

Neurogenesis in the aging brain

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Abstract: Neurogenesis, or the birth of new neural cells, was thought to occur only in the developing nervous system and a fixed neuronal population in the adult brain was believed to be necessary to maintain the functional stability of adult brain circuitry. However, recent studies have demonstrated that neurogenesis does indeed continue into and throughout adult life in discrete regions of the central nervous systems (CNS) of all mammals, including humans. Although neurogenesis may contribute to the ability of the adult brain to function normally and be induced in response to cerebral diseases for self-repair, this nevertheless declines with advancing age. Understanding the basic biology of neural stem cells and the molecular and cellular regulation mechanisms of neurogenesis in young and aged brain will allow us to modulate cell replacement processes in the adult brain for the maintenance of healthy brain tissues and for repair of disease states in the elderly.

Keywords: neurogenesis, aging, brain, neural stem cells, subgranular zone, subventricular zone

Until recently, a central assumption in neuroscience had been that new neurons do not arise in the adult mammalian brain. This idea prevailed in spite of reports, published in prominent journals, that showed that new neurons could arise in specialized areas of the brain (Altman 1963; Altman and Das 1965, 1966; Kaplan and Hinds 1977; Kaplan 1981). In the last few years, however, this belief has been challenged by numerous studies that demonstrated that certain areas of the brain retain pluripotent precursors with the capacity of self-renew and differentiation into new neural lineages in adult mammals such as rodents (Bayer 1983; Kuhn et al 1996; Kempermann et al 1997; Maslov et al 2004), non-human primates (Pencea, Bingaman, Freedman et al 2001), and humans (Eriksson et al 1998; Kukekov et al 1999; Magavi et al 2000). In rodents, it was shown that undifferentiated neural stem/progenitor cells (NSCs) are concentrated in the subventricular zone (SVZ) of the lateral ventricle wall (Maslov et al 2004) and the subgranular zone (SGZ) of the dentate gyrus of the hippocampus (Gage 2000). Cells born in the rodent SVZ during adult life travel anteriorly through the rostral migratory stream into the olfactory bulb (OB), where they differentiate into interneurons (Alvarez-Buylla 1997). Cells born in the SGZ of the dentate gyrus migrate a short distance to integrate in the granular layer (Gage 2000). The SGZ of the dentate gyrus in young adult rats contains about 9,400 dividing cells proliferating with a cell cycle time of 25 hours, which would generate 9,000 new cells each day, or more than 250,000 per month (Cameron and McKay 2001) and a high proportion of them differentiate into neurons (Hastings and Gould 1999; van Praag et al 2002). However, only about half of these newly generated neurons will survive after the first few weeks (Cameron et al 1993; Dayer et al 2003). Those that survive seem to integrate into preexisting hippocampal circuits and may permanently replace granule cells born during development (Dayer et al 2003). Remarkably, production overweighs loss of proliferating progenitors in the rat hippocampus such that neuronal cell numbers increase continuously until middle-age (Bayer et al 1982).

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That NSCs also exist in adult primate and human brain has now been well established (Kukekov et al 1999; Pencea, Bingaman, Freedman et al 2001; Bedard et al 2002; Bernier et al 2002; Bedard and Parent 2004) for the subependymal zone (Roy, Benraiss et al 2000), for the hippocampus (Eriksson et al 1998; Roy, Wang et al 2000) and very recently for the human olfactory bulb (Bedard and Parent 2004; Sanai et al 2004; Curtis et al 2007). The dentate gyrus and the hilus in cornu ammonis 4 (CA4) region of the human hippocampus are, however, the most active areas of NSC proliferation in adult non-human primates (Kornack and Rakic 1999) and humans (Eriksson et al 1998). NSCs are maintained in specialized microenvironments in these brain regions (Alvarez-Buylla and Lim 2004), in which they may undergo symmetrical division at a very low rate maintaining their pluripotency, or alternatively undergo asymmetric division to differentiate into neuronal precursors (NPs) (Ohnuma and Harris 2003; Sommer and Rao 2002).

Together with the refutation of the paradigm of 'brain constancy', a 'neurocentric' view of the brain is also being reconsidered. In addition to having an essential role in neural function, which can be thought of as mediated by neuronal-glial systems as a whole (Lie et al 2004), the studies of Alvarez-Buylla and coworkers (Lois et al 1996; Alvarez-Buylla et al 2001) and other groups (Anthony et al 2004) demonstrated that astrocytes in the SVZ and SGZ are NSCs in mammals and that radial glia may function as progenitors for the majority of neurons in mammalian central nervous system (CNS).

The neurogenicity of SVZ and SGZ NSCs in the young adult mammalian brain is restricted by signals from their local environment, as demonstrated with transplantation experiments that showed that SVZ cells lose their neurogenic potential if placed into non-spontaneously neurogenic regions of the brain (Alvarez-Buylla and Lim 2004). Conversely, after heterotopic transplantation into the hippocampus, NSCs isolated from the adult spinal cord can integrate in the granular cell layer and differentiate into cells characteristic of this region, whereas engraftment into other hippocampal regions resulted in the differentiation of cells with astroglial and oligodendroglial phenotypes. These observations suggested that multipotent adult progenitor cells from a non-neurogenic region are not lineage-restricted to their developmental origin but can generate region-specific neurons *in vivo* when exposed to the appropriate environmental cues (Shihabuddin et al 2000). Not surprisingly, developmental signal molecules and morphogens such as Notch (Artavanis-Tsakonas et al 1999; Givogri et al 2006), bone morphogenetic proteins, Noggin and sonic hedgehog (Pozniak and Pleasure 2006),

have been implicated in the maintenance of adult neurogenic microenvironments (Lim et al 2000) containing glial and endothelial cells (Shen et al 2004).

The function of adult neurogenesis is still not known. In 2001, however, Shors et al (2001) showed that performance of a hippocampus-dependent learning task was dependent on the presence of replicating NSCs, suggesting that neurogenesis in the adult hippocampus has a role in learning memory (Shors et al 2001), although not all forms of hippocampal-dependent memory are associated with neurogenesis (Shors et al 2002; Meshi et al 2006). Deisseroth et al (2004) demonstrated that activity and neurogenesis are coupled, a process that would implement a form of network plasticity conceptually analogous to plasticity at the synaptic level, but occurring at the cellular network level. Indeed, organismal-level stimuli that entail an increase in neuronal activity such as learning (Gould, Beylin et al 1999; Leuner et al 2004), exposure to environmental enrichment (van Praag et al 1999; Brown et al 2003), exposure to hippocampal-dependent learning tasks (Dayer et al 2003; Leuner et al 2004), and voluntary running (van Praag et al 1999; Brown et al 2003) have been shown to stimulate neurogenesis and enhance the survival of new neurons in the adult mammalian hippocampus, which in the case of running required vascular endothelial growth factor (VEGF) systemically (Fabel et al 2003; Cao et al 2004). Although neither of these behavioral interventions increased adult neurogenesis in the SVZ/OB (Brown et al 2003), proliferation in these areas was influenced by olfactory sensory enrichment. The observed increase in newborn neurons was concomitant with improved olfactory memory in enriched animals (Rocheffort et al 2002). A pivotal role for adult neurogenesis in plasticity at the organismal level was indicated by recent studies showing that new granular cells formed in the epileptic rat dentate gyrus, but not in other conditions of neurogenesis stimulation, exhibited functional connectivity consistent with reduced excitability (Jakubs et al 2006). Taken together, these observations strongly suggest that activity of specific networks stimulates local neurogenesis and the survival of differentiated progenitors, which in turn contribute to enhanced function (Rocheffort et al 2002), or act to mitigate dysfunction (Jakubs et al 2006).

Stem cells in neurogenic areas respond to other types of injury. Acute insults, such as focal ischemia induced by middle cerebral artery occlusion in rat, stimulate the proliferation of NSCs after extensive damage has occurred in the striatum and parietal cortex (Arvidsson et al 2002). Traumatic brain injury has also been reported to induce neurogenesis (Chirumamilla

et al 2002), and this response can persist in the long term in the adult brain (Chen et al 2003). The activation of neurogenic processes as a response to chronic damage is much less well documented, although some (Curtis et al 2003; Jin, Galvan et al 2004; Jin, Peel et al 2004) but not all (Haughey, Liu et al 2002; Haughey, Nath et al 2002; Lazic et al 2004; Donovan et al 2006) studies have supported the hypothesis that slow neurodegenerative damage may also induce NSC proliferation. The evidence for *de novo* neurogenesis induced by chronic injury, however, is far from being definitive.

Although neurogenesis continues throughout life, its rate declines with increasing age in rodents (Seki and Arai 1995; Kuhn et al 1996; Kempermann et al 2002) and non-human primates (Gould, Reeves et al 1999). In aged rats, the proliferation rate of NSCs in the SGZ of the dentate gyrus is reduced by 80% (Jin et al 2003). The bulk of age-related decreases in SGZ neurogenesis takes place between 3 and 12 months of age (Kuhn et al 1996). In addition, the proportion of these NSCs that survive to become mature neuronal cells is reduced to half of that of young animals (Tang et al 2007). In contrast, the SVZ, the other prominently neurogenic area in rodent brain, suffers no significant (Kuhn et al 1996) or less severe (Jin et al 2003; Luo et al 2006) decreases in the rate of NSC proliferation.

The age-associated reduction in adult neurogenesis may be due to an intrinsic decline in NSC responsiveness to stimulating environmental cues, to a decrease in or disappearance of these environmental cues, or to the appearance or accumulation of inhibitory factors. Supporting a role for environmental cues in the age-associated decline in neurogenesis, it was shown that exogenous addition of growth factors such as insulin-like growth factor I (IGF-I) (Lichtenwalner et al 2001), epidermal growth factor (EGF) and fibroblast growth factor (FGF-2) (Jin et al 2003) or a reduction of corticosteroid levels by adrenalectomy (Cameron and McKay 1999) can, at least partially, negate the effects of age in the rate of NSC proliferation. Consistent with these observations, repeated social stress significantly decreased the rate of NSC proliferation in mice (Mitra et al 2006), while environmental enrichment (Kempermann et al 2002) and voluntary exercise (van Praag et al 1999) significantly reversed age-related decreases in NSC proliferation. Newly born neurons in aged mice were morphologically indistinguishable from those generated in young animals (van Praag et al 1999), and their increased numbers were accompanied by substantial and sustained behavioral improvements (Kempermann et al 2002). The observed increase in adult born neurons in older animals

were at the expense of newly generated astrocytes, arguing that the effects of environmental enrichment affect the fate choice of proliferating multipotent progenitors or alternatively, specifically promote survival of newly born neurons. Environmental conditions may therefore have a crucial role in the modulation of neurogenesis during aging in rodents since like in young rodents experience, the stimulation of neurogenesis and improved functional outcomes may be causally linked in aged brains as well.

Age-associated memory deficits are broadly similar to those induced by damage to the hippocampus, which is one of several limbic structures implicated in the pathophysiology of mood disorders. It was recently shown that stress (Bremner et al 2003) and depression (Lloyd et al 2004; Stockmeier et al 2004; Frodl et al 2006) lead to hippocampal atrophy, while chronic antidepressant treatments result in an increase in hippocampal neurogenesis. Antidepressant action may require neurogenesis in mice (Santarelli et al 2003), although hippocampal neurogenesis was not required for the anxiolytic effects of environmental enrichment (Meshi et al 2006). It has been proposed that the age-related decline in neurogenesis may underlie age-associated learning and memory declines and may contribute to pathological conditions such as Alzheimer's disease (Haughey, Liu et al 2002; Haughey, Nath et al 2002; Donovan et al 2006). Although neurogenesis may contribute to function in the adult human CNS, the process does not suffice to preserve function during normal aging, or when injury or degenerative processes have ensued. However, that stimulation of NSC proliferation and possibly survival may be enhanced by growth factors or behavioral interventions even in older rodents (Benraiss et al 2001; Jin et al 2003; Pencea, Bingaman, Wiegand et al 2001) suggests that the endogenous neurogenic response could be modulated exogenously. Even though the overall level of endogenous neurogenesis is decreased in all mammals examined to date, the responsiveness of NSC proliferation is retained in aged mouse brains (Jin et al 2003) and human brains (Eriksson et al 1998). Remarkably, and albeit the sample number precluded drawing quantitative conclusions, Eriksson et al (1998) showed that the highest number of proliferating precursors in the granule cell layer and in the hilus of the dentate gyrus in human adults were found in subjects of middle and advanced age. How and to what extent our knowledge about neurogenic processes in rodents will ultimately translate to neurogenic processes in the adult primate brain is still unknown. In rodents, cells born in the SVZ travel anteriorly through the RMS into the OB, where they differentiate into interneurons (Alvarez-Buylla 1997). This process is referred

to as “chain migration” (Lois and Alvarez-Buylla 1994). The RMS that continues to supply replacement interneurons to the rodent OB is weak in humans, possibly reflecting the reduced functionality of the human OB. This is consistent with a reduced functionality of olfaction, as evidenced by the substantial loss of functional olfactory receptor genes in the human genome when compared to rodents. In 2004, however, a report by Bedard and Parent (2004) described cells expressing cell cycle markers and markers for immature neurons in the human OB, suggesting that precursor proliferation may also occur, albeit at a much reduced rate, in this region of the adult human brain. The human RMS was finally demonstrated around a lateral ventricular extension reaching the OB, the ventriculo-olfactory neurogenic system (VONS) which, in contrast to the rodent brain, takes a caudal path en route from the SVZ to the olfactory cortex as a consequence of the pronounced enlargement of the frontal cortex in the human forebrain that places the rostral caudate, SVZ and frontal cortex rostral to the olfactory tubercle (Curtis et al 2007). In contrast, the dentate gyrus and the hilus in CA4 region of the human hippocampus, which were detected earlier, are possibly the most active areas of progenitor proliferation in adult primates (Pencea, Bingaman, Freedman et al 2001) and humans (Eriksson et al 1998).

Apart from differences that likely reflect differential evolutionary paths in rodents and primates, available knowledge for neurogenesis in the two mammalian orders so far point to a fairly large degree conservation in the general regulation and in the impact of the aging in neurogenic processes.

Endogenous augmentation of trophic factor expression (such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and FGF-2) in brains of laboratory animals has been achieved by behavioral interventions (Mattson 2004) such as enriched experience, voluntary exercise (Klintsova et al 2004) and training/learning (Will et al 2004). Both enriched housing and training have been shown to increase synaptogenesis (Carro et al 2002) and neurogenesis (van Praag et al 1999) as well. IGF-I has neuroprotective and neurogenic effects (Trejo, Carro, Garcia-Galloway et al 2004; Trejo, Carro, Lopez-Lopez et al 2004) and it has been shown that peripheral infusion of IGF-I can increase NSC proliferation, selectively induce neurogenesis (Aberg et al 2000) and ameliorate the age-related decline in hippocampal neurogenesis in rats (Lichtenwalner et al 2001). The protective effects of physical exercise were shown to be mediated by circulating IGF-I (Carro et al 2001). A thorough consideration of the challenges to the design of treatment strategies based on the simulation of endogenous

neurogenesis for replacement of affected networks, mainly centered on the delivery of growth factors, can be found in the review article by Lie et al (2004).

The ultimate requirement for neurogenesis to be beneficial in the adult is that it contributes to function, according to its cognitive and psychological definition (Kempermann et al 2004). Survival and acquisition of a neuronal phenotype by NSCs are dependent not only on network activity, but also on the existence of a complete environment capable of supporting survival, maturation and function by the production of neurotrophins and other regulators of proliferation and differentiation (Leavitt et al 1999; Olier et al 2001; Smit et al 2001; Ullian et al 2001). When the network structures in which NSCs can integrate are compromised, as in normal aged brains or in neurodegenerative conditions, increased proportions of proliferating progenitors may die. Would ongoing neurogenic processes positively contribute to enhanced function in all circumstances, or might there be a requirement for a minimal degree of integrity of network structures for neurogenesis to be beneficial? It is conceivable that the role of neurogenesis during the course of aging may be dictated by the degree of permissibility of the environment in which the process is taking place.

The discovery of neurogenesis and its role in the adult mammalian brain opened up exciting possibilities for the development of therapeutic interventions that might mitigate age-related learning and memory declines, and mood disorders. Even though the gaps in our understanding of the neurogenic process are not insignificant, it is likely that continuing investigation into the basic biology of adult NSCs will allow us to modulate cell replacement processes in the adult brain. As simple behavioral interventions can stimulate neurogenesis in rodent experimental models and possibly in humans, it is reasonable to suggest that lifestyle changes may constitute a therapeutic approach of low risk, albeit of variable efficacy, for the early prevention of age-associated or pathological cognitive decline. Behavioral interventions such as the diffusion of information required for lifestyle choices, the socialization of institutions providing access to continuing education, creative occupation, physical activity and the enjoyment of the arts may help societies increase their overall “cognitive reserve” and reduce the human, economic and social burden associated with increased numbers of cognitively impaired elderly in developed societies with high life expectancy.

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