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Adult neurogenesis in the mammalian brain : exogenous and endogenous influences *

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Abstract Until the past three decades , the general scientific community did not regard adult mammalian neurogenesis as an actual phenomenon. However , with the advent of new scientific methods and techniques , researchers have been able to identify and characterize new cells proliferating in several brain regions , including the dentate gyrus of the hippocampus , subventricular zone , and amygdala. Recently , studies have provided evidence that environmental factors , both external and internal , may influence adult neurogenesis. Specifically , the addition and/or survival of newly proliferated cells in various regions of the adult brain may be increased by environmental enrichment , voluntary activity , positive social interactions , short-day length , chemosensory stimuli , or increased levels of neurotransmitters including serotonin and brain-derived neurotrophic factor. Adult neurogenesis may be inhibited/decreased by negative social interactions or the stress hormone corticosterone. Interestingly , gonadal steroid hormones may exert positive or negative effects depending on the species and sex of the animal. Finally , current evidence supports the contention that these new cells do become functionally significant in the adult brain [*Acta Zoologica Sinica* **49** (2) : 151 - 162 , 2003].

Key words Cell proliferation , DG, SVZ , Amygdala , Environmental complexity , Steroid hormones

哺乳动物成体神经元的再生：内、外环境因子的作用

摘 要 哺乳动物成体神经元的再生现象是最近三十年才被科学家们所认识并逐渐接受的。随着科研方法与实验技术的发展，在成年哺乳动物的一些特定脑区，比如海马齿状回 (Dentate gyrus of the hippocampus)、室下区 (Subventricular zone) 和杏仁核 (Amygdala) 中发现了新生细胞。研究表明，内外环境因子可影响成体神经元的再生。具体表现在环境多样性、自主活动、有益社会交往、短日光照、化学刺激以及诸如 5 - 羟色胺和脑源性神经营养因子等神经递质水平的增加，都会促进新生细胞的增生或存活。而负面社会交往及应激激素皮质酮对成体神经元的再生有抑制和降低作用。研究还表明，根据种和性别的差异，类脂醇激素对成体神经元的再生起到促进或抑制作用。最新的实验证实新生细胞在成体中具有显著功能 [动物学报 **49** (2) : 151～162 , 2003]。

关键词 细胞增生 海马齿状回 室下区 杏仁核 环境多样性 类脂醇激素

1 Introduction

Postnatal neurogenesis in the mammalian brain was first reported in the 1960's (Altman , 1969 ; Altman *et al*. , 1966) and neurogenesis in adulthood in the 1970's (Kaplan *et al*. , 1977). Although the zeitgeist of the time accepted the possibility of new glia being born in the adult brain , the concept of new neurons in the adult was heartily rejected , despite the identification of neuronal characteristics in new cells with the use of electron microscopy (Kaplan , 2001 ; Kaplan *et al*. , 1977). Indeed , the belief that neurogenesis in the mammalian brain only occurs during a discrete period in development was not extensively questioned until (1) the acceptance of adult neurogenesis in non-mammalian species , such as birds and lizards , and (2) the advent of cell-type specific markers to identify neuronal phenotype. Throughout the

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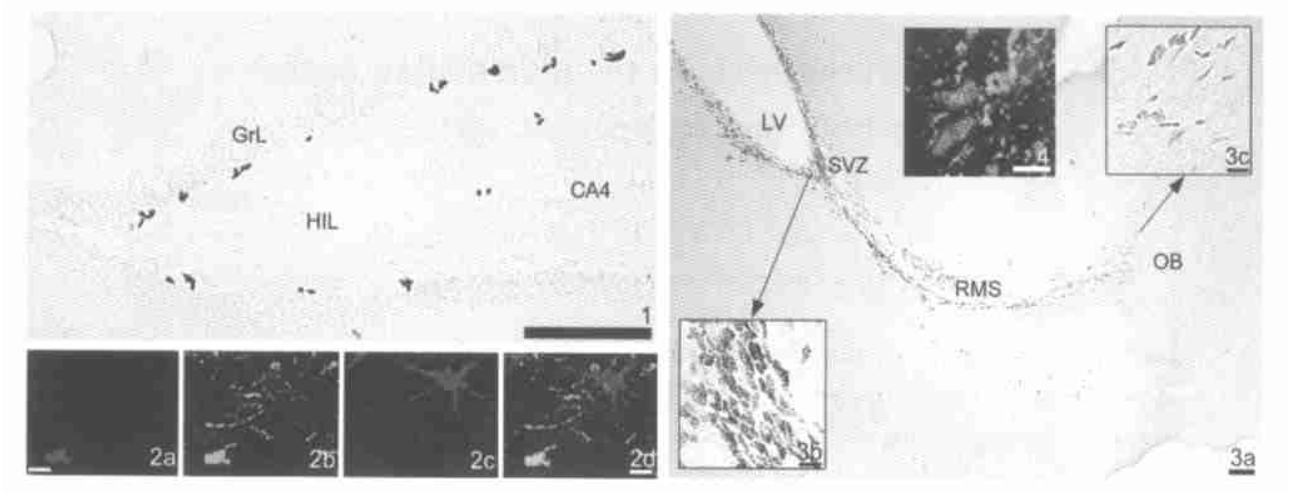

Fig. 1 Photomicrographs of new cells in the dentate gyrus (DG), subventricular zone (SVZ), rostral migratory stream (RMS) and olfactory bulb (OB)

1. Newly proliferated cells are mainly located on the border of the granule cell layer (GrL) and hilus (HIL) in the DG. Scale bar = 100 μm. CA4: CA4 region of the hippocampus 2. Confocal laser microscope images of cells stained for BrdU (2a), a neuronal marker (MAP-2, 2b), an astroglial marker (GFAP, 2c), and all three markers (2d) in the DG. The BrdU and MAP-2 colocalized cells display a yellow image. Scale bar = 5 μm 3a. Two days after a BrdU injection, the majority of the BrdU-labeled cells are found in the SVZ and RMS but few are present in the OB. Scale bar = 100 μm 3b displays densely packed cells labeled for BrdU in the SVZ (Scale bar = 10 μm) while 3c displays scattered cells labeled for BrdU in the OB (Scale bar = 10 μm) LV: lateral ventricle 4. Confocal laser microscope images of cells colocalized (yellow) with BrdU (red) and a neuronal marker (TuJ1, green) in the SVZ. Scale bar = 5 μm

current scientific community, most have come to embrace the fact that new neurons are produced in the brains of adult mammals, and adult neurogenesis has been identified in a variety of mammalian species, including rats (Kaplan *et al*., 1977), mice (Kempermann *et al*., 1998), hamsters (Huang *et al*., 1998), voles (Fowler *et al*., 2002; Ormerod *et al*., 2001), tree shrews (Gould *et al*., 1997), non-human primates (Bernier *et al*., 2002; Gould *et al*., 1999a), and even humans (Eriksson *et al*., 1998). In fact, it has been estimated that adult-born neurons represent around 10 % - 20 % of the total neuronal population, at least in the dentate gyrus of the hippocampus (Jacobs *et al*., 2000).

To identify newly proliferated cells, researchers have utilized markers that are incorporated into the DNA of mitotically active cells during S-phase; these include ^{3}H-thymidine and 5-bromo-2'-deoxyuridine (BrdU). Using these techniques, two regions, the dentate gyrus of the hippocampus (DG) and the subventricular zone (SVZ), have been identified as the main areas for cellular proliferation in the adult mammalian brain (Fig. 1). In the DG, cells proliferate in the subgranular zone and migrate into the granule cell layer where the majority develop into neurons (Cameron *et al*., 1993; Gould *et al*., 1997; Kuhn *et al*., 1996). In the SVZ, cells proliferate and migrate along the rostral migratory stream (RMS) into the olfactory bulb (Menezes *et al*., 1995; Peretto *et al*., 1999) where they disperse and differentiate into granule or periglomerular neurons in the main olfactory bulb (Luskin, 1993; Peretto *et al*., 1999) or into granule neurons in the accessory olfactory bulb (Bonfanti *et al*., 1997; Peretto *et al*., 1999). Multipotent progenitor cells can be found throughout the DG, SVZ and RMS; however, the presence of stem cells has been generally accepted in the SVZ while remaining debatable in the DG (Seaberg *et al*., 2002; Song *et al*., 2002b). Interestingly, a recent report suggests that astrocytes in the adult brain may function as neural stem cells (Seri *et al*., 2001).

Although most studies have focused on the DG and SVZ, several other brain regions have been found to contain newly proliferated cells. These regions include the amygdala and hypothalamus in voles and hamsters (Fowler *et al*., 2002; Huang *et al*.,

1998) , amygdala and neocortex in primates (Bernier *et al*. , 2002; Gould *et al*. , 1999a) , and striatum , septum and thalamus in rats (Pencea *et al*. , 2001) . Since ^{3}H-thymidine and BrdU label proliferating neurons and glia , cell type specific markers have been used to verify neuronal or glial phenotype in all of these brain regions , but even so , the identification of new neurons in the neocortex using these markers has not gone without debate and still remains controversial (Gould *et al*. , 2001; Kornack *et al*. , 2001) .

In the current paper , we will briefly review recent developments in the field of adult mammalian neurogenesis by focusing on changes in the exogenous and endogenous environments that increase or decrease the rate of cell proliferation and/or survival.

2 Exogenous influences on adult neurogenesis

2.1 Environmental enrichment

Gerd Kempermann and colleagues were among the first to examine the effects of external environment on adult neurogenesis (Kempermann *et al*. , 1997; Kempermann *et al*. , 1999) . In their first study , adult mice were exposed either to an enriched environment , composed of group housing , tubes , a tunnel , a running wheel , and extra food treats , or to a standard laboratory environment. All animals were housed in their respective environment for 40 days , and the cell proliferation marker BrdU was injected during the last 12 days of this period. Thereafter , animals were sacrificed at either 1-day or 4-weeks post-injection , and their brain sections were processed for BrdU immunocytochemistry to visualize the newly proliferated cells in the DG. Mice housed in the enriched environment displayed a larger number of BrdU-labeled cells in the DG than did controls at 4-weeks , but not 1-day , post-injection , suggesting that environmental enrichment enhances the survival of the new DG neurons. Furthermore , the enriched animals performed better on a spatial learning task than did the controls , elucidating the possible functional significance of the new cells. Using similar housing conditions , these findings were then replicated in rats (Nilsson *et al*. , 1999) . Since many variables went into creating an "enriched environment", it was unclear whether certain aspects of the enrichment (e. g. , group housing , running wheel , toys , etc.) or whether the enriching experience as a whole affected the survival of these new DG neurons. Therefore , in a further study examining the specific effects of physical activity on adult neurogenesis , mice given voluntary access to a running wheel displayed a significant increase in the number of BrdU-labeled cells in the DG relative to inactive controls (van Praag *et al*. , 1999) . When compared to the enriched environment condition , the voluntary wheel running animals had a similar number of surviving cells , suggesting that the wheel running access significantly contributed to the effects seen in the prior study.

The act of learning itself may also influence new cell numbers; training on hippocampal-dependent tasks induces a substantial increase in the number of adult-generated neurons in the DG of rats (Gould *et al*. , 1999b) . In addition , the long-term survival of the new neurons in the DG may depend upon a continuously changing environment , independent of the presence of enriching experiences. In "enriched environment" mice , those that were withdrawn and subsequently housed in standard lab conditions exhibited an enhanced DG cell survival , as compared to those that remained in the enriched environment (Kempermann and Gage , 1999) .

2.2 Social interaction

Interaction with conspecifics has also been found to influence adult neurogenesis; this finding has been best demonstrated in studies using microtine rodents (voles) . The female prairie vole , *Microtus ochrogaster*, is highly social , can be induced into behavioral estrus by male exposure , and forms selective social attachment after mating; thus , it provides an excellent opportunity to study the effects of environmental and endocrine changes on physiology and behavior (Carter *et al*. , 1993; DeVries *et al*. , 1996; Wang *et al*. , 1998) . In our study (Fowler *et al*. , 2002) , female prairie voles that were exposed to a male for 48 hrs with mating had more BrdU-labeled cells in the amygdala than did females housed in social isolation , a difference which persisted even 3 weeks

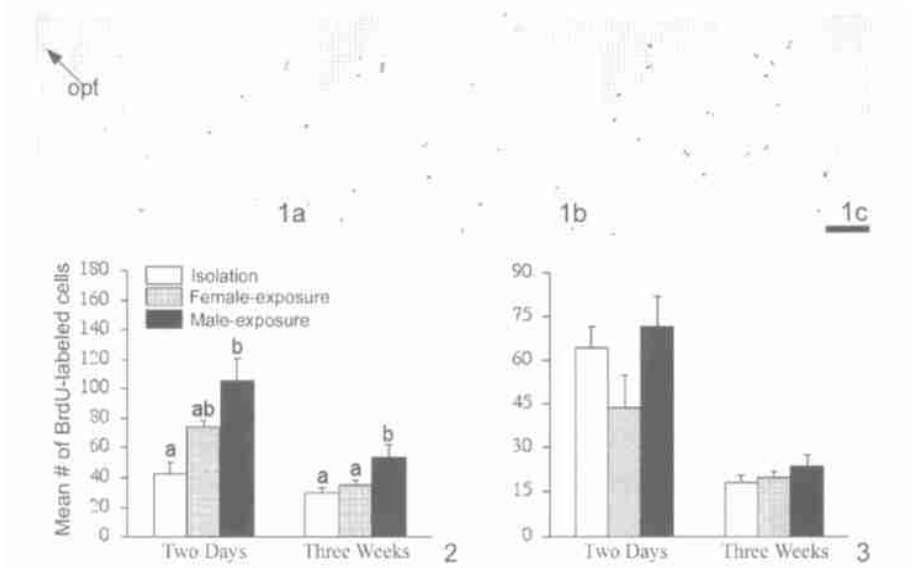

Fig. 2 The effects of social environment on new cells in the amygdala

1. Photomicrographs of BrdU-labeled cells in the amygdala after two days of social environment exposure. Female prairie voles were isolated (1a), exposed to a female (1b), or mated and exposed to a male (1c). Scale bars = 100 μm 2. In the amygdala, mean number of BrdU-labeled cells per brain section across groups 3. In the dentate gyrus (DG), mean number of BrdU-labeled cells per brain section across groups. Letters represent the results of the post hoc test; shared letters indicate no statistical difference; and error bars indicate standard error of the mean

later (Fig. 2). These effects were site-specific, as group differences were not found in the DG. In a separate study, 48 hrs of mating significantly increased the number of new cells in the anterior division of the SVZ in female prairie voles (Smith *et al*., 2001). Together, these data suggest that experience with a male enhances the proliferation and/or survival of new neurons in a site-specific manner in the brain of adult female prairie voles.

On the other hand, certain negative social interactions have been shown to decrease neurogenesis. In adult male tree shrews, exposure to an unfamiliar male decreases the number of proliferating cells in the DG, possibly due to psychosocial stress (Gould *et al*., 1997). In female prairie voles, social isolation appears to be stressful since it induces an increase in the levels of serum corticosterone (Kim *et al*., 1996), and in relation to neurogenesis, socially isolated females show significantly less BrdU-labeled cells in the amygdala than those exposed to males, but such differences are not seen in the SVZ or DG (Fowler *et al*., 2002). These data may suggest the presence of different stress-induced neuronal mechanisms among the different species.

2.3 Season

Seasonal changes in brain structure and function have been well established in songbirds: incorporation and/or survival of new neurons are found in brain regions critical for song production and spatial memory (Alvarez-Buylla *et al*., 1997; Barnea *et al*., 1994; Patel *et al*., 1997). Recent studies have also demonstrated seasonal rhythms in adult mammalian neurogenesis. In male golden hamsters, constant short day photoperiod, which mimics the winter months, enhances the birth and/or survival of new cells in the DG, hypothalamus, and cingulate cortex (Huang *et al*., 1998). In wild-captured meadow voles (*Microtus pennsylvanicus*), fluctuations can be found during the different seasons. Non-breeding females showed an increase in new cell number in the granule cell layer of the DG when compared to breeding females; however, no seasonal differences were found among males of this species (Galea *et al*., 1999). This seasonal change in DG neurogenesis in the female meadow vole has been correlated with changes in hormonal levels, territory size and spatial performance (Galea *et al*., 1995; Galea *et al*., 1999; Sheridan *et al*., 1988). However, additional studies are necessary to determine whether a direct relationship exists between seasonal changes in cell proliferation and in be-

havior and/or neuroendocrine functions.

2.4 Chemosensory stimuli

Since a large proportion of the cells proliferating in the adult rodent brain migrate from the SVZ to the olfactory bulb, one may question whether a sensory feedback mechanism exists which regulates the proliferation and/or migration of the new cells destined for the olfactory bulb. In the adult mouse, exposure to an odor-enriched environment enhances the survival of newly proliferated cells in the olfactory bulb (Rochefort *et al*., 2002), and following unilateral naris closure, a decreased number of BrdU-labeled cells and an increased number of pyknotic nuclei are present in the obstructed bulb when compared to the unobstructed bulb (Corotto *et al*., 1994). This concept has been further confirmed in an elegant study utilizing ansomic mice lacking the olfactory cyclic nucleotide gated channel. Relative to wild types, the ansomic mice have a reduced number of surviving BrdU-labeled granule neurons in the olfactory bulb (Petreanu *et al*., 2002). Studies have also incorporated more drastic olfactory input restriction by disconnecting the olfactory bulb from the brain in adult animals. Unilateral bulb separation and complete bulb removal resulted in a decreased number of proliferating cells in the RMS on the lesioned side of the mouse brain, suggesting that the lack of olfactory input negatively affects cell proliferation (Jankovski *et al*., 1998; Kirschenbaum *et al*., 1999). However, the animals with unilaterally lesioned bulbs also showed a decrease in the "control" bulb when compared to unlesioned animals. Thus, the decrease in proliferation may be attributable to the side effects from bulb injury or to removal of contralateral and/or reciprocal connections, rather than merely sensory deprivation.

The effects of olfactory input on adult neurogenesis have not been limited to the SVZ and olfactory bulbs; the amygdala has also been studied in this regard since it receives direct input from the olfactory bulb (Davis *et al*., 1978; Meredith, 1991; Winans *et al*., 1970) and plays an important role in the regulation of social behavior (Demas *et al*., 1997; Kirkpatrick *et al*., 1994; Wang *et al*., 1997). Male exposure with mating induced an increase in the number of BrdU-labeled cells in the amygdala of female prairie voles (Fowler *et al*., 2002), and in a follow-up study, exposure to male bedding alone was sufficient to influence cellular proliferation in the amygdala (Liu *et al*., 2001a) (Fig. 3). Female prairie voles that were exposed to the bedding from a conspecific male for 48 hrs had more BrdU-labeled cells in the amygdala, particularly in the medial and cortical nuclei, than did females exposed to their own bedding. Interestingly, this bedding effect on cell proliferation was sexually dimorphic, as no group differences were found in the male prairie vole. Although the mechanisms underlying these sex differences are still unknown, it is possible that the female system is more responsive to opposite-sex pheromonal exposure than the male system; for example, female prairie voles rely on male exposure for estrus induction, whereas males may need less cues to induce copulatory actions.

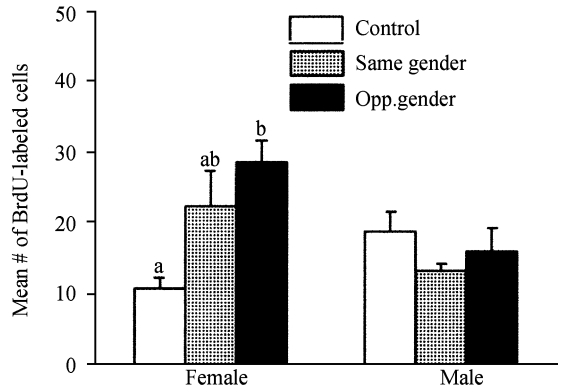

Fig. 3 The effects of soiled-bedding exposure on the mean number of BrdU-labeled cells in the amygdala

Letters represent the results of the post hoc test, shared letters indicate no statistical difference, and error bars indicate standard error of the mean

3 Endogenous factors regulating adult neurogenesis

Since aspects of the animal's external environment likely influence neuronal and physiological processes that, in turn, alter cell proliferation/survival, attempts have been made to identify these internal factors and to examine their influences on adult neurogenesis.

3.1 Steroid hormones

Since the structure and function of certain brain areas depend on the levels of circulating hormones during adulthood (Garcia-Segura *et al*., 1994; McEwen, 1999; McEwen *et al*., 1999), the influence of hormones on adult neurogenesis has become a fascinating research area. Recently, researchers have found that, in the DG of female rats, the number of new cells fluctuates during the estrus cycle, with the highest number of new cells during proestrus, and ovariectomy decreases, whereas estrogen replacement restores, new cell number relative to intact controls (Tanapat *et al*., 1999). Furthermore, it has been observed that dividing cells are often located near the vasculature in the subgranule zone of the adult DG (Palmer *et al*., 2000), supporting the contention that peripheral circulating hormones may cross the blood-brain-barrier to affect cellular proliferation. The effects of gonadal steroid hormones on adult neurogenesis were further studied using the vole as a model system. Female voles are induced ovulators and display an elevated level of estrogen following exposure to a conspecific male (Dluzen *et al*., 1979; Seabloom, 1985). Therefore, the exogenous environment may induce changes to the internal hormonal milieu, which then alter neurogenesis. In the DG of female meadow voles, differences in the number of new cells can be seen across the breeding season and may be attributable to the seasonal changes in estradiol or corticosterone levels (Galea *et al*., 1999). Furthermore, exposure to estradiol benzoate produces a transient increase, followed by a decrease, in the number of new DG neurons (Ormerod *et al*., 2001). Thus, it appears that the effects of male exposure/mating on cell proliferation are, at least in part, attributable to circulating levels of estrogen. This is further supported by findings in female prairie voles (Smith *et al*., 2001). Exposure to a male for 48 hrs induces an elevated level of serum estrogen associated with an increased number of BrdU cells in the SVZ. This effect can be prevented by ovariectomy and reinstated with estrogen treatment. In our most recent experiment, treatment with estrogen benzoate in ovariectomized voles had species-specific effects on neurogenesis; it decreased the number of

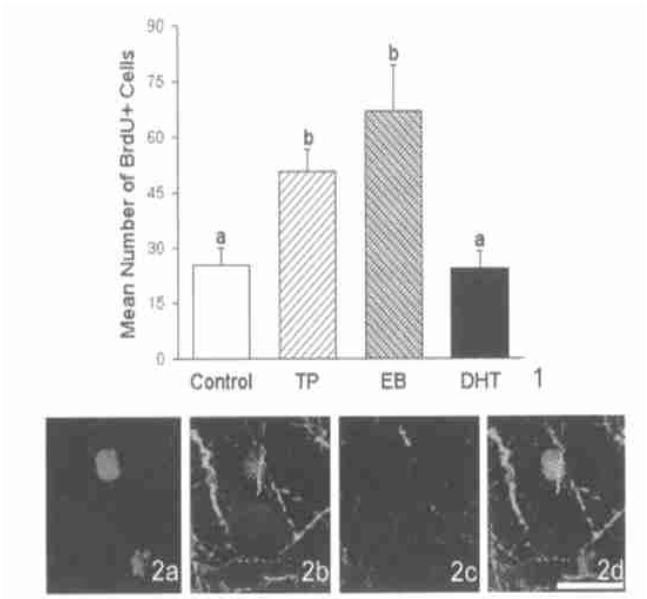

Fig. 4 Hormonal influences on new cells in the male meadow vole

1. The effects of testosterone (TP), estradiol benzoate (EB), or 5α-dihydrotestosterone (DHT) on the mean number of BrdU-labeled cells in male meadow voles. Letters represent the results of the post hoc test, shared letters indicate no statistical difference, and error bars indicate standard error of the mean 2. Confocal laser microscope images of cells stained for BrdU (2a), a neuronal marker (TuJ1, 2b), an astroglial marker (NG2, 2c), and all three markers (2d) in the amygdala of male meadow voles. BrdU and TuJ1 colocalized cells display a yellow image, and a BrdU only labeled cell displays a red image Scale bar = 10 μm

new cells in the Ventromedial nucleus of the hypothalamus (VMH), VMH of prairie voles and increased new cell number in the amygdala of meadow voles (Fowler and Wang, unpublished data).

Much less work has been done to investigate the effects of hormonal status on neurogenesis in males. We recently performed a study in which castrated male meadow voles were implanted with tubing filled with oil (control), testosterone, estradiol benzoate (EB), or 5α-dihydrotestosterone (DHT) (Fowler *et al*., 2001). Testosterone treatment up-regulated the number of BrdU-labeled cells in the amygdala, but not in the DG, when compared to the controls (Fig. 4). Interestingly, treatment with EB had a similar effect as testosterone, whereas DHT was ineffective. These data indicate that testosterone is most likely being converted into estrogen by aromatization and then regulates adult neurogenesis by acting through an estrogen-mediated mechanism in the male meadow vole.

The observed decreases in new cell number in the amygdala of socially isolated prairie voles (Fowler *et al*., 2002) and in the DG of psychosocially stressed tree shrews (Gould *et al*., 1997) may be attributable to changes in the levels of stress-associated hormones. Although not yet studied in voles or tree shrews, the effects of adrenal steroid hormones on adult neurogenesis have been studies in rats. Acute treatment with corticosterone induces a significant decrease in the number of new cells in the DG, whereas adrenalectomy enhances the number of new cells; however, the adrenalectomy-induced increase could not be reversed solely by corticosterone treatment, suggesting that other mechanisms beyond hormonal levels are involved in these differences (Cameron *et al*., 1994). In fact, N-methyl-D-aspartate (NMDA) receptor activation may underlie the stress-induced effects on DG neurogenesis: administration of a NMDA agonist prevents the adrenalectomy-induced increase in new DG cell number and receptor blockade with a NMDA antagonist blocks the corticosterone-induced decrease (Cameron *et al*., 1998).

3.2 Neurotransmitters

Since an animal's external environment may induce downstream effects on the extracellular environment, neurotransmitter systems are likely candidates for a neurogenesis-mediating mechanism. For example, serotonin (5-HT) appears to regulate adult neurogenesis in the rat: depletion of serotonin reduces the number of new cells in the DG and SVZ (Brezun *et al*., 2000), whereas an increase in serotonin or chronic antidepressant treatment enhances cell proliferation in the DG (Jacobs *et al*., 2000; Malberg *et al*., 2000).

Brain-derived neurotrophic factor (BDNF) also appears to play an important role in adult neurogenesis. BDNF synthesizing/containing cells are found in many brain areas (Castren *et al*., 1995; Conner *et al*., 1997; Hayashi *et al*., 1997; Hofer *et al*., 1990). *In vitro*, BDNF enhances the number and survival of new neurons derived from the SVZ (Goldman, 1998), and *in vivo*, BDNF infusions into the brain increase the number of new cells in several brain areas, including the olfactory bulb, striatum, and hypothalamus of rats (Pencea *et al*., 2001; Zigova *et al*., 1998). Recently, it has also been reported that astrocytes may secrete BDNF and induce neurogenesis in adult neural stem cells (Ikeda *et al*., 2001; Song *et al*., 2002a). Furthermore, endothelial cells may secrete BDNF and clusters of proliferating cells are found around vasculature (Leventhal *et al*., 1999; Palmer *et al*., 2000). Interestingly, the afore-mentioned effects of steroid hormones may occur through a BDNF-mediated mechanism. In rats, BDNF mRNA in the hippocampus fluctuates across the estrous cycle (Gibbs, 1998), and ovariectomy decreases, whereas estrogen administration in ovariectomized rats increases, BDNF mRNA expression in the hippocampus (Singh *et al*., 1995). Estrogen treatment also increases BDNF expression in the amygdala of female prairie voles (Liu *et al*., 2001b). Regarding the effects of stress hormones, adrenalectomy, which increases neurogenesis, has been found to also enhance BDNF mRNA expression in the hippocampus of rats (Schaaf *et al*., 1999). Finally, BDNF increases serotonin activity (Siuciak *et al*., 1996), and alternatively, serotonin reuptake inhibitors increase BDNF expression in the rat brain (Duman *et al*.,

1997), suggesting that BDNF and serotonin may act synergistically to regulate cellular proliferation in the adult brain.

4 Functional significance of the new cells

The olfactory bulb and amygdala have been implicated in olfactory/pheromonal processing (Luiten *et al*., 1985; Meredith, 1991), social learning and memory (Brennan *et al*., 1997; Cahill *et al*., 1996; Kirkpatrick *et al*., 1994), sexual and social behaviors (Dominguez *et al*., 2001; Harris *et al*., 1975; Williams *et al*., 1992) and fear conditioning (McNish *et al*., 1997; Walker *et al*., 2002), while the DG plays an important role in spatial learning and memory (Moser and Moser, 1998; Shors *et al*., 2001). Since new cells are being incorporated into these areas in adulthood, one is led to question the functional significance, if any, of the adult-born neurons. An early study demonstrated that cells produced in adulthood exhibit properties of functional neurons, such as synapses, axons, and vesicles (Kaplan, 2001). *In vitro* cultures from adult songbird brain tissue show that new neurons can become synaptically competent and develop stimulus-evoked and spontaneous action potentials (Goldman *et al*., 1992). More recently, *in vitro* studies have also shown that new cells from the adult rat hippocampus can become electrically active neurons and exhibit functional synaptic transmission (Song *et al*., 2002b).

The ability of these new cells to contribute to adult neural processing has also been demonstrated *in vivo*. In mice and golden hamsters, new cells in the olfactory bulb may become activated following odor exposure, as indicated by increased expression of the immediate early gene c-fos (Carlen *et al*., 2002; Huang *et al*., 2002). In addition, adult mice that have deficits in the migration of olfactory bulb neuronal precursors display impaired discrimination between odors (Gheusi *et al*., 2000), and an increase in the number of olfactory bulb neurons following odor enrichment is associated with enhanced short-term odor memory (Rochefort *et al*., 2002). Finally, treatment with an anti-mitotic drug prevents adult cell proliferation and results in hippocampal-dependent memory formation deficits; importantly, after recovery from the drug treatment, new neurons can be produced, and trace memory acquisition is restored (Shors *et al*., 2001).

5 Conclusions

In summary, neurogenesis in the adult brain has been identified in many mammalian species. The rate of proliferation and the fate of new neurons may be influenced by a variety of factors. Aspects of an animal's external environment may induce changes in its internal physiology, which, in turn, can act on neurochemical and/or neurotransmitter systems to affect cellular proliferation and/or survival. Although many studies have characterized the factors that increase or decrease new cell numbers, the cellular mechanisms that directly act on the proliferation and/or survival of these cells has yet to be elucidated. Furthermore, several studies have established relationships between the presence of newly proliferated cells and behavioral/cognitive functions, but more research needs to be done to determine the exact contribution of these new neurons. Brain areas that incorporate new cells in adulthood, including the hippocampus, olfactory bulb and amygdala, have been implicated in several neurological disorders such as depression, schizophrenia, and Alzheimer's disease (Arnold *et al*., 1998; Hyman *et al*., 1990; Klimek *et al*., 2002; Kromer Vogt *et al*., 1990; Nestler *et al*., 2002). Therefore, studies of adult neurogenesis may offer a better understanding of the mechanisms involved in these disorders and may even lead to the development of new therapeutic treatments for these neurological disorders.

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