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SPECIAL ISSUE

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Adult neurogenesis: a compensatory mechanism for neuronal damage

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Abstract It is now evident that the adult vertebrate brain including the human brain is efficiently and continuously generating new neurons. In the first part we describe the current view of how neurons are generated in the adult brain and the possible compensatory reactions to pathological situations in which neuronal damage might stimulate neural stem cell activity. In the second part, we discuss the current knowledge on the signals and cells involved in the process of neurogenesis. This knowledge is important because any neuronal replacement strategy depends on our ability to induce or modulate each step on the way to a new neuron: stem cell proliferation, cell fate determination, progenitor migration, and differentiation into specific neuronal phenotypes. Identification of the molecular signals that control these events are essential for the application of neural stem cell biology to develop repair strategies for neurodegenerative disorders.

Key words Neural stem cells · Proliferation · Migration · Differentiation · Molecular

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Abbreviations

BrdU – 5-bromo-2'-deoxyuridine
EGF – epidermal growth factor
FGF-2 – fibroblast growth factor-2
IGF-1 – insulin-like growth factor-1

Introduction

During neural development, the nervous system is created from cells that have the potential to proliferate, to reproduce themselves, and to differentiate into the appropriate neuronal and glial phenotypes. Although the adult brain has classically been thought of as a structure with very limited regenerative capacity, these neural stem cells have recently been shown to exist in the adult central nervous system (CNS) as well. It is now evident that the adult brain is efficiently and continuously generating specific neuronal populations. These new neurons are generated in discrete areas of the adult brain and it is from these neurogenic regions that neural stem cells were first isolated, cloned and expanded in culture (Gage et al., 1995; Reynolds and Weiss, 1992). In vitro and following transplantation, these cells are able to generate neurons, astrocytes and oligodendrocytes, the three major CNS cell types (for a recent review see Gage, 2000). In vivo, a multitude of factors have been described in recent years, which appear to influence stem cells and adult neurogenesis. The following review describes the current view of how neurons are generated in the adult brain. It will focus on possible compensatory reactions to pathological situations in which neuronal damage might stimulate neural stem cell activity. Moreover, we will discuss the current knowledge on the signals and cells involved in the process of neurogenesis, because any neuronal replacement strategy for degenerative events depends on our ability to induce or modulate each step on the way to a new neuron: stem cell proliferation, cell fate determination, progenitor migration and differentiation into specific neuronal phenotypes.

Neuronal replacement in the adult brain

In the adult brain, there are two regions of active proliferation in mammals that generate neurons continuously throughout life. The subependymal zone of the adult lateral ventricle gives rise to new neurons and is seen as a residual proliferative zone left over from the embryonic neural tube. Precursors generated in the adult subependymal zone enter the rostral migratory stream, complete their last divisions, and continue to migrate into the olfactory bulb where they differentiate into new neurons (Lois and Alvarez-Buylla, 1994; Luskin, 1993; Menezes et al., 1995). It is important to note that two neuronal phenotypes are generated in the olfactory bulb, GABAergic granule cells and dopaminergic periglomerular interneurons (Betarbet et al., 1996; McLean and Shipley, 1988). Moreover, retroviral fate mapping studies confirmed that multipotent neural stem cells in ventricle wall generate also glial cells (Goldman, 1995; Morshead et al., 1998). Therefore, within specific regions of the adult brain, all signals are present for instructing stem cells to generate glia and neurons with specific neurotransmitter phenotypes.

The second area of neurogenesis is found in the hippocampus, a structure intimately involved in the processing and storage of new information. During development of the hippocampus, a secondary germinal zone, separate from the ventricle wall, is formed along the border between the hilus and the granule cell layer, i. e., the subgranule zone (Altman and Bayer, 1990). Here, the progeny of proliferating neural stem cells or progenitors migrate locally to differentiate into neurons of the dentate granule cell layer (Cameron et al., 1993). Neurogenesis in the dentate gyrus continues throughout life, but does display a steady decline from early postnatal days (Kuhn et al., 1996). Nevertheless, neurogenesis is still detectable in very old age, which opens the possibility of enhancing neurogenesis in the aged brain to study changes in the age-related decline in hippocampus-dependent learning (Kempermann et al., 1998 b).

With tens of thousands of neurons being born every day in the adult rodent brain, it becomes apparent that cells must also be lost to maintain the brain within the limited confines of the bony skull. A recent study has shown that apoptosis is a common feature in regions of neurogenesis (Biebl et al., 2000). Cell death is several-fold higher in neurogenic areas than in any other area of the brain. Cells apparently die during all phases of neurogenesis: stem cell proliferation, progenitor migration and neuronal differentiation. In spite of these losses, neuronal cell numbers in the olfactory bulb and the dentate gyrus continuously grow suggesting that production outweighs loss over the life of the animal (Bayer et al., 1982; Kaplan et al., 1985).

Discovered initially in rodents, the production of new neurons has also been confirmed for the adult primate brain. Although early attempts to detect neurogenesis in adult primates were hampered by insensitive detection methods (Rakic, 1985), several reports now demonstrate the neurogenesis continues in the primate dentate (Gould et al., 1999 b; Gould et al., 1998; Kornack and Rakic, 1999) and possibly in other areas of the neocortex (Gould et al., 1999 c). Work with terminally ill patients has recently confirmed that humans also generate new neurons. The proliferation marker bromodeoxyuridine (BrdU) was injected into patients to monitor tumor cell proliferation. Some of these individuals subsequently died from their illness and small samples of hippocampus were evaluated for the presence of BrdU-labeled neurons. Since the drug was systemically administered, all dividing cells would have been labeled and, indeed, newborn neurons were detected in the granule cell layer of all individuals (Eriksson et al., 1998). These data unequivocally show that neurogenesis is a common phenomenon across mammalian species.

Neurogenesis in reaction to pathological situations

The adult CNS is classically known as a structure with very limited regenerative capacity. In this respect the existence of neural stem cells in the brain is seen as a paradox, since multipotent cells in other organs are generally in charge of cellular replacement after physiological or disease-related degeneration, whereas in the adult brain spontaneous structural recovery is usually not observed. But some of the compensatory reactions to injury, which were previously thought to represent synaptic or functional plasticity, could very well have their origin in a limited neuronal replacement. In this context it is important to note that several pathological conditions, e. g. ischemia, epilepsy and trauma, have been shown to upregulate neural stem cell activity in the subventricular zone and the dentate gyrus.

When epileptic activity is induced in animal models a prominent induction of neurogenesis is observed in the dentate gyrus (Gray and Sundstrom, 1998; Nakagawa et al., 2000; Parent et al., 1998; Parent et al., 1997; Scott et al., 1998). This increase in neurogenesis is observed regardless of the mechanism for the induction of seizures (e. g., chemical or electrical stimulation). When protective strategies like "environmental enrichment", which stimulate neurogenesis, was combined with seizure induction, the intervention showed to be effective in preventing seizures and neuronal cell death (Young et al., 1999). Nevertheless not all epilepsy-related structural changes are linked to altered neurogenesis, since after seizure progenitor proliferation was inhibited by irradiation whereas the synaptic remodeling of the mossy fiber pathway was not altered (Parent et al., 1999).

Brain injury induced by traumatic lesions can cause a transient increase in the proliferation of stem cells of the ventricle wall (Reznikov, 1975; Szele and Chesselet, 1996; Tzeng and Wu, 1999), but these studies were not able to demonstrate any neuronal contribution of stem cells to the lesion site. Focal and global ischemia were

also shown to be potent in inducing neurogenesis in the dentate gyrus (Liu et al., 1998; Takagi et al., 1999) and protective mechanisms, e. g., glutamate receptor blockade, reduced ischemia-induced neuronal cell death and stem cell proliferation alike (Bernabeu and Sharp, 2000).

All lesion studies described so far have only observed increased stem cell proliferation or increased neurogenesis of dentate gyrus granule cells, but no induction of neuronal production was reported in areas most susceptible to cell death like the CA regions of the hippocampus or the cortex. However, several recent studies suggest that neurogenesis can be induced or observed to a limited degree in the neocortex. In a study by Gu and colleagues, a photothromboic stroke lesion was created in the rat to induce transient focal ischemia within a defined somatosensory cortical region. In this setting, spontaneous proliferation in the area-at-risk is observed followed by specific labeling of the newborn cells with neuronal markers (Gu et al., 2000). Stem cell proliferation was also induced by photolytic lesions of layer VI cortico-thalamic neurons in the anterior cortex of adult mice (Magavi et al., 2000). Here, it was not only shown that new nerve cells were generated but also that the newborn neurons were able to send proper axonal connections to their target area in the thalamus. More important for the application to the human brain, spontaneous neurogenesis was reported in several cortical areas of the adult primate CNS (Gould et al., 1999 c). Taken together, these data suggest that signals are present throughout the mammalian brain, which allow limited neuronal regeneration to occur. This fundamental observation could change our view on neurodegeneration and the brain's regenerative capacity, without giving us the immediate ability to regenerate large or complex brain areas. Nevertheless, besides pathological stimuli, a variety of factors can positively influence neurogenesis in the adult brain and these interventions, which are reviewed in the following, could prove useful for novel therapeutic strategies against neurodegeneration.

Systemic influence on neurogenesis

Neurogenesis in the adult brain appears to be a continuation of early postnatal neuronal production. In this sense, the development of such structures as the olfactory bulb or the dentate gyrus never ends, since neurogenesis can be observed into very late stages of life (Kuhn et al., 1996), even in primates and humans (Eriksson et al., 1998; Gould et al., 1999 b). Nevertheless, in both rodents and macaque monkeys, cell production in the dentate gyrus declines during aging (Gould et al., 1999 b; Kuhn et al., 1996) and the decreased neuronal replacement could very well be partially responsible for age-related decline of function. This becomes apparent from studies, which analyze the stimulatory effect of the environment on neurogenesis (Kempermann et al., 1998 a; Kempermann et al., 1997; Kempermann et al., 1998 b). "Enriched environment" paradigms, where animals are placed into housing conditions that are more similar to their natural surrounding, have been shown to increase neurogenesis by stimulating a better survival of the newly generated cells. The "enriched" animals also showed improved motor skills and better performance in learning tasks. Most importantly the stimulatory effect on neurogenesis occurred at all ages, including senescence, even when the animals were housed under enriched conditions for only a few weeks.

Among the stimulatory factors within an enriched environment, voluntary physical activity appears to be a very strong activator of the proliferation of hippocampal neural stem cells (van Praag et al., 1999). The sole introduction of a running wheel into a standard laboratory home cage doubled hippocampal neurogenesis, suggesting that physiological parameters, such as blood flow, glucose uptake, and neovascularization could be mediators of this effect. Moreover, another parameter of a more complex environment, a hippocampus-dependent learning task, also improved the survival of newborn cells when used as the single source of stimulation (Gould et al., 1999 a). These results underline the truth in the ancient Greek proverb that a healthy mind can only exist in a healthy body. Rehabilitation strategies for stroke or trauma patients emphasizing on a multitude of sensory stimuli, motor tasks and complex training situations have already incorporated the concept of stimulatory effects from an enriched environment.

Collectively, these observations demonstrate that cell proliferation in the dentate gyrus can be modulated by environmental signals and experience. But environmental signals can also be detrimental to the functioning of neurogenesis. Stressful experiences are known to activate the hypothalamic-pituitary adrenal (HPA) axis and increase levels of circulating adrenal steroids. Several different types of stressful experiences, such as exposure to predator odor, subordination stress and resident-intruder stress, have been shown to inhibit granule cell production in the dentate gyrus of rats, tree shrews and marmoset monkeys (Gould et al., 1997; Gould et al., 1998; Tanapat et al., 1998). It is likely that these changes in granule cell genesis are the result of stress-induced activation of the HPA axis and ultimately elevations in glucocorticoid levels. However, not only stressful experiences in adulthood influence proliferation and survival of neurons in the differentiated mammalian brain. Prenatal stress in rats and rhesus monkeys induced a life span reduction in neurogenesis in the dentate gyrus (Kramer et al., 2000; Lemaire et al., 2000). These data strengthen pathophysiological hypotheses that propose an early neurodevelopmental origin for psychopathological vulnerability in adulthood.

Molecular signals regulating neurogenesis

Several neuromodulatory factors that regulate neurogenesis in the adult dentate gyrus have been identified.

Glucocorticoid hormones such as cortisol and corticosterone secreted by the adrenal cortex have been shown to inhibit the production of new granule neurons by suppressing the proliferation of granule cell precursors. On the other hand, removal of circulating glucocorticoids by adrenalectomy results in a clear increase in neurogenesis in the dentate gyrus of young adult rats (Cameron and Gould, 1994). In contrast to the suppressive effects of glucocorticoids on cell proliferation, the ovarian steroid estrogen has been shown to stimulate the proliferation of granule cell precursors in the dentate gyrus of adult female rats. This increase in the rate of cell proliferation occurs naturally across the rat estrous cycle, with maximal levels of cell production during proestrus, a time when estrogen levels are highest (Tanapat et al., 1999). This finding raises the interesting question about the mechanisms that mediate the survival of newly generated cells in females as well as in males.

Neural mechanisms have also been demonstrated to alter the production of granule cells in the dentate gyrus. Glutamatergic input to the dentate gyrus via the perforant path appears to suppress the proliferation of granule cell precursors. Lesion of the entorhinal cortex, the origin of the perforant path, or treatment with NMDA receptor antagonists stimulate the proliferation of granule cell precursors and the production of new granule cells. In contrast, treatment with NMDA receptor agonists inhibits cell proliferation in the dentate gyrus (Cameron et al., 1995). Interestingly, temporal lobe seizures produced by kainate or kindling resulted in a dramatic increase in proliferation. Detailed histological investigations demonstrated that the newborn neurons formed aberrant connections and did not extend neurits along the mossy fiber pathway to CA3 (Parent et al., 1997).

Recent evidence supports the view that other neurotransmitter systems influence the production of new granule neurons in the dentate gyrus. For example, serotonin may stimulate granule cell production (Gould, 1999), whereas depletion of serotonin reduces neurogenesis (Brezun and Daszuta, 1999). Therapeutic interventions, such as treatment with the antidepressant fluoxentine, that act on the serotonergic system augmented neurogenesis (Jacobs et al., 2000). In line with the growing body of evidence suggesting that mood stabilizers and antidepressants exert neurotrophic effects is a recent report that lithium treatment positively affected neurogenesis in mice (Chen et al., 2000).

Although these neuromodulatory signals trigger proliferation, the direct mitogenic stimulus to the progenitor cells appears to be mediated via growth factors. Dentate precursor cells are known to express EGF receptors and direct infusion of the growth factor into the dentate gyrus stimulates proliferation (Tanapat and Gould, 1997). Chronic infusion of EGF in the ventricular system of adult rats triggered neurogenesis predominately in the subventricular zone but was nearly ineffective in stimulating proliferation in the subgranular zone (Kuhn et al., 1997). Nevertheless, when using this route of administration, EGF induced a prominent phenotypic shift leading to more astrocytes and fewer neurons. Via peripheral application, selective induction of neurogenesis has also been achieved using FGF–2 (Wagner et al., 1999) or IGF–1 (Aberg et al., 2000). It is yet unclear whether growth factors can pass directly through the blood-brain barrier or whether other mechanisms such as angiogenesis are triggered, which have a secondary positive effect on neurogenesis.

Origin of neural stem cells

It has been assumed that the lateral ventricle wall of the adult brain harbors both the neural stem cells and the transient amplifying progenitor cells. Two recent reports suggest opposing views of which cell type within the ventricle wall assumes neural stem cell properties. One hypothesis proposes that ependymal cells could act as the neural stem cells (Johansson et al., 1999). This cell population is generally homogeneous and is characterized by the presence of cilia. One function of these ciliated cells is to circulate the cerebrospinal fluid around the ventricles, but a stem cell status has not been previously suggested. The study shows that isolated ependymal cells can produce neural stem cell cultures, suggesting that, in vivo, slowly dividing ependymal stem cells give rise to more rapidly dividing and migratory subependymal neural progenitor cells. A second study favors a specialized glia-like cell of the subependymal zone to have stem cell characteristics (Doetsch et al., 1999). These cells express the glial fibrillary acidic protein and the neural progenitor marker nestin and appear to be actively involved in regenerating the neurogenic activity of the ventricle wall after cytotoxic damage.

One problem with both models is the observation that many regions of the adult CNS, away from the ventricle system, are capable of generating neural stem cell cultures as well (Palmer et al., 1995). Even from the optic nerve, a structure that is devoid of neuronal cell bodies, neural stem cell cultures can be established (Palmer et al., 1999). It is, therefore, likely that an immature glial progenitor cell may retain the capacity to also undergo differentiation into neuronal phenotypes depending on the environmental cues (Kondo and Raff, 2000; Laywell et al., 2000). These cues seem to be preserved only in certain areas of the adult brain, which sustain continuous neurogenesis, but other brain regions may have the ability to upregulate signals for glial cells to enter a latent neurogenesis program upon lesion (Gu et al., 2000; Magavi et al., 2000).

The vascular niche

In an unperturbed rodent brain, neurogenesis is strictly limited to the hippocampus and the ventricle wall. Other areas of the brain contain an abundant population of

proliferative precursors but these cells only generate glia. The most common assumption is that neurogenic zones are defined by the location of the neural stem cells in the adult. However, this may not be true. Immature progenitors in white matter generate oligodendrocytes in vivo and in vitro (Horner et al., 2000; Wolswijk and Noble, 1992) but recent studies show that these "glial" progenitors can actually make neurons in culture if treated with the appropriate growth factors (Kondo and Raff, 2000; Palmer et al., 1999). This implies that the local environment, not the distribution of cells, is the key factor in defining where neurons are made.

A stem cell may "see" quite unique local environments depending on where it resides and it would react appropriately to the local signals being produced by neighboring cells. In the hippocampus, the stem cell neighbors include other precursors, glia, granule cell neurons and, surprisingly, vascular endothelium (Palmer et al., 2000). Work recently published shows that the neural stem/progenitor cells in the hippocampal subgranular zone proliferate in small clusters and that these clusters are located around the periphery of small capillaries. Dividing endothelium are found within the core of many proliferating clusters and this angiogenic microenvironment appears to be relatively unique to the hippocampal subgranular zone and the ventricular subependymal zone. Precursors in white matter do not associate with vessels and it is possible, though not yet shown, that this vascular environment provides some of the cues necessary for stem cells to generate neurons. The association of the hippocampal precursor with the vasculature also raises a second issue that has recently received considerable attention. It appears that stem-like cells from bone marrow have the potential to generate neurons in vitro (Sanchez-Ramos et al., 2000; Woodbury et al., 2000) and some of these cells actually migrate into the brain following a traditional bone marrow transplant (Brazelton et al., 2000; Mezey et al., 2000). The suspicious association of the hippocampal precursors with an area of angiogenesis implies that some of these granule cell precursors may actually come from the periphery. This speculation may not stand the test of time but if true, these "neural" stem cells may represent very immature circulating stem cells that alter their genetic program once resident within the hippocampus or the ventricle wall.

Outlook

The field of neural stem cells and adult neurogenesis is undergoing a fast development from the first studies of neural stem cell isolation in the early 1990s to a multitude of studies showing that neurogenesis can be augmented in the brain through a variety of stimuli. Neurogenesis persists in several areas of the adult mammalian brain including humans and we can therefore assume that the adult CNS can provide all stimuli and cellular elements for successful production of new neurons. Moreover, the therapeutic value of stem cell transplantation is currently assessed in animal models of neurodegeneration and first studies point towards a fast application of stem cell therapy to the clinical setting (for a recent review see Armstrong and Svendsen, 2000).

The in vitro data on neuronal differentiation from glial sources point towards the presence of a glial progenitor cell throughout the nervous system with the potential of neuronal differentiation. This provides at the same time the positive aspect of being able to generate neural stem cells from biopsy material for autologous transplantation but also the difficulty of having to find specific signals in order to assure proper neuronal differentiation.

Another aspect of stem cell biology is the emerging view that individual organ-specific stem cells share overlapping fate potentials and are able to transdifferentiate into cells specific for numerous organ systems. This has been demonstrated for neural and hematopoietic stem cells (Bjornson et al., 1999; Brazelton et al., 2000; Mezey et al., 2000) and may be true for stem cells in other organs as well. This leaves several questions open regarding the nature of adult stem cells. Are we, perhaps, dealing with a circulating multipotent stem cell which has the ability to home to individual organs? For neurological research these findings have several implications. Not only could a peripheral cell be used as a source for the generation of new neurons, but a new route of cellular therapy via the blood stream might also be employed.

The ability to generate neural stem cells from several tissue sources will shift the focus to the even larger challenge of generating all the neuronal cell types needed under specific pathological conditions. These neurons not only require individual neurotransmitter phenotypes but also very specific axonal and dendritic connections. It will therefore be essential to study the underlying molecular mechanisms of how neuronal precursors orient, move and establish synaptic contacts and how these newly generated neurons influence the functioning of the fully differentiated brain. We have learned from the adult brain the surprising fact that signals for "complete" neuronal replacement persist throughout life. Even neurons considered to be relatively immutable, i. e., corticothalamic neurons, can be faithfully reproduced by neural precursors within the adult (Magavi et al., 2000). Discovering the molecular signals that control these and other spontaneous regenerative events will be essential for the application of neural stem cell biology to repair strategies for neurodegeneration.

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