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Perspectives - Minireview

Adult Neurogenesis in Insulted Brain

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Although there are some questions about the venues of adult neurogenesis, it is undoubtedly accepted that new neurons are born in adult brains. Adult neurogenesis is regulated by a wide array of factors. Insults harmful to brain, such as neurodegenerative diseases, seizure, ischemia and exposure to drugs of abuse, are intricately related to adult neurogenesis. Whereas neurodegenerative diseases are characterized by death or functional loss of specific neurons, recent studies report that they can be accompanied by neurogenesis. In addition, alcohol and drugs of abuse which have been reputed to cause irreversible damage to brain can also generate newly born cells in adult brain. As yet, however, we have little knowledge of the functional significance and roles of adult neurogenesis under pathological settings, not to mention under physiological settings. Accordingly, in this review we briefly summarize the results of studies which focus on adult neurogenesis in insulted brain, instead of trying to draw hurried conclusion regarding the relationship between adult neurogenesis and brain insults.

Key words: Adult neurogenesis, Subgranular zone, Subventricular zone, Neurodegenerative disease, Seizure, Ischemia, Drug of abuse.

INTRODUCTION

Since Altman and Das reported ongoing neurogenesis throughout adulthood in rats in their pioneering work (Altman and Das, 1965), a huge body of work has demonstrated that new neurons are indeed born in the restricted regions of the adult mammalian CNS, including humans (Alvarez-Buylla *et al.*, 1988; Bedard and Parent, 2004; Eriksson *et al.*, 1988; Gage, 2000; Gould *et al.*, 1999a; Kornack and Rakic, 1999). While there exist controversies relating to the regions where adult neurogenesis happens (Bedard *et al.*, 2002; Dayer *et al.*, 2005; Gould, 1996b, 2007; Kokoeva *et al.*, 2005), it is generally accepted that neurogenesis persists in subventricular zone (SVZ) and hippocampal subgranular zone (SGZ) of adult brain.

In adult hippocampus, neural progenitor cells in the SGZ with rich vascular supply (Ohab *et al.*, 2006; Palmer *et al.*, 2000) divide asymmetrically, giving rise to progenitors cells and potential granule neurons. More than half of these newly born neurons die within 4 weeks after they are born (Dayer *et al.*, 2003; Tashiro *et al.*, 2007). The surviving neurons migrate into the granular layer and therein mature into future granule neurons. Electrophysiological studies have shown that these newly generated granule neurons start to receive synaptic inputs from the cortex within four to six weeks after birth, appearing to become functionally integrated in the circuit (van Praag *et al.*, 2007).

New neurons born in the adult SVZ undergo similar stages in their development (Alvarez-Buylla and Garcia-Verdugo, 2002). Neural stem cells located in the SVZ of the lateral ventricle proliferate and give rise to neuroblasts, which then migrate in the so-called rostral migratory pathway (RMP) through mature neural tissue. As early as 14 days after birth, some of the new neurons have reached the olfactory bulb and migrate radially in the olfactory bulb to their final positions (Conover and Allen, 2002).

Recent studies indicate that the rate of neurogenesis can be regulated by both internal and external factors (Abrous *et al.*, 2005; Lie *et al.*, 2004). Just as interna factors like genetics, age, growth factors, hormones anc neurotransmitters can control adult neurogenesis in both a positive and negative manner, so external factors such as environmental or pharmacological stimuli car do in both ways. For example, while enriched environment and voluntary exercise increase the rate of adul

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neurogenesis in dentate gyrus (Nithianantharajah and Hannan, 2006; Olson *et al.*, 2006), stress and alcohol are known to decrease adult neurogenesis (Agartz *et al.*, 1999; Bengochea and Gonzalo, 1990; Fuchs *et al.*, 2006; Walker *et al.*, 1980). However, as studies advance more deeply and broadly, it has been revealed that more adult neurogenesis is not always better (Parent *et al.*, 2006; Saxe *et al.*, 2007; Scharfman and Hen, 2007) and global effect of some factors on brain does not necessarily go in parallel with the adult neurogenesis, both of which make it more difficult to understand the functional roles of adult neurogenesis in physiological as well as pathological settings.

In this brief review, we focus on the effects which conditions generally considered to be toxic or harmful to brain, such as ischemia, neurodegenerative disorders and exposure to drugs of abuse, exert on adult neurogenesis, rather than on detailed mechanisms underlying the change of adult neurogenesis associated with each condition, and try to present a clearer picture of the adult neurogenesis under brain-unfriendly settings.

ADULT NEUROGENESIS AND NEURODEGENERATIVE DISEASES

Alzheimer's disease. Alzheimer's disease (AD) is a neurodegenerative disorder of the brain characterized clinically by progressive loss of memory and other cognitive skills. Its pathological hallmarks include neuronal and synaptic loss, amyloid plaques, and neurofibrillary tangles containing hyperphosphorylated τ-protein. Aβ and phospho-τ-protein may be neurotoxic, leading to progressive neuronal degeneration and death. Some studies using mouse model of Alzheimer's disease indicate that Aβ disrupts neurogenesis in the SVZ and the hippocampus (Donovan *et al.*, 2006; Haughey *et al.*, 2002a; Zhang *et al.*, 2007). The molecular basis for this impairment is still unknown, although Aβ peptide, which is the principal component of senile plaques, may be directly toxic to neural progenitor cells (Haughey *et al.*, 2002b). In contrast, the enhancement of neurogenesis has been observed in the hippocampus and SVZ in mouse models of Alzheimer's disease (Jin *et al.*, 2004a; Lopez-Toledano and Shelanski, 2004; Ziabreva *et al.*, 2006) and in the hippocampus of AD patients (Jin *et al.*, 2004b). This discrepancy may be explained by fact that molecular stimulus to neurogenesis in Alzheimer's disease is unknown and other factors than Aβ may also influence this process (Jin *et al.*, 2004b).

Parkinson's disease. Parkinson's disease (PD) is caused by the degeneration of dopaminergic midbrain neurons resulting in striatal dopamine depletion. The depletion of dopamine in rodents decreases precursor cell proliferation in both the SVZ and the SGZ, and this process involves D2-like receptor activation (Hoglinger *et al.*, 2004). Consistently, the numbers of proliferating cells in the SVZ and neural precursor cells in the SGZ and olfactory bulb are reduced in postmortem brains of individuals with Parkinson's disease (Hoglinger *et al.*, 2004). These observations suggest that the generation of neural precursor cells in the dentate gyrus and in the olfactory bulb is impaired in Parkinson's disease as a consequence of dopaminergic denervation (Borta and Hoglinger, 2007; Hoglinger *et al.*, 2004). On the other hand, recent works report that new dopaminergic neurons are generated in the substantia nigra of adult rodents under physiological conditions (Zhao *et al.*, 2003) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine(MPTP)-induced Parkinson's disease-like mice (Shan *et al.*, 2006), and in the postmortem substantia nigra of human PD patients (Yoshimi *et al.*, 2005).

However, some efforts have failed in obtaining evidence of spontaneous generation of dopaminergic neurons in the substantia nigra of normal adult rats and mice (Chen *et al.*, 2005; Frielingsdorf *et al.*, 2004; Mao *et al.*, 2001; Reimers *et al.*, 2006). Other groups also tried unsuccessfully to provide evidence that the loss of dopaminergic cells induced in rats by the injection of 6-hydroxydopamine (6-OHDA) into either the medial forebrain bundle (Cooper and Isacson, 2004; Frielingsdorf *et al.*, 2004; Mao *et al.*, 2001) or the striatum (Steiner *et al.*, 2006) induces neurogenesis in the substantia nigra.

Huntington's disease. Huntington's disease (HD) is a progressive neurodegenerative disease that leads to neuronal loss in the caudate-putamen which is caused by a mutated form of the huntington genes, but the mechanism of cell loss is not fully understood (Walling *et al.*, 1998). The striatum and cortex are affected in early stages of the disease and more recent evidence suggests hippocampal dysfunction as well (Rosas *et al.*, 2003). Hippocampal neurogenesis is decreased in the R6/1 and R6/2 transgenic mouse models of Huntington's disease, although cell proliferation in the hippocampus is similar in younger asymptomatic R6/1 mice and wild type control (Gil *et al.*, 2005; Lazic *et al.*, 2004). In contrast, current findings have shown the increase in cell proliferation in the SVZ in the postmortem brain of Huntington's disease patients (Curtis *et al.*, 2003) and in the striatum of the quinolinic acid lesion model of Huntington's disease (Tattersfield *et al.*, 2004), although the extent to which these new cells form functional neurons is not known. These pioneer data indi-

cate that the diseased adult brain is still capable of neuronal regeneration, which opens new avenues in the treatment of neurodegenerative diseases.

ADULT NEUROGENESIS AND BRAIN INJURY

Seizure and epilepsy. Seizure-induced brain injury results in various forms of plasticity in the adult rodent dentate gyrus, such as axonal reorganization, reactive gliogenesis, dendritic remodeling and dispersion of the granule cell layer (Parent and Lowenstein, 1997). Adult neurogenesis has relatively recently been added to this list based on studies using animal models of seizure or epilepsy. A number of studies indicate that seizures promote neurogenesis in the dentate gyrus and SVZ. Dentate granule cell neurogenesis is found to increase after pilocarpine-induced status epilepticus (SE), intermittent perforant pathway stimulation or hippocampal stimulation (Bengzon *et al.*, 1997; Parent *et al.*, 1997). Kainic acid-induced SE, and amygdala or perforant pathway kindling also produce newborn neurons in the dentate gyrus (Gray and Sundstrom, 1998; Nakagawa *et al.*, 2000; Parent *et al.*, 2002; Scott *et al.*, 1998; Smith *et al.*, 2006). However, there is conflicting evidence concerning the effect of epilepsy and seizures on neurogenesis. A study by Kralic and colleagues demonstrates that although acute status epilepticus, induced by kainic acid injection in a mouse model, increases cell proliferation in the subgranular zone and dentate gyrus, models of temporal lobe epilepsy show a marked reduction in neurogenic potential (Kralic *et al.*, 2005). This is attributed to the dispersion of dentate granule cells seen in the brains of these mice - a feature also observed in many patients with temporal lobe epilepsy. Other works also report that seizure or chronic temporal lobe epilepsy reduces neurogenesis in rat hippocampal slice culture, the adult hippocampus of rat model of temporal lobe epilepsy and human fascia dentate (Hattiangady *et al.*, 2004; Mathern *et al.*, 2002; Sadgrove *et al.*, 2005).

Ischemic brain injury. Accumulating evidence suggests that ischemic brain injury potently increases neurogenesis in SVZ and SGZ of the adult rodent brain. Since the description by Liu *et al.* about prominent increase of cell proliferation in the dentate gyrus after transient global ischemia in the adult gerbil (Liu *et al.*, 1998), many studies confirm that transient focal or global ischemia potently stimulates proliferation in the dentate gyrus in mice (Takagi *et al.*, 1999; Tureyen *et al.*, 2004) and rats (Choi *et al.*, 2003; Darsalia *et al.*, 2005; Takasawa *et al.*, 2002). Neurogenesis in the SGZ is also increased by stroke induced by middle cerebral artery occlusion (MCAO) (Arvidsson *et al.*, 2001; Komitova *et al.*, 2002). These newly generated cells in the ischemic brain follow a time course of neuronal maturation similar to that in normal animals. According to Tanaka *et al.* (2004), with increasing time after ischemia, newly generated cells move from the subgranular zone to the granule cell layer, shift from coexpression of immature to mature neuronal markers, and increase in measures of dendritic length.

In addition to the adult neurogenesis in dentate gyrus, forebrain ischemic injury increases SVZ cell proliferation and neurogenesis. Stroke induced by MCAO leads to increased cell proliferation and increased numbers of immature neurons in the ipsilateral SVZ (Jin *et al.*, 2001; Parent *et al.*, 2002; Zhang *et al.*, 2001). Using an MCAO model in adult rats, Zhang *et al.* have shown increased SVZ BrdU labeling and neurogenesis that peaks 7 days after ischemia (2001). SVZ neurogenesis also increases in the adult rat SVZ after transient MCAO (tMCAO) (Jin *et al.*, 2001). New neurons appear to migrate to the damaged striatal area and differentiate into regionally appropriate types of neurons. After tMCAO, SVZ neuroblasts that migrate to the injured striatum express markers of medium spiny neostriatal projection neurons (Arvidsson *et al.*, 2002; Parent *et al.*, 2002), suggesting that they have the potential to replace neurons lost after focal ischemia.

ADULT NEUROGENESIS AND DRUGS OF ABUSE: OPIATES, PSYCHOSTIMULANTS AND ALCOHOL

Psychostimulants and opiates. Repeated or chronic exposure to drugs of abuse leads to brain region-specific neuroadaptations that correlate with measurable changes in behavior (Everitt *et al.*, 2001). While the main interest in drug-induced neuroadaptations has been the dopaminergic "reward" circuitry (Spanagel and Weiss, 1999), recent evidence underscores a prominent role for limbic brain regions, like the hippocampus, in drug addiction (Fuchs *et al.*, 2005; Pelchat *et al.*, 2004). Since Eisch *et al.* first reported the decrease of neurogenesis in adult rat hippocampus treated chronically with morphine and heroin (2000), many recent studies have addressed the in vivo impact of opiates and psychostimulants on adult neurogenesis and reported detrimental effects of drug exposure on adult neurogenesis.

The psychomotor stimulants methamphetamine and cocaine have been shown to negatively influence neurogenesis in the dentate gyrus. Single exposure to methamphetamine transiently diminished cell prolifera-

tion in the gerbil dentate gyrus (Teuchert-Noodt *et al.*, 2000). In turn, chronic and repeated cocaine exposure decreased cell proliferation but did not interfere with survival and maturation of the newborn cells (Dominguez-Escriba *et al.*, 2006; Yamaguchi *et al.*, 2005). Herna'ndez-Rabaza et al. studied the influence of binge exposure to 3,4-methylenedioxymethamphetamine (MDMA, also known as 'ecstasy') on proliferation, survival and maturation of progenitors in the rat dentate gyrus. Binge dosing with MDMA does not affect neurogenesis in the adult dentate gyrus but compromises the survival of neural precursors causing a decrease in the survival two weeks after the MDMA challenges (2006).

Studies with opiate drugs in rats indicated that morphine and heroin decreased cell proliferation and long-term cell survival following repeated, but not acute exposure (Eisch *et al.*, 2000). Chronic morphine treatment resulted in altered neuronal phenotypes in adult rat hippocampus (Kahn *et al.*, 2005) and premature mitosis of progenitors in adult mice hippocampus (Mandyam *et al.*, 2004). It is noteworthy that the decreased adult neurogenesis induced by exposure to drug of abuse is selective to the SGZ, while another region of adult neurogenesis, the anterior subventricular or subependymal zone is relatively spared (Eisch and Harburg, 2006; Nixon and Crews, 2004).

Alcohol. Although it is well recognized that alcohol disrupts the formation of new cells in the developing brain (Crews *et al.*, 2003; Luo and Miller, 1998), the direct relationship between alcohol intake and structural changes in the hippocampus was first reported by Walker *et al.* (1980). Thereafter, imaging studies and postmortem analysis of brain structure have confirmed that alcohol induces neurodegeneration in regions such as the hippocampus (Agartz *et al.*, 1999; Bengochea and Gonzalo, 1990; Laakso *et al.*, 2000). Many studies concur that alcoholic neurodegeneration may result from decreased adult neurogenesis, even if there is a work that reports a positive relationship between adult neurogenesis and moderate alcohol consumption (Aberg *et al.*, 2005).

Acute or short term exposures appear to decrease cell proliferation in almost all reports (Jang *et al.*, 2002; Nixon and Crews, 2002). Longer-term exposures also produce similar effects on cell proliferation (He *et al.*, 2005; Rice *et al.*, 2004). However, 10 days, 30 days (Rice *et al.*, 2004) or 6 weeks (Herrera *et al.*, 2003) of chronic alcohol exposure do not influence cell proliferation, possibly due to compensatory response. Alcohol has specific effects on neurogenesis according to the dose, timing, or duration of alcohol exposure. The timing of alcohol exposure has not yet been shown to affect neuronal progenitor cell proliferation. Duration of alcohol exposure has also not appeared to be a factor when cell proliferation is affected with single doses (Nixon and Crews, 2002), or through chronic diet drinking models (He *et al.*, 2005). In contrast, alcohol dose-dependently reduces the proliferation of progenitors in adolescent rats when administered acutely (Crews *et al.*, 2006) or administered in acute doses over 3 days (Jang *et al.*, 2002).

In addition to its effect on proliferation, alcohol compromises the survival of newly born cells, exerting inhibitory effect on neurogenesis, which is consistent with reports that alcohol causes cell death in the DG (He *et al.*, 2005; Herrera *et al.*, 2003; Obernier *et al.*, 2002). Though dentate granule cells are affected in these models of alcohol exposure, it is not decided whether newborn cells are more susceptible to alcohol's toxic effects or alcohol kills stem/progenitor cells.

CONCLUDING REMARKS

Given that, in principle, new neurons can be generated following brain insults, one of the urgent questions that we must answer is whether and how adult neurogenesis after brain insults contributes to functional recovery. However, after all our effort to clearly depict the adult neurogenesis related with various forms of brain insults, the adult neurogenesis is a phenomenal event in the face of which we still feel lost about the meanings and roles in pathological as well as physiological settings, which is natural, considering that we are so far from indisputable consensus with regard to many aspects associated with adult neurogenesis. Nevertheless, at least there is reason to believe that cells with proliferating potential in neurogenic areas respond to injury. Seizure, ischemia and some neurodegenerative diseases augment the precursor cell proliferation, provided that the proliferating potential itself of progenitor/stem cells is preserved. In addition, there exists some works reporting that nonneurogenic regions also respond to injury and participate directly or indirectly in adult neurogenesis (Leavitt *et al.*, 1999; Magavi *et al.*, 2000; Parent *et al.*, 2002). These findings lead us to the conclusion that adult neurogenesis is an intrinsic program to spontaneously operate to repair the lesioned circuits by replacement, when confronted with any kinds of brain insults. However, it is premature to conclude that adult neurogenesis is always beneficial and that all brain insults lead adult neurogenesis toward the same direction. For example, whereas Jakubs *et al.* reported that epileptic seizure-generated hippocampal granule

cells show reduced excitatory synaptic input and decreased excitability so that their functional integration is adjusted to the prevailing functional state in the network (2006), other works report that granule cells born after seizure behave strangely or aggravate the status quo (Overstreet-Wadiche *et al.*, 2006; Scharfman *et al.*, 2000). In addition, as is mentioned above, prolonged seizure, certain neurodegenerative diseases and exposure to drugs of abuse seem to decrease adult neurogenesis.

At this stage, we have few answers to the many questions surrounding adult neurogenesis under pathological conditions, such as the identity of factors driving adult neurogenesis in either way, the timing of de novo neurogenesis with relation to specific brain insults and the relationship between newly born cells and preexistent circuits. Accordingly, the challenge ahead appears overwhelming, even if it is true that we have seen a glimpse of hope regarding insulted brain.

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