past century. As early as 1912, and subsequently in 1932, 1938 and 1944, cytological investigations examining mitotic divisions in the postnatal and adult rodent brain revealed the SVZ as mitotically active (for review, [1,2]). The advent of autoradiography then made possible the identification of DNA synthesis by incorporation of tritiated thymidine into nascent strands of DNA allowing cell proliferation to be monitored in the mammalian SVZ [3-5]. However, the fate of these proliferating cells was not clear; most cells produced in the SVZ during embryonic development were thought to differentiate into neurons, while only the production of glial cells was described in the postnatal and adult SVZ. Studies lagged until improved immunohistochemical techniques allowed more definitive characterization and identification of SVZ progeny. Interestingly, it was studies in songbirds that inspired the advance of mammalian neurogenesis. In 1983 Nottebohm and colleagues demonstrated that new neurons are produced in the telencephalon of adult male songbirds [6]. These neurons appear to be required for the production of new elemental components of song that allow embellishment of song each season [7]. In addition, it was found that acquisition of new neurons is hormonally regulated and therefore seasonally controlled to correspond to the mating season [7]. Full acceptance of postembryonic mammalian neurogenesis did not take hold until just over a decade ago

when Luskins [8] described neurogenesis in the anterior portion of the SVZ in postnatal mice, Lois and Alvarez-Buylla [9] demonstrated neurogenesis in the adult mouse SVZ and several groups built upon previously shown neurogenesis in the SGL of the hippocampus [10-13]. The possibility for other adult neurogenic regions exists and the search for sites of adult neurogenesis continues.

The SVZ Niche: The Largest Site of Adult Neurogenesis

During development the mammalian brain forms from a layer of cells surrounding fluid-filled compartments, called ventricles. This region of actively dividing cells, the ventricular zone, generates neurons that migrate to form all structures of the brain. A second germinal zone, the subventricular zone (SVZ), forms later in embryogenesis beneath the ventricular zone and generates both neurons and glia. Following postnatal development, these proliferative zones diminish until only a thin SVZ remains and it is this residual SVZ that persists into adulthood (Fig. 1a,1b). Ultrastructural analysis of the adult SVZ using electron microscopy reveals that four major cell types constitute this zone [14] (Fig. 1c). A monolayer of ependymal cells lines the ventricle. Adjacent to the ependymal layer are clusters of neuroblasts that migrate as tightly apposed chains of cells through the SVZ (Fig. 1b,1d,1e), eventually congregating in the rostral migratory stream (RMS) that leads to the olfactory bulb (OB). Astrocytes surround the neuroblast chains and transitory amplifying progenitor (TAP) cells are found interspersed amoungst the chains (Fig. 1b,1c). The TAP cell is the most actively dividing of the SVZ cells types and has an immature phenotype, lacking morphological or immunohistochemical characteristics of either glia or neuroblasts [14]. Is the TAP cell the neural stem cell capable of supporting adult neurogenesis? While originally a strong candidate, the TAP cell was found to be a progenitor cell derived from a neural stem cell [1,15-17]. The ensuing search for the neural stem cell has generated much controversy and still is not fully resolved.

The presence of neural stem cells in the SVZ was suggested based on the finding that a subpopulation of SVZ cells can be dissociated and grown as free-floating spheres, neurospheres, in culture in the presence of mitogen (EGF or FGF2) [18]. Some of these primary spheres are capable of generating secondary spheres upon dissociation and can be renewed through many passages. This self-renewing population is multipotent, capable of generating neurons, oligodendrocytes and astrocytes, upon removal of mitogen. Thus, these cells qualify in fulfilling the criteria of stem cells: self-renewable and multipotential. However, the precise identification of neural stem cells in vivo is currently mired by the lack of sensitive and specific immunological markers to identify cell types of the SVZ.

Recent studies in which the SVZ was temporarily depleted of proliferating cells using the anti-mitotic agent cytosine-β-D-arabinofuranoside (Ara-C) revealed that cells positive for glial fibrillary acidic protein (GFAP) and displaying astrocytic characteristics repopulated the SVZ upon withdrawal of Ara-C [19]. In addition, these GFAP-positive cells are capable of generating neurospheres [19]. Most recent studies now support the claim that neural stem cells have some characteristics of astrocytes [20-22]. However, it is unlikely that all astrocytes are neural stem cells, so it becomes important to distinguish the subpopulation of SVZ astrocytes that are neural stem cells. Cell-specific markers together with investigations into the regulatory mechanisms that contribute to the maintenance of stem cell renewal and neurogenesis will reveal how this adult germinal zone persists into adulthood.

Hormonal Influences on Adult Neurogenesis

Studies conducted over the past several years have identified steroid hormones (e.g., adrenal steroids, testosterone and estrogen) and peptide hormones (such as prolactin) as potential regulators of adult neurogenesis. The cyclical fluctuations of sex hormone levels raise the possibility of corresponding cyclical waves of neurogenesis.

Estrogen and Testosterone

In adult songbirds, integration and survival of new neurons in the vocal control nucleus is modulated by the gonadal steroids testosterone and estradiol [23-26]. In mammals, estrogen has been implicated in hippocampal function, with sex differences observed in long-term potentiation [27] and performance of hippocampal-dependent tasks [28-31]. During proestrus, a time when estrogen levels are high, cell proliferation in the SGL increases, compared with estrus and diestrus, when estrogen levels are lower [32] (Fig. 2a). Accordingly, removal of circulating estrogen by ovariectomy results in a significant decrease in the proliferation of hippocampal granule cell precursors. This decrease can be prevented by replacement of estrogen in ovariectomized rats [32]. Whether the effects of estrogen on cell proliferation in the SGL are exerted directly on the progenitors via estrogen receptors or indirectly through other receptor systems is unclear but serotonin appears to mediate the estrogen-dependent proliferative effect [33]. Combining ovariectomy with inhibition of serotonin synthesis using p-chlorophenylalanine (PCPA) treatment produced approximately the same decreases in the SGL as ovariectomy alone; administration of 5-hydroxytryptophan, to stimulate serotonin production, restored cell proliferation decreased by ovariectomy. Whereas estradiol is unable to reverse this change in ovariectomized rats treated with PCPA [33]. Surprisingly, the remarkable increase in ovarian hormones detected during the first and third trimester of pregnancy has no effect on cell proliferation in the SGL, suggesting that concomitant
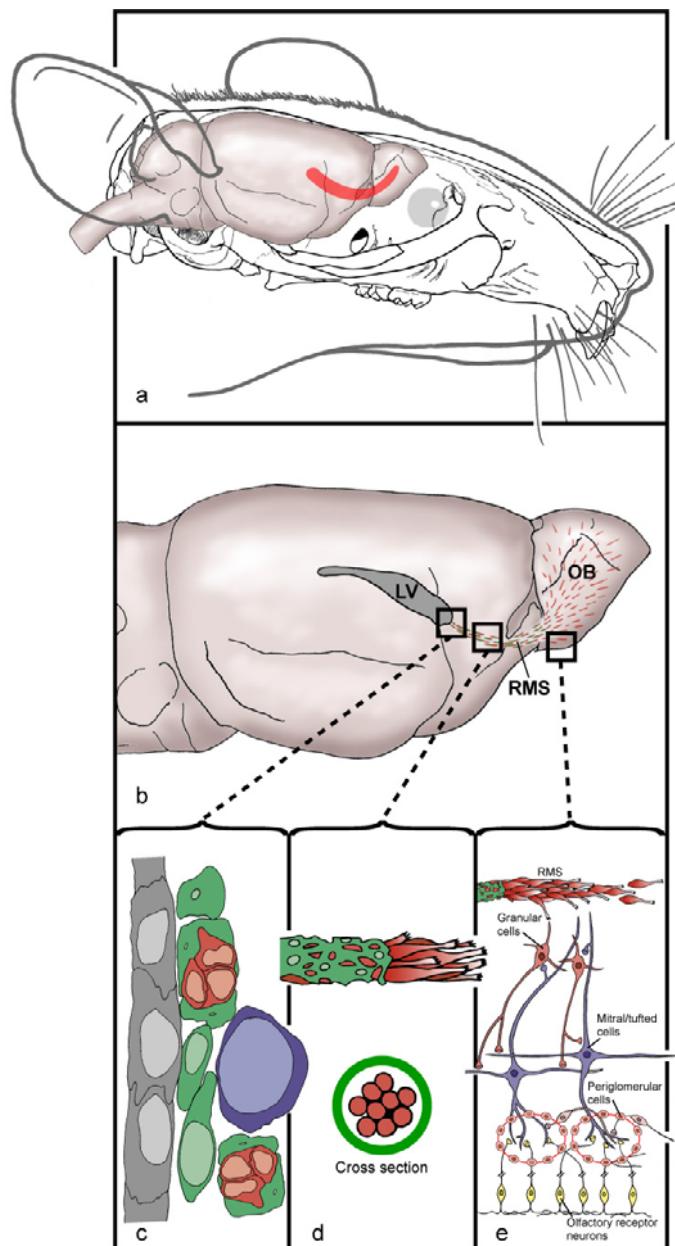
Figure 1
(a) Head of a mouse showing the location of the brain and the rostral migratory stream, RMS, (in red) along which newly generated neuroblasts migrate from the SVZ of the lateral ventricle into the olfactory bulb (OB). (b) The migration of newly generated neuroblasts begins at the lateral ventricle, continues along the RMS and terminated in the OB, where mature interneuron populations are generated. (c) Schematic based on electron microscopy showing the cytoarchitecture of the SVZ along the ventricle. Ependymal cells (gray) form a monolayer along the ventricle with astrocytes (green), neuroblasts (red) and transitory amplifying progenitors (TAP) (purple) comprising the SVZ. (d) Schematic showing the migration of neuroblasts along the RMS. Astrocytes (green) ensheath the migrating neuroblasts (red) and are thought to restrict and contain the neuroblasts to their specific pathway. (e) Migrating neuroblasts enter the OB, migrate radially and give rise to granule or periglomerular cells.
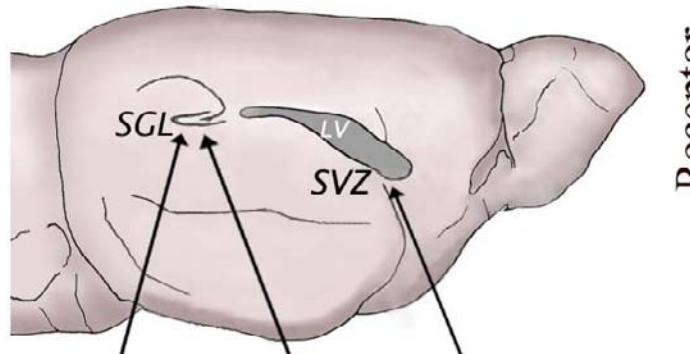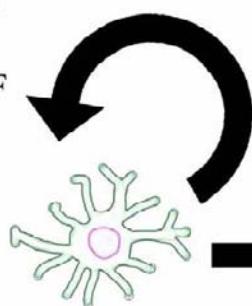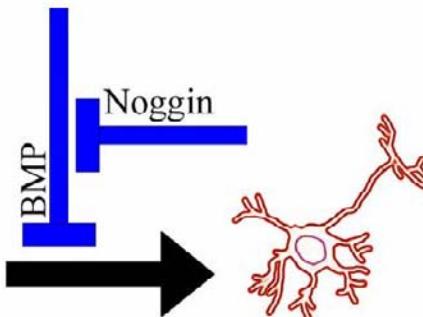
Figure 2
(a) Hormonal regulation of neurogenesis in the mammalian brain. Subgranular layer, SGL; subventricular zone, SVZ; lateral ventricle, LV. (b) Current view of the regulation of adult neurogenesis.

changes in other factors, perhaps glucocorticoids, may counterbalance the positive regulation of cell proliferation by estradiol and serotonin [33,34]. No study has yet thoroughly explored the effect of hormone fluctuations on SGL cell proliferation throughout the entire period of pregnancy and parturition.

Prolactin
While estradiol's effect is in the hippocampal SGL and does not affect cell proliferation in the SVZ, prolactin stimulates the production of neuronal progenitors in the SVZ [34] (Fig. 2a). Prolactin is a hormone that increases during the first half of pregnancy and also at postpartum, signaling lactation. A recent study showed that neurogenesis rates jump during pregnancy by 65%, peaking on the seventh day of the mouse's 21-day gestation period and again after delivery [34]. In addition to observing cell proliferation, this study tracked integration of the new neurons in the OB. The premise behind this study is that olfactory discrimination is critical for recognition and rearing of offspring. A doubling of olfactory interneurons may thereby enhance olfactory function following pregnancy, providing the mother with enhanced olfactory capability [34]. The increase in olfactory neurons associated with pregnancy and the implicated heightened sense of smell does not come as a surprise to anyone who has experienced pregnancy and the associated acute sense of smell that can often trigger nausea.

Corticosteroids/Adrenal stress steroids
Adrenal steroids, on the other hand, have been shown to inhibit adult neurogenesis by suppressing cell proliferation in the hippocampal SGL (Fig. 2a). Aged rats and monkeys exhibit diminished cell proliferation in the SGL as well as elevated levels of circulating glucocorticoids [13,35,36]. Removal of adrenal steroids by adrenalectomy increases cell proliferation in the SGL in both aged and young adult rats [37]. Moreover, the number of new SGL cells in adrenalectomized aged rats was threefold higher than the number in young control rats, indicating that adrenalectomized aged rats have rates of proliferation that surpass those normally found in young adults [37]. The absence of adrenal steroid receptors on granule cell precursors in the SGL suggests that the effects of adrenal steroids on cell proliferation occur indirectly through other factors [38].

Regulation and Maintenance of the SVZ
The SVZ is a specialized niche where functions such as cell fate, cell adhesion, migration, polarity and proliferation are regulated in part by secreted and membrane-bound ligands signaling through their cognate receptors (for review see [16]). These initiating extracellular signals then set off a cascade of intracellular reactions that ultimately control cellular gene expression. Below we discuss recent findings and associated controversies concerning six ligand/receptor families and their roles in SVZ function.

EGF and FGF2
SVZ neural stem cells continue to generate new neurons in the adult brain. When dissociated from the adult SVZ, neural stem cells require either epidermal growth factor (EGF) or basic fibroblast growth factor (FGF2) for self-renewal and long-term survival in culture [18,39]. Analysis of EGF and FGF2 responsiveness in the developing telencephalon indicates that early growth factor choice is temporally regulated [40,41]. FGF2 response is present as early as E8.5, a time when EGF receptors (EGFRs) are not expressed on neural stem cells. By E14.5 neural stem cells expressing EGFR emerge [40]. In the adult, the vast majority of SVZ cells expressing EGFR also express FGFR1 supporting the finding that most EGF-responsive cells can also be stimulated by FGF2 [42]. However, EGF and FGF2 appear to differ in their mechanisms of support, with EGF promoting faster expansion of the stem cell-like pool (symmetric division) compared to FGF2 [42]. This may be the result of differential control of cell cycle length by each growth factor, with SVZ stem-like cells cycling faster in the presence of EGF [42]. Alternatively, since the SVZ has two subsets of mitotically active cells, the neural stem cells (a relatively quiescent population with a cell cycle length up to 28 days) [43,44], and the transitory amplifying progenitor (TAP) cells (cell cycle length approximately 12 h), these two growth factors may preferentially target one cell type (Fig. 2b). The latter appears to be supported by the work of Kuhn et al. [39] and Doetsch et al. [17]. Kuhn et al. found that intracerebroventricular infusion of FGF2 into the lateral ventricle resulted in increased numbers of new neurons in the OB, while EGF infusion reduced the number of neurons reaching the OB, but substantially increased generation of astrocytes in the OB and the neighboring striatum. Extension of this study by Doetsch et al. [17] suggests that TAP cells are EGF receptive and these cells become invasive and glia-like, diverting neurogenesis to gliogenesis. In contrast, Craig et al. [45] found increased SVZ neurogenesis and associated migration of neuroblasts into the OB following a 6 day infusion of EGF, similar to FGF2 infusion. It is hard to reconcile these disparate results, however, improving our ability to uniquely identify neural stem cells (likely a subset of SVZ astrocytes) [17] will allow discrimination between neural stem cells and SVZ progenitor cells and aid in our understanding of the molecular dynamics regulating this germinal zone.

CNTF and LIF
Other signaling pathways have been implicated in the decision between self-renewal through symmetric division or promotion of neural stem cell differentiation. The cytokine ciliary neurotrophic factor (CNTF) signaling

through its heterotrimeric receptor complex of CNTF receptor α, LIF receptor β and gp130 subunits supports embryonic stem cell self-renewal and pluripotency [46] and has recently been reported to support neural stem cell self-renewal [47,48] (Fig. 2b). This action appears to be mediated via Notch signaling [48].

Notch

Activation of the Notch1 receptor inhibits neurogenesis (Fig. 2b). Controversy then arises as to whether Notch signaling maintains stem cell pluripotency or actively instructs glial cell fate (for review see [16]). Neural stem cells are depleted in Notch-/- mice and in mice lacking key regulators of Notch signaling activity [49]. However, transient Notch activation induced by exogenous Notch ligand caused rapid and irreversible loss of neurogenic capacity accompanied by accelerated glial differentiation [50]. Similarly, introduction of activated Notch into the mouse embryonic forebrain by retroviral vector and tracked by ultrasound imaging revealed that Notch–infected cells became radial glia [51]. Recent findings indicate that proliferative radial glia, while originally thought to be part of the glial lineage, can also function as neuronal precursors [52,53] (for review see [1]). Interestingly, many of the Notch-infected cells eventually became periventricular astrocytes, the same cells shown to be the neural stem cells in the adult SVZ [19], evoking the interesting possibility that radial glia and SVZ astrocytes are of the same lineage [51]. This possibility helps to resolve the apparent contradictory findings that Notch signaling is instructive for gliogenesis and for maintaining neural stem cells in an undifferentiated state (Fig. 2b).

BMPs

What then are the instructive signals for neurogenesis in the SVZ? The neurogenic environment of the SVZ has been attributed in part to the local antagonistic interplay between noggin and bone morphogenetic proteins (BMPs) [54]. BMPs are negative regulators of neural determination; noggin reverses this effect by binding BMPs, preventing their signal activation [55,56] (Fig. 2b). BMPs are expressed by the SVZ cells, while noggin is expressed by ependymal cells [54]. This arrangement of interacting signals from the ependymal cells and the adjacent SVZ may provide the necessary regulation of neurogenesis and gliogenesis in the adult brain.

Conclusions

Much still needs to be learned about how extracellular signaling pathways coordinate the intricate balance of neurogenesis, gliogenesis and stem cell renewal in the adult SVZ. From the data accumulated so far, it does appear that neurogenic strategies of the adult SVZ recapitulate some themes and mechanisms used in the developing embryonic nervous system. Thus, information gathered from one developmental system will offer clues as to how the other system may function.

References

1. Alvarez-Buylla A, Garcia-Verdugo JM, Tramontin AD: **A unified hypothesis on the lineage of neural stem cells.** *Nature Reviews* 2001, **2:**287-293.
2. Rakic P: **Adult neurogenesis in mammals: an identity crisis.** *J Neurosci* 2002, **22(3):**614-618.
3. Smart I: **The subependymal layer of the mouse brain and its cell production as shown by radioautography after thymidine-H3 injection.** *J Comp Neurol* 1961, **116:**325-347.
4. Altman J: **Autoradiographic investigation of cell proliferation in the brains of rats and cats.** *Anat Rec* 1963, **145:**573-591.
5. Altman J: **Are neurons formed in the brains of adult mammals?** *Science* 1962, **135:**1127-1128.
6. Goldman SA, Nottebohm F: **Neuronal production, migration, and differentiation in a vocal control nucleus of the adult female canary brain.** *Proc Natl Acad Sci U S A* 1983, **80(8):**2390-2394.
7. Nottebohm F: **A brain for all seasons: cyclical anatomical changes in song control nuclei of the canary brain.** *Science* 1981, **214(4527):**1368-1370.
8. Luskins MB: **Restricted proliferation and migration of postnatally generated neurons derived from the forebrain subventricular zone.** *Neuron* 1993, **11:**173-189.
9. Lois C, Alvarez-Buylla A: **Proliferating subventricular zone cells in the adult mammalian forebrain can differentiate into neurons and glia.** *Proc Natl Acad Sci U S A* 1993, **90(5):**2074-2077.
10. Altman J, Das GD: **Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats.** *J Comp Neurol* 1965, **124(3):**319-335.
11. Kaplan MS, Bell DH: **Mitotic neuroblasts in the 9-day-old and 11-month-old rodent hippocampus.** *J Neurosci* 1984, **4(6):**1429-1441.
12. Cameron HA, Woolley CS, McEwen BS, Gould E: **Differentiation of newly born neurons and glia in the dentate gyrus of the adult rat.** *Neuroscience* 1993, **56(2):**337-344.
13. Kuhn HG, Dickinson-Anson H, Gage FH: **Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation.** *J Neurosci* 1996, **16(6):**2027-2033.
14. Doetsch F, Garcia-Verdugo JM, Alvarez-Buylla A: **Cellular composition and three-dimensional organization of the subventricular germinal zone in the adult mammalian brain.** *J Neurosci* 1997, **17:**5046-5061.
15. Alvarez-Buylla A, Garcia-Verdugo JM: **Neurogenesis in adult subventricular zone.** *J Neurosci* 2002, **22(3):**629-634.
16. Conover JC, Allen RL: **The subventricular zone: new molecular and cellular developments.** *Cell Mol Life Sci* 2002, **59(12):**2128-2135.
17. Doetsch F, Petreanu L, Caille I, Garcia-Verdugo JM, Alvarez-Buylla A: **EGF converts transit-amplifying neurogenic precursors in the adult brain into multipotent stem cells.** *Neuron* 2002, **36(6):**1021-1034.
18. Reynolds BA, Weiss S: **Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system.** *Science* 1992, **255(5052):**1707-1710.
19. Doetsch R, Caille I, Lim DA, Garcia-Verdugo JM, Alvarez-Buylla A: **Subventricular zone astrocytes are neural stem cells in the adult mammalian brain.** *Cell* 1999, **97:**703-716.
20. Imura T, Kornblum HI, Sofroniew MV: **The predominant neural stem cell isolated from postnatal and adult forebrain but not early embryonic forebrain expresses GFAP.** *J Neurosci* 2003, **23(7):**2824-2832.
21. Laywell ED, Rakic P, Kukekov VG, Holland EC, Steindler DA: **Identification of a multipotent astrocytic stem cell in the immature and adult mouse brain.** *Proc Natl Acad Sci U S A* 2000, **97(25):**13883-13888.
22. Chiasson BJ, Tropepe V, Morshead CM, van der Kooy D: **Adult mammalian forebrain ependymal and subependymal cells**

demonstrate proliferative potential, but only subependymal cells have neural stem cell characteristics. *J Neurosci* 1999, **19(11):**4462-4471.

23. Nordeen EJ, Nordeen KW: **Estrogen stimulates the incorporation of new neurons into avian song nuclei during adolescence.** *Brain Res Dev Brain Res* 1989, **49(1):**27-32.
24. Rasika S, Nottebohm F, Alvarez-Buylla A: **Testosterone increases the recruitment and/or survival of new high vocal center neurons in adult female canaries.** *Proc Natl Acad Sci U S A* 1994, **91(17):**7854-7858.
25. Hidalgo A, Barami K, Iversen K, Goldman SA: **Estrogens and non-estrogenic ovarian influences combine to promote the recruitment and decrease the turnover of new neurons in the adult female canary brain.** *J Neurobiol* 1995, **27(4):**470-487.
26. Johnson F, Bottjer SW: **Differential estrogen accumulation among populations of projection neurons in the higher vocal center of male canaries.** *J Neurobiol* 1995, **26(1):**87-108.
27. Maren S, De Oca B, Fanselow MS: **Sex differences in hippocampal long-term potentiation (LTP) and Pavlovian fear conditioning in rats: positive correlation between LTP and contextual learning.** *Brain Res* 1994, **661(1–2):**25-34.
28. Roof RL, Havens MD: **Testosterone improves maze performance and induces development of a male hippocampus in females.** *Brain Res* 1992, **572(1–2):**310-313.
29. Roof RL, Zhang Q, Glasier MM, Stein DG: **Gender-specific impairment on Morris water maze task after entorhinal cortex lesion.** *Behav Brain Res* 1993, **57(1):**47-51.
30. Galea LA, Kavaliers M, Ossenkopp KP: **Sexually dimorphic spatial learning in meadow voles Microtus pennsylvanicus and deer mice Peromyscus maniculatus.** *J Exp Biol* 1996, **199(Pt 1):**195-200.
31. Kavaliers M, Ossenkopp KP, Prato FS, Innes DG, Galea LA, Kinsella DM, Perrot-Sinal TS: **Spatial learning in deer mice: sex differences and the effects of endogenous opioids and 60 Hz magnetic fields.** *J Comp Physiol [A]* 1996, **179(5):**715-724.
32. Tanapat P, Hastings NB, Reeves AJ, Gould E: **Estrogen stimulates a transient increase in the number of new neurons in the dentate gyrus of the adult female rat.** *J Neurosci* 1999, **19(14):**5792-5801.
33. Banasr M, Hery M, Brezun JM, Daszuta A: **Serotonin mediates oestrogen stimulation of cell proliferation in the adult dentate gyrus.** *Eur J Neurosci* 2001, **14(9):**1417-1424.
34. Shingo T, Gregg C, Enwere E, Fujikawa H, Hassam R, Geary C, Cross JC, Weiss S: **Pregnancy-stimulated neurogenesis in the adult female forebrain mediated by prolactin.** *Science* 2003, **299(5603):**117-120.
35. Gould E, Reeves AJ, Fallah M, Tanapat P, Gross CG, Fuchs E: **Hippocampal neurogenesis in adult Old World primates.** *Proc Natl Acad Sci U S A* 1999, **96(9):**5263-5267.
36. Sapolsky RM: **Do glucocorticoid concentrations rise with age in the rat?** *Neurobiol Aging* 1992, **13(1):**171-174.
37. Cameron HA, McKay RD: **Restoring production of hippocampal neurons in old age.** *Nat Neurosci* 1999, **2(10):**894-897.
38. Cameron HA, Woolley CS, Gould E: **Adrenal steroid receptor immunoreactivity in cells born in the adult rat dentate gyrus.** *Brain Res* 1993, **611(2):**342-346.
39. Kuhn HG, Winkler J, Dempermann G, Thal LJ, Gage FH: **Epidermal growth factor and fibroblast growth factor-2 have different effects on neural progenitors in the adult rat brain.** *J Neurosci* 1997, **17(15):**5820-5829.
40. Tropepe V, Sibilia M, Ciruna BG, Rossant J, Wagner EF, van der Kooy D: **Distinct neural stem cells proliferate in response to EGF and FGF in the developing mouse telencephalon.** *Dev Biol* 1999, **208(1):**166-188.
41. Maric D, Maric I, Chang YH, Barker JL: **Prospective cell sorting of embryonic rat neural stem cells and neuronal and glial progenitors reveals selective effects of basic fibroblast growth factor and epidermal growth factor on self-renewal and differentiation.** *J Neurosci* 2003, **23(1):**240-251.
42. Gritti A, Frolichsthal-Schoeller P, Galli R, Parati EA, Cova L, Pagano SF, Bjornson CR, Vescovi AL: **Epidermal and fibroblast growth factors behave as mitogenic regulators for a single multipotent stem cell-like population from the subventricular region of the adult mouse forebrain.** *J Neurosci* 1999, **19(9):**3287-3297.

43. Morshead CM, van der Kooy D: **Postmitotic death is the fate of constitutively proliferating cells in the subependymal layer of the adult mouse brain.** *J Neurosci* 1992, **12(1):**249-256.
44. Morshead CM, Reynolds BA, Craig CG, McBurney MW, Staines WA, Morassutti D, Weiss S, van der Kooy D: **Neural stem cells in the adult mammalian forebrain: a relatively quiescent subpopulation of subependymal cells.** *Neuron* 1994, **13(5):**1071-1082.
45. Craig CG, Tropepe V, Morshead CM, Reynolds BA, Weiss S, van der Kooy D: **In vivo growth factor expansion of endogenous subependymal neural precursor cell populations in the adult mouse brain.** *J Neurosci* 1996, **16(8):**2649-2658.
46. Conover JC, Ip NY, Poueymirou WT, Bates B, Goldfarb MP, DeChiara TM, Yancopoulos GD: **Ciliary neurotrophic factor maintains the pluripotentiality of embryonic stem cells.** *Development* 1993, **119:**559-565.
47. Shimazaki T, Shingo T, Weiss S: **The ciliary neurotrophic factor/leukemia inhibitory factor/gp130 receptor complex operates in the maintenance of mammalian forebrain neural stem cells.** *J Neurosci* 2001, **21(19):**7642-7653.
48. Chojnacki AT, Shimazaki C, Gregg G, Weinmaster G, Weiss S: **Glycoprotein 130 signaling regulates Notch1 expresssions and activation in the self-renewal of mammalian forebrain neural stem cells.** *Journal of Neuroscience* 2003, **23(5):**1730-1741.
49. Hitoshi S: **Notch pathway molecules are essential for the maintenance, but not the generation, of mammalian neural stem cells.** *Genes Dev* 2002, **16(7):**846-858.
50. Morrison SJ, Perez SE, Qiao Z, Verdi JM, Hicks C, Weinmaster G, Anderson DJ: **Transient Notch activation initiates an irreversible switch from neurogenesis to gliogenesis by neural crest stem cells.** *Cell* 2000, **101(5):**499-510.
51. Gaiano N, Nye JS, Fishell G: **Radial glial identity is promoted by Notch1 signaling in the murine forebrain.** *Neuron* 2000, **26(2):**395-404.
52. Malatesta P, Hartfuss E, Gotz M: **Isolation of radial glial cells by fluorescent-activated cell sorting reveals a neuronal lineage.** *Development* 2000, **127(24):**5253-5263.
53. Noctor SC, Flint AC, Weissman TA, Dammerman RS, Kriegstein AR: **Neurons derived from radial glial cells establish radial units in neocortex.** *Nature* 2001, **409(6821):**714-720.
54. Lim DA, Tramontin AD, Trevejo JM, Herrera DG, Garcia-Verdugo JM, Alvarez-Buylla A: **Noggin antagonizes BMP signaling to create a niche for adult neurogenesis.** *Neuron* 2000, **28(3):**713-726.
55. Gross RE, Mehler MF, Mabie PC, Zang Z, Santschi L, Kessler JA: **Bone morphogenetic proteins promote astroglial lineage commitment by mammalian subventricular zone progenitor cells.** *Neuron* 1996, **17(4):**595-606.
56. Shou J, Rim PC, Calof AL: **BMPs inhibit neurogenesis by a mechanism involving degradation of a transcription factor.** *Nat Neurosci* 1999, **2(4):**339-345.