ACTA NEUROBIOLOGIAE EXPERIMENTALIS

Review Acta Neurobiol Exp 2012, 72: 309–324

Endogenous neurogenesis induced by ischemic brain injury or neurodegenerative diseases in adults

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The discovery of neurogenic response subsequent to brain injuries has led to the hypothesis that the expansion of the pool of endogenous progenitors could augment the regenerative capacity of the damaged areas. However, it occurred that endogenous spontaneous neurogenesis is insufficient for replacing the lost neurons and to achieve global repair, particularly in aging brain. Until today, a great effort has been made attempting to promote "reactive neurogenesis" more successful. It was found that small chemical molecules exert stimulation of neurogenesis and probably might help to induce neuronal endogenous cell replacement in various neurological diseases. In this review we briefly highlight the current data regarding effect of brain ischemia and age-related neurodegenerative diseases on neural stem cells *in situ* and potential therapeutic effect of their stimulation.

Key words: neural progenitors, neurogenic zones, adult brain disorders, epigenetic agents

INTRODUCTION

Adult mammalian neurogenesis has been firmly established across distinct species including humans. Neural stem cells defined on *in vitro* criteria as cells with long-term self-renew capability, proliferation and the ability to differentiate into all types of neural cells, including neurons, astrocytes and oligodendrocytes have been discovered postnatally in central nervous system (CNS). In adult mammals, persistent neurogenesis has been convincingly demonstrated in two specific brain areas – the subventricular zone (SVZ) that borders the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus (DG) (Lois and Alvarez-Buylla 1994, Kuhn et al. 1996, Eriksson et al. 1998, Kornack and Rakic 2001). Whether neurogenesis occurs in the brain areas other than SVZ and SGZ still remains controversial. However, many subsequent reports confirmed the existence of neurogenic events in other CNS regions, most of which are summarized in previous review articles (Magavi et al. 2000, Emsley et al. 2005, Gould 2007, Bonfanti and Ponti 2008, Migaud et al. 2010).

Neural stem cells residing in SVZ give rise to neuroblasts that migrate a long distance along the rostral migratory stream (RMS) to reach the olfactory bulb (OB) where they mature into granular and periglomerular neurons (Lois and Alvarez-Buylla 1994) (Fig. 1). The function of persistent OB neurogenesis is largely unknown, but increasing evidence supports the contribution of these new neurons to olfactory learning (Petreanu and Alvarez-Buylla 2002, Magavi et al. 2005).

In contrast, the progeny located in SGZ disperse and migrate a short distance to the adjacent granular layer of the DG and differentiate into granular neurons (Kuhn et al. 1996, Eriksson et al. 1998) (Fig. 2). Although the precise function of DG cells generated in adulthood is unknown, experimental depletion of new neurons disrupts cognitive tasks (Shors et al. 2001), suggesting that these newly-formed cells play a role in hippocampal-dependent learning and memory (Kempermann et al. 1998, Schinder and Gage 2004, Bendel et al. 2005).

The persistent production of neural progenitors in the adult brain raises the exciting possibility that the brain mounts an intrinsic regenerative potential to repair itself. It is therefore tempting to speculate, that

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Received 06 September 2012, accepted 12 December 2012

the amplification of self-repair mechanisms might in the future become a therapeutic modality in acute or chronic brain disorders (Kuhn et al. 2001, Parent 2003, Lie et al. 2004). It is of note that many experimental studies have highlighted that neural stem cells, like other tissue-specific stem cells, reveal the capacity to respond actively to specific physiological and pathological conditions, migrate to areas of injury (Arvidsson et al. 2002, Emsley et al. 2005, Curtis et al. 2007, Ohira et al. 2010), and secrete neuroprotective molecules, in addition to their potential for generating a variety of new functional cell types (Ourednik et al. 2002). These findings have begun to imply the potential use of neural progenitors for novel strategy which utilizes the latent regenerative capacity of endogenous progenitors for neurologic disorders after conventional medical treatment would no longer be effective.

NEUROGENESIS INDUCED BY ISCHEMIC INSULT IN EXPERIMENTAL ANIMALS

Ischemic brain damage is caused by two different types of insults. Occlusion of cerebral artery, that is, ischemic stroke, gives rise to irreversible damage in the core region and partially reversible changes in the surrounding penumbral zone. In contrast to stroke, cardiac arrest or coronary arterial occlusion, which leads to abrupt and near-total interruption of cerebral blood flow, causes selective neuronal death of certain vulnerable neuronal populations, such as hippocampal CA1 pyramidal neurons (Kokaia and Lindwall 2003). This type of insult is a less common in humans and results from events such as myocardial infarction, carbon monoxide inhalation or drowning.

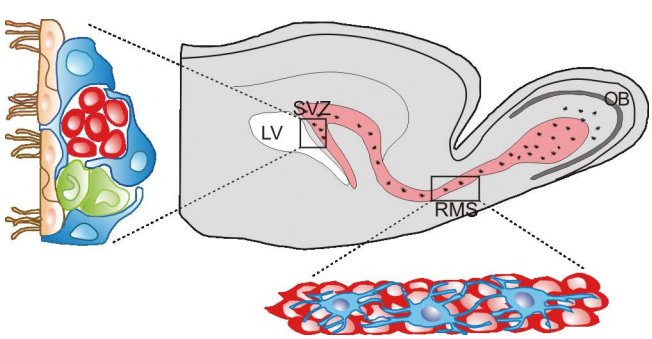

Fig. 1. Neurogenic subventricular zone of lateral ventricles. Neuroblasts arising from neural stem cells residing in subventricular zone (SVZ) migrate along the rostral migratory stream (RMS) to the olfactory bulb (OB). (LV) lateral ventricle. (Lledo et al. 2006).

Ischemic insults are common causes of death and disability in humans. Although a plethora of neuroprotective compounds have shown positive effects in animal models, almost no treatment to date proved satisfactory in clinical trials (Dirnagl 2006). Recombinant tissue plasminogen activator (rt-PA), the only approved drug for ischemic stroke treatment, improves outcome for a small proportion presenting very early (not later than 3–4.5 hours) after symptom onset (Nakashima and Minematsu 2009, El Amki et al. 2012). In the background of this urgent clinical need, several studies have recently been published investigating the therapeutic potential of endogenous stem cells in experimental models of global and focal brain ischemia, which replicate either the consequences of cardiac arrest and coronary artery occlusion or the consequences of stroke, respectively

Neurogenesis after global forebrain ischemia

The increased hippocampal neurogenesis following global ischemia induced by transient bilateral carotid artery stenosis in gerbils was for the first time reported by Liu and coworkers (1998). It was found that proliferation of progenitors in SGZ was upregulated several fold during 1–2 weeks after ischemic insult and roughly half of postischemic precursors acquired further neuronal phenotype in the granular cell layer of DG. Since this initial publication many follow-up studies have confirmed stimulation of neurogenesis in the dentate SGZ across various model species (Takagi et al. 1999, Kee et al. 2001, Yagita et al. 2001, Tonchev et al. 2003b, Wójcik et al. 2009). Further, newly generated granular neurons were able to extend dendrites into the molecular layer of DG establishing synapses with mature neurons born during development (Tanaka et al. 2004). These studies provide no evidence of SGZ neural stem cells migration into CA1 to replace neurons lost after global ischemia. In contrast, CA1 area merely displays gliogenesis (Tonchev et al. 2003b, Tonchev and Yamashima et al. 2006, Wójcik-Stanaszek et al. 2011).

Interestingly, Nakatomi and colleagues (2002) reported that intraventricular infusion of growth factors – fibroblast growth factor-2 (FGF-2) and epidermal growth factor (EGF) after global ischemia leads to substantial regeneration of hippocampal CA1 pyramidal neurons. The newly-formed neuronal cells originated in the brain periventricular area (caudal to the SVZ), adjacent to CA1, have the capacity to migrate

into the ischemia injured structure, integrate into the existing brain circuitry and form functional synapses. The growth factor-induced hippocampal neuronal replacement was associated with partial restoration of spatial learning and memory. Likewise, Bendel and coauthors (2005) observed that spontaneous replacement of CA1 neurons correlates with the time-course of learning and memory improvement. However, in spite of these interesting observations there remains much doubt regarding the contribution of new neurons to the restoration of cognition. The development of new transgenic animal models that allow selective ablation of newly born neurons might be necessary to address this question more definitely.

Furthermore, the use of the growth factors for mobilizing NSCs, although beneficial, may in addition cause unanticipated adverse effects. Direct ICV infusion of bFGF in the adult brain may promote microglial and glial reactivity concurrent with disruption of oligodendrocyte function and myelin production leading to the appearance of demyelinating lesions (Butt and Dinsdale 2005a,b). It is also worth to point that replacement of lost CA1 pyramidal neurons after ischemia, reported by Nakatomi and coworkers (2002) and Bendel and others (2005), until today has not been reproduced by other investigators. These obvious discrepancies could be explained by differences in tissue injury model employed.

Since the first demonstration that global cerebral ischemia stimulates neurogenesis (Liu et al. 1998), we have come to know that generation of new neurons after ischemic episode primarily occurs in subgranular zone of the DG. Interestingly, Ohira and coworkers (2010) have reported the existence of neurogenic processes in non-neuroproliferative brain region. Authors, by employing a recombinant retrovirus vector expressing membrane-targeted green fluorescent protein (GFP), detected neural progenitor cells that settled in the rat neocortical layer 1. Furthermore, these progenitors proliferated actively in response to global forebrain ischemia. At later time points after ischemic insult numerous neuronal precursors became GABAergic neurons that migrate to the deep cortical layers and integrate into the neuronal circuitry. The above results asserted that the adult rodent cortex, which is non-neurogenic in the intact animals, is capable of neuronal regeneration by activating endogenous progenitors in response to specific forms of injury and under appropriate conditions.

Neurogenesis induced by focal ischemia

Focal ischemia appears more popular model used in experimental studies than global ischemia. Mostly it is induced by the occlusion of the medium carotid artery (MCAO), which leads to infarction of the striatum and overlaying cortex. Ischemic stroke induced by MCAO in rodents leads to the marked enhancement of cell proliferation in the SVZ and in dentate subgranular zone with a peak at around 1-2 weeks after injury and an increased number of immature neurons in the ipsilateral side of infarction (Jin et al 2001, Arvidsson et al. 2002, Parent et al. 2002, Komitova et al. 2005).

The expanded neuroblast population deviates from their normal route toward the OB and migrates into the damaged striatal area to replace the destroyed medium

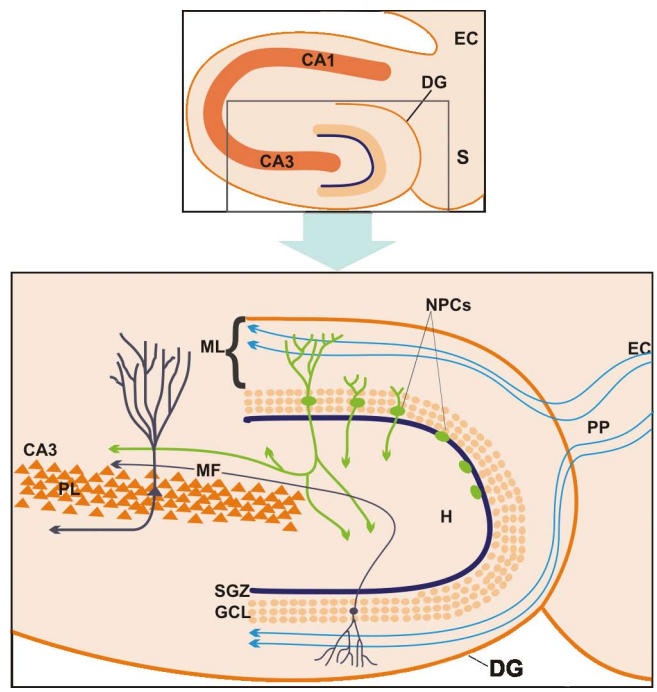

Fig. 2. Neurogenesis in the adult dentate gyrus. Top: transverse section of the rodent hippocampal formation illustrating the major cytoarchitectonic divisions. (DG) dentate gyrus; (EC) entorhinal cortex; (S) subiculum. Bottom: Neural progenitor cells (NPCs) are distributed along the subgranular zone (SGZ), the boundary between the granule cell layer (GCL) and the hilus (H). The SGZ is the neurogenic region where NPCs proliferate, differentiate into neurons (mainly granule cells), and migrate superficially through the GCL toward the molecular layer (ML). Cell bodies stay at the GCL, dendrites project through the ML, and axons project toward the hilus and CA3. (PP) perforant path; (MF) mossy fibers; (PL) pyramidal layer (Schinder and Gage 2004).

spiny neurons (Arvidsson et al. 2002, Parent et al. 2002). Indeed, some of these cells differentiate into mature neurons of the type lost due to the insult. According to the published reports new neurons continue to be added to the striatum for at least a number of months (Thored et al. 2006, Leker et al. 2007), or even a year (Kokaia et al. 2006) after the insult. However, the majority of newly-generated cells fail to survive and die between 2 and 5 weeks after ischemic stroke (Arvidsson et al. 2002, Parent et al. 2002, Jin et al. 2003a). This probably reflects the unfavorable environment for the newly formed neurons and lack of appropriate trophic support and connections, but also the exposition to the detrimental action of damaged tissue. Although the population of striatal neurons replaced by the neural stem cell progenies represented only about 0.2% of the lost cells (Arvidsson et al 2002), this is the proof that the brain is, within a limited extent, programmed to repair itself through the replacement of its cellular components.

Increased neurogenesis in SVZ has also been observed after intracerebral hemorrhagic (ICH) stroke, induced by injection of bacterial collagenase or blood (Masuda et al 2007, Yang et al. 2008, Xu et al. 2012). Newly-born neurons migrate into region surrounding the hematoma. However, the majority of these new cells do not survive longer than 3 weeks (Otero et al. 2012), which is reminiscent of what is seen in rodent models of ischemic stroke. Surprisingly, there is almost lack of information concerning neurogenic process after experimental subarachnoid hemorrhage (SAH), caused mostly by endovascular perforation of anterior cerebral artery. Available fragmentary data showed initial reduction in the number of proliferated cells in both neurogenic zones – SGZ and SVZ. At later time points (7 days) after the insult the number of these cells had recovered to the control level. The numerous proliferating cells relocate into GCL and become mature granular neurons (Mino et al. 2003). Until now, the analysis of neurogenesis after SAH remains far from being complete.

Several reports confirmed the presence of proliferating cells after stroke in the cortical penumbra. Some of these cells express neuronal markers (Gu et al. 2000, Jiang et al. 2001). The site of origin of these cortical newborn neurons is uncertain. In the light of data that neurogenesis in cortical layer II–III was observed already at 72 hours after stroke induction, a long-distance migration of stem cells from SVZ in described experimental setup seems unlikely. Therefore, it is conceivable that the newborn cortical neurons in this study might originate from quiescent potential neural stem cells that already reside within the neocortex. The existence of neurogenesis inside the cortex after stroke may be also supported by data showing that neural stem cells isolated from adult rat cerebral cortex can generate neurons after exposure to FGF-2 (Palmer et al. 1999). Thus, different origin of newborn neuronal cells might depend on the degree and the kind of brain injury.

Although little is known about the functional status of newly generated neurons, available data raise the possibility, that appropriate treatment to stimulate endogenous neurogenesis may improve neuronal recovery in stroke disorders. Whether these new cells play a role in the improvement of ischemia-impaired sensorimotor function, needs to be proven. Demonstration of electrophysiological action in neurons born in response to focal ischemia requires improved techniques to label NSCs more efficiently for lineage tracing.

The problem is that most of the experimental studies of stroke are most frequently performed in young adult animals whereas human stroke insult usually occurs in the aged. Given that aging is a risk factor for ischemic injury and other neurological disorders, developing effective regenerative strategies may require a better understanding of how neural progenitors in the brain respond to insults during senescence. In fact, stroke-induced recruitment of neural stem cells is preserved in aged animals (Jin et al. 2004a). However, the amplitude of this process is reduced probably due to decline of neurogenesis and reduction of neural stem cells number during aging (Maslov et al. 2004). Also the survival of adult-born cells decreases remarkable in the aged animals. The total number of newly-generated cells observed one month after ischemia is approximately seven-fold lower in older animals than in young counterparts (Yagita et al. 2001). In addition, migration of neuroblasts into the ischemic striatum was also reduced in old rats compared with young ones (Jin et al. 2004a).

However, several lines of evidence suggest, that the decrease of neurogenesis with age may reflect changes in the brain microenvironment rather than alterations in the number of properties of NSC themselves. It is well known that the levels of several cytokines, including FGF-2, IGF-1 and VEGF are reduced with age

(Shetty et al. 2005) and infusion of these molecules in old animals reverses age-derived decline of the generation of new neurons (Lichtenwalner et al. 2001, Jin et al. 2003b). These data suggest that a similar neurogenic potential may in fact be present in aged brain, and be available to respond to injury. Accordingly, MCAO occlusion induced in 3- and 15-month-old rats revealed a similar magnitude of striatal neurogenesis (Darsalia et al. 2005). Furthermore, analysis of postmortem brain tissue from advanced age humans suffered from ischemic stroke reveals the increase in proliferating SVZ cells and neuroblasts (Jin et al. 2006, Macas et al. 2006, Minger et al. 2007). However, the detection of the above process does not guarantee an increase in the net number of functional neurons. Nevertheless, these data are consistent with experimental results showing that stroke induces neurogenesis in aged animals, although basal neurogenesis is attenuated (Jin et al. 2004a, Luo et al. 2006, Zhang et al. 2006). So far, experiments performed in animals have predicted relatively well the process of neurogenesis and its alteration to some pathological states. The presence of stroke-induced neurogenesis in primate models (Tonchev et al. 2003b, 2006) suggests that mobilization of endogenous progenitors is a reasonable therapeutic avenue to pursue in human stroke patients.

Many parameters, however, are more amenable to treatment in experimental animals than in patients. While there are similarities in cerebrovascular anatomy and pathophysiology between rodents and humans, there are also important differences, including brain size, length and structure of perforating arteries, and the ratio of gray and white matter (Krafft et al. 2012). Moreover, experimental stroke generally model only certain aspects of the disease and do not reflect the heterogeneity in severity, pathology and comorbidities of human stroke.

At present only sparse information are available about the occurrence of neurogenesis in the human brain under ischemic conditions. The first evidence of rapid neurogenic response to ischemic stroke in human was provided by Jin and coauthors (2006). Authors, using sections obtained from human brain biopsies performed for the diagnosis of ischemic stroke, found cells that express markers associated with newborn neurons in ischemic penumbra.

The existence of neurogenic events in perihematomal regions in patients after intracerebral and subarachnoid hemorrhage (ICH and SAH) was also confirmed recently (Sgubin et al. 2007, Shen et al. 2008). The site of origin of NSCs in the perihematomal region in humans is unknown. Nevertheless, the greater migration distance that would be required in human, compared with rodent brain, raises the possibility that NSCs might arise locally. However, the extent to which stroke-induced neurogenesis in human brain results in the production of functional neurons with the capacity to integrate into brain circuitry is uncertain. Otherwise, the new neurons could serve purposes other than cell replacement, such as providing cytoprotective or trophic factors to cells surrounding a hematoma (Shen et al. 2008).

Regulation of ischemia-induced neurogenesis

The molecular mechanism(s) regulating ischemia-induced neurogenesis are not fully understood. It is hypothesized, that following ischemic insult, neurogenesis proceeds as it does during embryonic development, involving the same concerted action of cell surface and extracellular matrix molecules, signaling molecules, sex hormones and others thereby providing an environment which may be instructive or permissive to neurogenesis-associated processes (Bovetti et al. 2007). Several of these molecules that are critical during embryonic development of the nervous system continue to modulate NSC activity and adult neurogenesis. In accordance, both the stroke-generated striatal cells (Arvidsson et al. 2002) and the cells in the posterior periventricle that had proliferated in response to global ischemia (Nakatomi et al. 2002) initially express several developmental transcription factors.

The regulation of neurogenesis in adults' brain after ischemia seems to be more complex and specific in comparison to physiological conditions. For example under physiological conditions neuroblasts born in the SVZ of the adult rodent migrate to the olfactory bulb (Doetsch et al. 1997, Garcia-Verdugo et al. 1998). However, after stroke insult neuroblasts generated in the SVZ migrate to the ischemic boundary (Ohab et al. 2006, Thored et al. 2007, Jablonska and Lukomska 2011). It indicates that there are a number of not defined yet factors which facilitate mobilization of endogenous progenitors to areas of ischemia damage and also appear to influence the severity of stroke and the functional outcome of disorders. Also intriguing is the finding that NMDA receptor blockage enhances

neurogenesis in the intact DG, but it suppresses generation of the new neurons in the ischemic brain. It seems likely, that other glutamate-mediated changes in the ischemic brain, such as increased synthesis of growth factors, may override the normal action of glutamatergic mechanisms on adult neurogenesis. Interestingly, distinct glutamatergic receptors are involved in the modulation of neurogenesis following MCAO from those following global ischemia. Whereas NMDA receptor is involved in neurogenesis induced by the two types of ischemic insult, AMPA receptor seems not to be engaged in neurogenic processes stimulated after the middle cerebral artery occlusion (Bernabeu and Sharp 2000, Arvidsson et al. 2001).

Several studies suggest that growth and neurotrophic factors are candidates for mediating ischemia-induced neurogenesis and the recruitment of endogenous progenitors to the sites of damage. Brain ischemia increases the expression of several of these factors, including BDNF, bFGF and GDNF (Kokaia et al. 1995, Lin et al 1997, Kitagawa et al. 1999) and sustained upregulation of these factors may mediate stroke-induced neurogenesis and neuroblasts migration. Stimulation of particular nurogenic-associated processes observed by a number of authors after delivery of neurotrophic factors to the intact brain strongly support their contribution in post-ischemic neurogenesis. However, promotion of neurogenesis after ischemic brain insult is a controversial issue in many cases.

For example prolonged delivery of BDNF to the hippocampus counteracts neuronal differentiation but does not influence cell proliferation or the survival of newly formed cells in DG after global ischemia. Another potentially safe molecule that participates in postischemic neurogenesis is erythropoietin (EPO) (Shingo et al. 2001). This cytokine is produced as a part of the ischemic-hypoxic response. Intraventricular EPO infusion leads to the increased generation of olfactory bulb neurons.

In spite of the uncertainty over the details of the regulation of neurogenesis induced by ischemia, accumulating evidence clearly points to the involvement of glutamatergic mechanism (Cameron et al. 1995). Stimulation of glutamatergic receptors and calcium influx can trigger a cascade of secondary events leading, among others, to the increased production of nitric oxide which has also recently emerged as an important regulator of stroke–induced neurogenesis (Zhang et al. 2001).

The recent findings highlight the broad range of multiple factors (e.g,. neurotransmitter systems, sex hormones, paracrine signaling molecules, such as Wnt, Notch, bone morphogenic proteins, Sonic hedgehog) that effectively regulate various aspects of the neurogenesis. A detailed discussion on their role can be found in reviews elsewhere (see, e.g., Hagg 2005, Balu and Lucki 2009, Mu et al. 2010). The function of these factors may be modulated in result of ischemia. Thus, the final outcome depends on the spatial and temporal expression of factors with inhibitory or stimulatory roles following brain injury. The elucidation of the molecular cues regulating endogenous neural progenitors and their response to brain damage needs to be attained prior to the development of stem cell based therapy.

NEUROGENESIS ACCOMPANIES NEURODEGENERATIVE DISEASES

In contrast to stroke that can cause necrosis in different brain regions deprived from blood flow supply, neurodegeneration affects specific brain areas leading to selective neuronal loss over a long time period. Although neuronal degeneration touches or starts with particular neuronal populations, including dopaminergic neurons in Parkinson's disease, striatal medium spiny neurons in Hungtington's disease, and cortical and hippocampal cholinergic neurons in Alzheimer's disease, there are many similarities between different neurodegenerative disorders. These include atypical protein assemblies and oligomerization as well as induced cell death. It is also known that chronic degeneration has different impacts on neurogenic process involving stem cell maintenance, proliferation, survival and functional integration (Curtis et al. 2003, Jin et al. 2004b).

A number of studies performed in adult animal using different models of neurodegenerative diseases shows diverse and variable results. Transgenic models vary in promoters used, age of animal, age of disease onset, transgene expression, neurotransmitter content and amount of disease-causing protein. Moreover, the transgenic animals usually present only some, but rarely all, of the neuropathological findings in the respective brain regions (see Winner et al. 2011 for review).

Human brain diseases were studied by analyzing *postmortem* brain tissue. This tissue rather often repre-

sent the end-stage of the disease. It also remains questionable how well preserved were analyzed samples. A significant difficulty in understanding human neurogenesis in degenerative diseases comes from inadequate labeling methods of neuroblasts in human adult brain. Improvement of the imaging techniques will lead to the development of tools that hopefully will permit the visualization of newly generated cells (Couillard-Despres et al. 2008).

Parkinson's disease

Parkinson's disease (PD) is a common late-onset neurodegenerative disorder. PD is a synucleinopathy, with accumulation of misfolded alfa-synuclein that forms intracellular inclusion in neurons called Lewy bodies. Prominent clinical features of PD are progressive loss of muscle rigidity and tremor, and slowing the physical movement and non-motor-related symptoms such as olfactory deficits, autonomic dysfunction, depression, cognitive deficits and sleep disorder. Different alfa-synuclein-overexpressing and mutant mice under various promoters present certain aspects of PD, however, they do not show Lewy bodies (see Sulzer 2010 for review).

Experimental overexpression the wild-type or mutant forms of human alfa-synuclein in mice significantly decreases the survival of newborn neurons in both SGZ and SVZ, without affecting cell proliferation. A decrease of adult neurogenesis was also present in the A53T mutant transgenic models expressing variant alpha-synuclein (full-length, 140 amino acid isoform). Here, a decrease in proliferation was present in the DG and OB (Crews et al. 2008, Winner et al. 2008). Reduced adult neurogenesis was also present in OB of a mouse model with conditional expression of A30P alfa-synuclein. Suppression of the transgenes restores completely the negative influence of alfa-synuclein on OB neurogenesis (Marxreiter et al. 2009). The effect of decreased neurogenesis in alfa-synuclein models was still present in aging mice (Winner et al. 2008). Primary cause of Parkinson's disease (PD) is a loss of dopaminergic neurons within the substantia nigra of the midbrain, that project to the striatum and control movement. Mitotic decline in the SVZ of patiens attained by PD may result from the disruption of dopaminergic supply (Kadir and Nordberg 2010). So the ablation of dopaminergic neurons in the substantia nigra is a classical method of modeling PD in animals. Animal models of this disease relay on the use of toxins – 6-hydroxydopamine (6-OHDA) or 1-methyl-4-phenyl-1,2,3,5-6-tetrahydropyridine (MPTP) to destroy dopaminergic fibers. Although both toxins resulted in the decline of proliferation in SVZ (Baker et al. 2004, Hoglinger et al. 2004, Winner et al. 2009, Cova et al. 2010), an increase in dopaminergic neurogenesis in the OB glomerular layer was observed. This finding is very interesting because a rise in dopaminergic olfactory neurons has been described in the OB of patients with PD (Huisman et al. 2004).

Huntington's disease

Huntington's disease (HD) is a rare, hereditary neurodegenerative disorder with the hallmark being a loss of coordinated movements, as well as additional symptoms such as progressive cognitive decline, muscle atrophy and psychiatric syndromes (see Walker 2007 for review). The Huntington's disease is caused by CAG-trinucleotide repeat expansion within the *huntingtin/IT15* gene, which encodes an extended polyglutamine tract in huntingtin protein. During HD, neurons are progressively lost. The striatum is the brain region most prominently affected, although multiple other regions including substantia nigra, cortex, and cerebellum are also struck by HD. Spiny neurons of the striatum appear to be most vulnerable cellular subtype.

Among the widely used animal models for HD are transgenic mice R6/1 and R6/2 lines and a full length human mutant huntingtin mice with 97 glutamine repeats (Gray et al. 2008), that develop a progressive neurological phenotype that exhibits many of the HD features. Analysis of neurogenesis in both models (R6/1 and R6/2) has disclosed reduced progenitor proliferation rates in dentate gyrus (Lazic et al. 2004, Phillips et al 2005, Kohl et al. 2007) which resulted in the reduction of the newly generated neurons, although in most reports neuronal differentiation was not compromised. In contrast, SVZ proliferation remained unchanged but the number of newly generated neurons was decreased.

In addition, a rat model of transgenic HD has been established, which carries a truncated huntingtin cDNA fragment with 51 CAG repeats under control of the native rat huntingtin promoter (von Horsten et al. 2003). This model recapitulates many of the features of HD and reflects more closely the human disease.

Moreover, longer survival time of these animals allows age-related studies. Investigation of neurogenesis in 8- and 12- month old rats shows the decrease in hippocampal progenitor cells accompanied by an expansion of the quiescent stem cell pool (Kandasamy et al. 2010).

Adult neurogenesis has also been studied in HD models produced with quinolinic acid which causes excitotoxic lesion with selective destruction of striatal cells. The analysis shows augmented mitotic activity in the adjacent SVZ, which leads to the production of neuroblasts with migration capacity towards the lesioned striatum. However, these cells are not able to survive and form functional striatal neurons (Tattersfield et al. 2004, Phillips et al. 2005, Kohl et al. 2010). It is possible that striatal microenvironment provides stimulus for abnormal migration of the newly generated cells but does not allow functional integration. Strong support for the notion that environmental cues from dying cells in the striatum may promote progenitor cell proliferation comes from the recent work on the role of activating transcription factor-2 (ATF-2) in neurogenesis. This protein is highly expressed in the brain stem, substantia nigra and also in the granule cells of the hippocampus. Although levels of ATF-2 are decreased in the hippocampus in a number of neurological diseases including Huntington's, one study has demonstrated that ATF-2 levels actually increased in the subependymal layer in HD (Pearson et al. 2005), a region reported to contain increased numbers of proliferating progenitor cells. It is possible that ATF-2 is activated by environmental cues related to cell death in the HD striatum and that its increased level compared to the control brain (without diagnosed HD) reflects the proliferative response of SVZ progenitors to striatal cell death. Such a mechanism could, in part, account for the increased neurogenesis observed in the SVZ of human HD brains at postmortem (Grote and Hannan 2007).

Alternatively, ATF-2 acts as an effector of cell proliferation in the SVZ, and its reduction in the HD hippocampus may prevent progenitor cell proliferation, as seen in transgenic R6/1 and R6/2 lines. Although further work is needed to confirm whether aberration in the levels of ATF-2 occur also in mouse model of HD, these findings suggest that ATF-2 and other microenvironmental cues, possibly from the striatum, influence adult neurogenesis in an, as yet unknown manner.

Alzheimer's disease

Alzheimer's disease (AD) is the most common of all neurodegenerative disorder. The pathology of AD includes deposition of amyloid-beta protein in senile plaques and neurofibrillary tangles due to hyperphosphorylated tau proteins in the basal forebrain cholinergic neurons as well as in the hippocampus, cerebral cortex and other subcortical structures. Affected individuals undergo a general cognitive decline, behavioral changes and, as disease advances, motor complications and severe dementia develop, rendering them incapacitated. Clinical trials offer some symptomatic relief, but no lasting benefit as they fail to address the underlying biology of AD.

Studies of transgenic AD models showed a compromised neurogenesis in both neurogenic regions of adult brain (Lazarow and Marr 2010, Marlatt and Lucassen 2010). According to the study using different transgenic AD models, neurogenesis may be either decreased or increased (Verret et al. 2007, Ihunwo and Schliebs 2010). For example, a single mutation in amyloid precursor protein (APP) (Indiana mutation) has negative effect on adult neurogenesis at late symptomatic stage after amyloid deposition (Donovan et al. 2006). Similarly, the decreased proliferation of neuronal progenitors was also noted in mice harboring 3 mutant genes encoding APP, PSEN1 and tau protein (Rodriguez et al. 2008). Contrary, double and triple mutations of APP (Swedish and Indiana) under many circumstances result in increased proliferation and, in some cases, survival of new neurons (Mirochnic et al. 2009).

These multiple and divergent findings suggest multiple and complex mechanisms involved in neurogenesis deregulation that illustrates the need for a more thorough understanding of this aberrant action.

A detailed analysis of the several reports on adult neurogenesis in AD models indicated that most of these estimates were performed in young mice, and only one report investigated old mice and found a reduction of adult neurogenesis up to 18 months of age (Zhang et al. 2007). Therefore a systemic comparison of different AD transgenic models under the same promoter, sex, age, would be necessary to draw relevant conclusions.

Post-mortem studies of human brain tissue have led to seemingly variable results. Whereas most data described the significant decline of dividing cells, one study reported increased hippocampal neurogenesis in

patients with AD (Jin et al. 2004b). These findings suggest that the increase might be a compensatory mechanism in the neurodegenerative process.

Whether altered adult neurogenesis contributes to the deficits observed in neurodegenerative diseases is still not clear. Subsequently, we do not know whether restoring generation of new neurons to physiological levels would be sufficient to alleviate the process of the disease. The classical neuropathological hallmarks of Parkinson's, Huntington's, and Alzheimer's disease are late-stage effects and therefore they do not reflect early disease mechanisms. Understanding the mechanism responsible for the disordered generation and development of NSC at the presymptomatic and early symptomatic stage of these diseases is needed to better follow the disease conditions at a cellular level. An additional target might be to use stimulation of endogenous NSC as a means for neuroregenerative therapy.

STIMULATION OF ENDOGENOUS STEM CELLS AS A POTENTIAL THERAPEUTIC STRATEGY

Neural stem cells-based therapy is a promising strategy to regenerate damaged tissue and to recover the functions lost in various neurological diseases including ischemia. Therapeutic strategies are focused on either endogenous or exogenous (grafted) neural stem precursors (NPCs). While the regeneration potential of transplanted cells is great, direct delivery of neural stem cells to the brain, with all the difficulties of neurosurgery in the elderly, also faces the challenge of distributing cells throughout the brain. It particularly concerns diseases characterized by a not uniform but diffuse pattern of degeneration (e.g. Alzheimer's disease). In such circumstances microenvironments of degenerating versus already degenerated neuronal circuits' present challenges for integration of neural progenitors and their phenotypic differentiation. On other hand, the results of cell transplantation in PD patients, though encouraging, are fraught with various problems (see Arias-Carrion and Drucker-Colin 2007 for review).

An alternative strategy to exogenous delivery of NSCs is to promote proliferation of endogenous cells within the brain. Neuronal replacement relaying on endogenous progenitors avoids many of the potential technical and ethical limitations associated with fetal or stem cell transplantation. Although several brain injuries stimulate neurogenesis, the capacity of endogenous regeneration seems to be rather limited and insufficient for replacing the lost neurons and to achieve global repair, particularly in aging brain. Thus, strategies are being sought to amplify the endogenous regenerative response by introducing molecules that might expand the stem cell pool and be useful for providing adequate cellular substrate for a neuroregenerative response (Fig. 3).

The most impressive example of cytokine (EGF and bFGF)-mediated neuroregeneration following ischemia was provided by Nakatomi and coauthors (2002), as described elsewhere in this report. It is worth noting that bFGF also promotes the cortical cell replacement

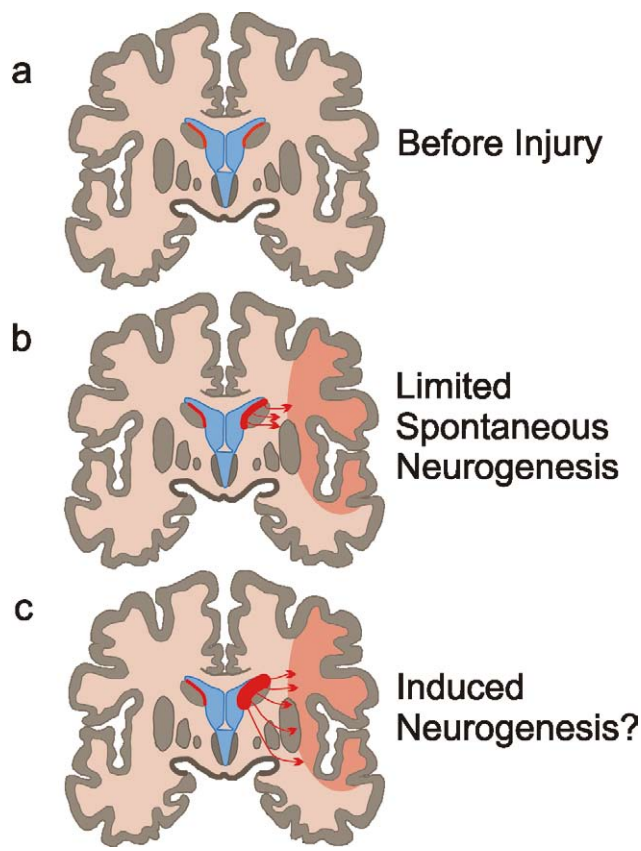

Fig. 3. Mobilization of endogenous neural stem cells. (a, b) Neural stem cells exist in the subventricular zone of adult humans (red in a). Proliferation of these neural stem cells increases after injury, and gives rise to a small number of new neurons (b). (c) Mobilization of NSCs such as via administration of cytokines may further promote NSC proliferation, migration, differentiation, and survival in rodent models of ischemia. However, the distance to which such cells may migrate in the relatively large human brain remains unclear. Pictures drawn based on human MRI images (Burns et al. 2009).

after cortical injury in rats (Leker et al. 2007). Similar results were obtained with transforming growth factor alfa in a rodent model of PD. Recruited neural progenitor cells differentiated into a phenotype of injured dopamine neurons, stimulating improvement in motor behavior (Cooper and Isacson 2004, Androutsellis-Theotokis et al. 2009).

Although the beneficial effect of various factors for mobilizing NSCs results in a great enthusiasm, the potential for unanticipated adverse effect should be also considered. It was reported that direct intraventricular infusion of bFGF in the adult brain promotes microglial and glial reactivity concurrent with disruption of oligodendrocytes function and myelin production leading to the appearance of demyelinating lesions (Butt and Dinsdale 2005a,b). Moreover, growth factors with large molecular weight do not readily cross the blood-brain barrier and thus require direct infusion into the brain. According to our knowledge, there is one report indicating that neural stem cells can be attained by intranasal administration of growth factors to promote brain repair. Diffusion of heparin binding EGF (HB-EGF) mobilized neural stem cells towards lesions experimentally induced in an animal model of multiple sclerosis and promoted replacement of the lost oligodendrocytes (Cantarella et al. 2008). However, this observation needs to be confirmed.

In an effort to promote "reactive neurogenesis" more successful, it was found that the chemical approaches offer a complimentary strategy by directly modulating endogenous tissue-specific stem/progenitor cells *in vivo* for therapeutic benefits (Zaruba et al. 2009, Covic et al. 2010). Mounting evidence indicate that small chemical molecules exert stimulation of brain neurogenesis by modifying targets of signaling pathway or epigenetic mechanisms, which could be sensors of environmental changes and fine modulators of hippocampal neurogenesis (Covic et al. 2010). Many of these compounds are active at nanomolar concentrations, non-toxic, capable of penetrating blood-brain barrier and stable in mice and rats (MacMillan et al. 2011). The first synthetic molecule named P7C3 was found to repair the structure and function of the DG in mice deficient in the *npas3* gene, a genotype characterized by an absence of hippocampal neurogenesis (Pieper et al. 2005). It also enhanced neurogenesis in the DG, impeded neuron cell death, and preserved cognitive capacity as a function of terminal aging in rats.

Recently epigenetic agents have received considerable attention and have spurned justified hope as therapeutic approaches against both acute injury and neurodegenerative diseases. This is particularly true for histone deacetylase inhibitors (HDACi) (Abel and Zukin 2008, Kazantsev and Thompson 2008, Haberland et al. 2009). Decreased histone acetylation in AD was found to be reversible by these factors. This event was accompanied by other alleviating effects for these disorders (see Graff et al. 2011 for review). So far, it is unknown whether the amelioration of pathological symptoms in these diseases is related to the increase of neurogenesis. Interestingly, several groups have reported that treatment with various histone deacetylase inhibitors - sodium butyrate or trichostatin – prior or following stroke induction, confers neuroprotection. The neuroprotective effect resulted in a decrease in infarct volume, behavioral improvements, decreased expression of several factors associated with apoptosis, in addition to stimulation of neurogenesis. It has been hypothesized that these agents provide a suitable option for brain in the clinical manifestation of stroke to facilitate successful translation of experimental ischemia research to clinical trials (Kim et al. 2009, Gibson and Murphy 2010). Whether a treatment regimen with general HDAC inhibitors in humans is feasible for prolonged periods remains unresolved question. Likewise, little is known about the downstream effect, as the epigenetic machinery is characterized by an efficient cross-talks (Latham and Dent 2007, Cedar and Bergman 2009).

The neuroprotective effect of HDAC inhibitors observed *in vivo* may be explained by the influence of these compounds on oxidative pathway and/or downstream components of excitotoxicity, as well as by the increased level of BDNF (above the sham-operated control) and reduced expression of several factors associated with cellular inflammation (Kim et al. 2007, Langley et al. 2009).

Heurteaux and colleagues (2010) reported very interesting approach for treatment of stroke at different stages of the disease. They demonstrated that NeuroAid II (MLC901), a traditional medicine that consist of several types of herbs, improves not only survival of animals subjected to focal ischemia but also decreases postischemic functional deficit. Moreover, it induces endogenous neurogenesis.

CONCLUSION

So far, animal experiments provided considerable evidence suggesting that pharmacological intervention might lead to reconstruction CNS tissue based on stimulating endogenous stem cell activity. Such strategy would have an enormous impact on the current views of CNS diseases therapies. However, it still remains to be seen how data on neurogenesis obtained from rodent brain can be translated into human brains, and whether in the future we will be able to govern human neurogenesis in such a way that would enable replacement of the lost neurons and restore functional activity.

ACKNOWLEDGEMENT

This work was supported by MSHE grant 0154/B/P01/2010/38 and by the Mossakowski Medical Research Centre PAS in Warsaw from its statutory funds.

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