Neurogenesis as a therapeutic strategy to regenerate the central nervous system

O. Arias-Carrión [a], R. Drucker-Colín [b]

NEUROGENESIS AS A THERAPEUTIC STRATEGY TO REGENERATE CENTRAL NERVOUS SYSTEM

Summary. Introduction. *In the past few years, it has been demonstrated that the adult mammalian brain maintains the capacity to generate new neurons from neural stem/progenitor cells. These new neurons integrate into pre-existing systems through a process referred to as 'neurogenesis in the adult brain'.* Development. *This discovery has modified our understanding of how the central nervous system functions in health and disease. Until today, a great effort has been made attempting to decipher the mechanisms regulating adult neurogenesis, which might help to induce neuronal endogenous cell replacement in various neurological diseases.* Conclusions. *In this revision, we will attempt to shed some light on the neurogenesis process with respect to diseases of the central nervous system and we will describe some therapeutic potentials in relation to neurodegenerative diseases. [REV NEUROL 2007; 45: 739-45]*

Key words. *Adult neurogenesis. Neurodegenerative diseases. Progenitor. Regeneration. Stem cell. Transplantation.*

INTRODUCTION

Since Ramón y Cajal, neuroscience had maintained the concept that the adult mammalian brain was one sophisticated organ, condemned to an inevitable temporal gradient, incapable of generating new neurons or regenerate them after a lesion [1]. In the last decade, the presence of neurogenesis in the adult mammalian brain, including the human brain, has repeatedly been demonstrated [2-4]. This discovery has modified our understanding of how the central nervous system (CNS) functions in health and disease. Neurogenesis, a process which involves the generation of new neurons, has been shown in the hippocampus and in the olfactory bulb of adult mammalians [4]. The primary precursors have been identified in specialized zones called 'neurogenic niches'. A population of neural stem/progenitor cells (NSCs) preserve enough embryonic character to maintain neurogenesis throughout life. Once they have differentiated, they integrate into the already existing neuronal networks [3,4]. This capacity of the adult brain has stimulated a huge interest in view of its potential therapeutic applications in several neurological diseases.

The NSCs maintain the capacity of auto-renovation (a characteristic of stem cells), though until today, it has only shown to be able to develop specific cells (astrocytes, oligodendrocytes and neurons) [2]. For this reason, the endogenous manipulation of the NSCs or the transplantation of derived differentiated adult NSCs, represents a possibility to replace the neurons which degenerated in Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD) and multiple sclerosis (MS) [5-8]. Therefore it is necessary to understand the mechanisms by which the brain becomes diseased and at the same time, to understand the factors that regulate neurogenesis in the adult brain. All this allows to envision an ample series of strategies for replacing lost neurons in neurodegenerative diseases. Until today, one of the most ambitious projects pretends to increase the proliferation in neurogenic zones in the adult brain, favoring cell migration of NSCs into the damaged area, inducing then, their differentiation into specific cellular types which could integrate and survive in the pre-existing networks and cause functional recovery.

In this revision, we will shed some light on neurogenesis, which occurs as a result of different lesions of the CNS as well as discussing the therapeutic potential of adult NSCs in neurodegenerative diseases.

NEUROGENIC MICROENVIRONMENT IN THE ADULT BRAIN

During the postnatal stage and adult life, on various species it has been demonstrated that new neurons continue to be generated in the subventricular zone (SVZ) and in the dentate gyrus subgranular zone (SGZ) of the hippocampus [4]. The new neurons integrate in the pre-existing networks by means of a process named 'neurogenesis in the adult brain'. The neurogenesis which is present in these areas, shares some characteristics with the neurogenesis occurring during the embryonic and postnatal development, including: proliferation of NSCs, specific target of the cells which proliferate, migration, neuronal maturation and synapse formation.

Areas outside these two neurogenic niches have been dubbed 'non-neurogenic', but within them, NSCs proliferate and contribute to gliogenesis (the production of glial cells). However, under pathological conditions or in *in vitro* studies, these NSCs are capable to produce neurons as well as glia, which suggests that there are NSCs with neurogenic potential in other areas of the adult CNS [4,9,10].

In the hippocampus, NSCs can be localized in the SGZ, between the *hilus* and the granular layer of the dentate gyrus (Fig. 1c).

Accepted: 21.09.07.

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Acknowledgements. The authors would like to thank Julia Schaper and Teresa Torres-Peralta for editing the manuscript and Marcela Palomero-Rivero for the excellent technical support.

This work was supported by grants of the CONACYT, DGEP y DAAD postdoctoral fellowship to OAC, fideicomiso UNAM to RDC and IMPULSA-UNAM.

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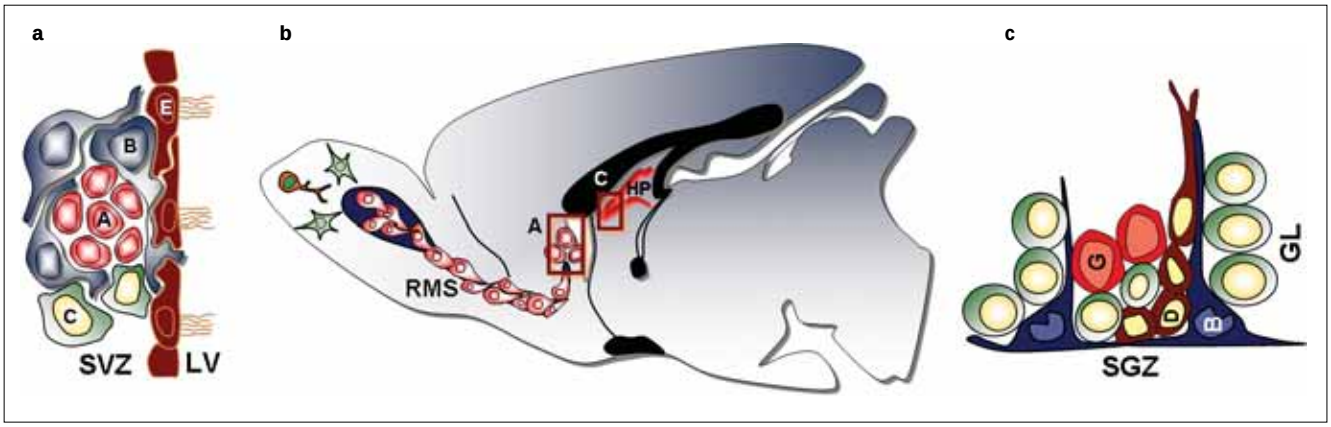

Figure 1. Neurogenesis in the adult brain: a) Anatomy of the subventricular zone (SVZ) is shown at higher magnification. Schematic drawing of the composition and cytoarchitecture of the adult rodent SVZ. Type B cells (blue) are specialized astrocytes that serve as neuronal stem cells in the SVZ. Type C cells (green), derived from the B cells. Type C cells give rise to Type A cells (red). These cells are separated from the lateral ventricles (LV) by a monolayer of ependymal cells (brown); b) Sagittal view of a rodent brain showing the sites of neurogenesis in the SVZ/olfactory bulb (OB) system. Cells proliferate mainly in the SVZ and migrate along the rostral migratory stream (RMS) to reach the OB; c) Architecture of the subgranular zone (SGZ). Astrocytes (blue) give rise to progenitors (D cells, brown) and generate G cells (red, new granule cells). The newly cells integrate into the dentate gyrus granule cell layer (GL).

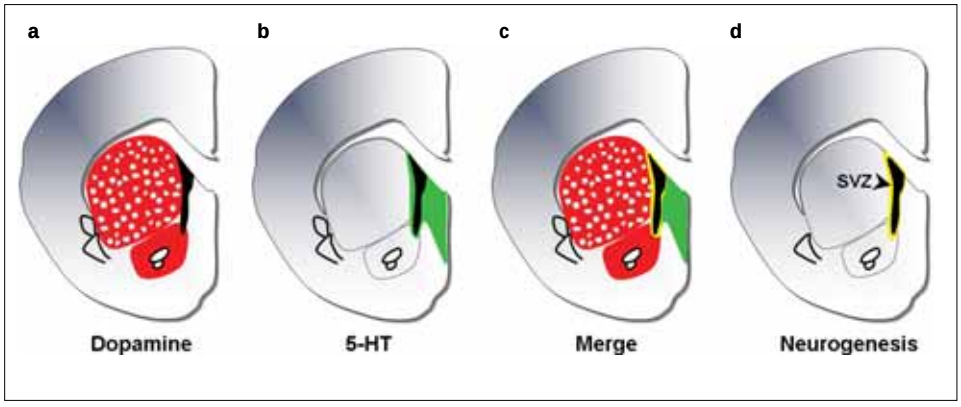

Figure 2. Neurogenesis in adult subventricular zone (SBZ). The figure illustrates two of the most important neurotransmitters in the brain. The dopaminergic (a) and serotoninergic projections (b) intersect at the SVZ (c). This suggests the cooperation of the two neurotransmitters to generate this neurogenic niche in the adult brain of rodents (d).

Type B cells (radial astrocytes) proliferate and generate type D cells (neuroblasts), which migrate a short distance in order to differentiate into granule neurons [11, 12]. These new neurons develop axons and neuritic processes, which integrate synaptically 2-4 weeks later [12].

In the lateral ventricles, the adult NSCs (type B cells) persist in the SVZ, a region localized close to the ependymal cells (Fig. 1a). These cells proliferate and generate neuroblasts (type A cells) [4]. Type A cells migrate through the rostral migratory stream (RMS) to the olfactory bulb, where they differentiate into two types of interneurons: granule cells and periglomerular cells (Fig. 1b). Recently, this process has been described in the human brain [13,14].

Neurogenesis in the adult brain is a dynamic process influenced by factors like: growth, neurotransmitters, pathological conditions, lesions and external stimuli [3,4]. Studies *in vivo* have revealed that NSCs respond to numerous physiological and pathological conditions, including: epilepsy [15,16], ischemia [17-19], depression [20], enriched environments [21], neurodegenerative diseases [3] and exercise [21].

The cellular and molecular mechanisms which regulate neurogenesis in the adult brain are still unknown [12]. The anatomical and histological properties of neurogenic niches seem to play an essential role in the regulation of adult NSCs due to their proximity to endothelial cells [22], capillaries [23], astrocytes [24-26] and ependymal cells [27].

In addition, various growth factors regulate the cell cycle of the NSCs, including the epidermal growth factor (EGF), the fibroblast growth factor (FGF-2) and the *Sonic hedgehog* (Shh) [11]. Various molecules which regulate the specification of NSCs have also been reported, such as the bone morphogenic protein (BMP), which promotes gliogenesis *in vitro* and in vivo [27]. The secreted noggin of the SVZ and the neurogenesin-1 of the SGZ act like antagonists of the BMP, which means that these factors participate in the generation of neurogenic niches [27,28]. Wnt, which is secreted by the astrocytes of the adult neurogenic areas, promote the proliferation of neuroblasts and regulates the neuronal specification [29]. If the Wnt is inhibited, neurogenesis in the hippocampus is reduced significantly. On the other hand, over-expression of Wnt-3 increases it. Retinoic acid is an important factor of neuronal differentiation and shares signalling pathways with Wnt. It has also been demonstrated that it participates in the generation of neurogenic niches in the adult brain [30].

Recently, the participation of various neurotransmitters as factors, which regulate the proliferation, migration, neuronal maturation and synaptic integration has been described (Fig. 2). Among the most frequently studied transmitters are: glutamate, GABA and monoamines such as serotonin (5-HT), noradrenaline and dopamine [4].

NEUROGENESIS AND NEURODEGENERATIVE DISEASES

Recent evidence has promoted the idea that new neurons con-

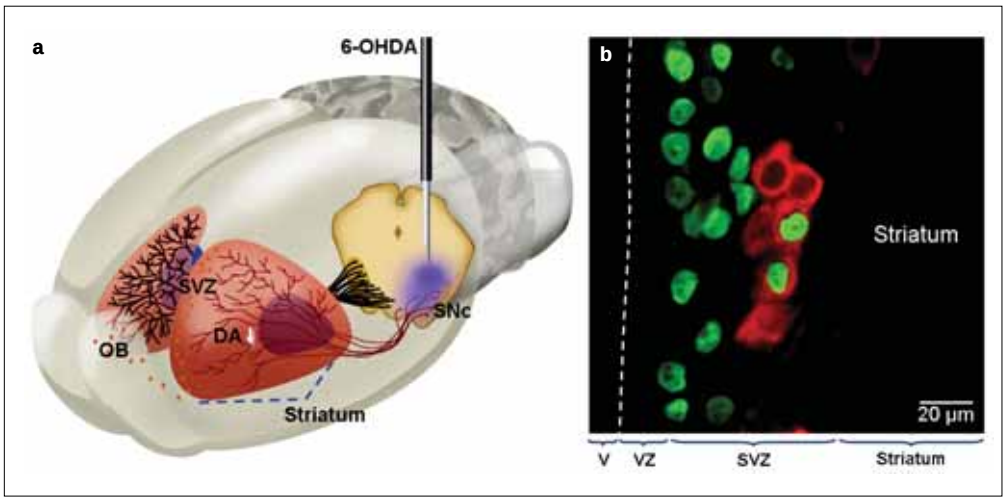

Figure 3. Dopamine and adult neurogenesis: a) In the 6-OHDA animal model of Parkinson's disease, the nigral dopaminergic neurons are destroyed unilaterally by means of a stereotactic injection of the toxin, as indicated by the needle. The consecutive depletion of dopamine in the striatum leads to a decreased proliferation of progenitor cells in the SVZ; b) New dopaminergic neurons in the SVZ. Confocal micrograph obtained from the SVZ of a rat with SNc-lesion and intrastriatal transplant of chromaffin cells. Some nucleus marked with BrdU (green) colocalize with the cytoplasmatic TH (red).

tinue being generated in the adult mammalian brain. The functional significance of the new neurons is still under investigation. However, some surprising results suggest that new neurons are integrated in the adult brain and participate in different cognitive processes [12,31-35]. On the other hand, different reports indicate that a significant reduction in the rate of neurogenesis in the adult brain is possibly implicated in the physiopathology of different neurodegenerative diseases [3].

Parkinson's disease

In PD, dopaminergic neurons of the substantia nigra (SNc) are degenerated, which results in a deficit of dopamine in the projection areas (mainly the caudate nucleus and putamen) [36]. By experimentally inducing dopamine depletion in rodents through intracerebral administration of the toxin 6-hydroxidopamine (6-OHDA), a decrease of cell proliferation in the SVZ and SGZ can be observed (Fig. 3a) [37]. This response is prevented with ropinirole; an agonist of D_2 receptors. The cellular proliferation in the SVZ and the number of NSCs in the dentate gyrus and the olfactory bulb are diminished in *post mortem* brains of individuals presenting PD [37]. These observations suggest that dopamine is one of the factors that regulate the neurogenesis rate in the adult mammalian brain, including the human one (Fig. 2a).

On the other hand, there are contradictory experimental evidences which indicate that the adult SNc maintains some sort of repair mechanisms [38]. In such paper, Zhao et al showed that dying dopaminergic neurons are replaced at a very low frequency (20 new cells per day). This replacing rate doubles when the dopaminergic system is lesioned using the neurotoxin 1-metil-4-fenil-1,2,3,6-tetrahidropyridine (MPTP). It has to be mentioned that these results have not been reproduced by other authors [39]. However, if neurogenesis is present in the human CNS, it would have important clinical applications, specially in cell replacement strategies and in PD pathogenesis. The evolution of this disorder might be determined not only by the degeneration rate of dopaminergic neurons of the SNc, but also by the generation of new neurons [38].

On the other hand, the neuronal precursors which are generated in the SVZ migrate through the RMS to replace interneurons in the olfactory bulb. However, it has been shown recently that in response to a lesion of the SNc, some precursors which proliferate in the SVZ (identified by a thymidine analogue) differentiate *in situ* into tyrosine hydroxylase-positive (TH +) cells, TH being the limiting enzyme in the synthesis of catecholamines. This process increases in presence of transplants of chromaffin cells in the denervated striatum and/or transcranial magnetic stimulation (Fig. 3b) [7]. In addition, it has been shown that no TH+ cell was immunoreactive to GFAP (a glial cell marker), that 60% of the TH+ cells expressed NeuN (a neuronal marker) and that 45% of the TH+ cells were co-localized with the dopamine transporter (DAT). In an additional study, functional properties of TH+ cells generated in the SVZ were examined [8]. Under whole-cell patchclamp, most SVZ cells recorded from lesioned and grafted animals were non-excitable (Fig. 4d). Nevertheless, a small percentage of SVZ dopaminergic-like cells showed the electrophysiological properties of mature dopaminergic neurons and presented spontaneous postsynaptic potentials (Fig. 4h). Also, dopamine (DA) release was measured in the SVZ and striatum from both control and SNc-lesioned rats. As expected, 12 weeks after SNc lesion, DA release decreased drastically. Nevertheless, 8 weeks after chromaffin cells grafts, release from the SVZ of SNc-lesioned rats recovered and even surpassed that of control SVZ, suggesting that newly formed SVZ dopaminergic-like cells release DA [8]. This study shows for the first time that in response to SNc-lesions and chromaffin cells grafts, neural precursors within the SVZ change their developmental program, by not only expressing tyrosine hydroxylase (TH) and neuronal markers, but more importantly by acquiring excitable properties of mature dopaminergic neurons. Additionally, the release of DA in a Ca^{2+}-dependent manner and the attraction of synaptic afferents from neighboring neuronal networks give further significance to the overall findings, whose potential importance is as yet unknown.

Alzheimer's disease

Alzheimer's disease is a progressive neurodegenerative disorder. The brain regions which are associated with superior mental functions, particularly the neocortex and the hippocampus are the most affected areas. Histologically, it is characterized by senile plaques containing deposits of β-amyloid peptide (Aβ), and by the intracellular formation of neurofibrillary tangles of hyperphosphorylated tau. Moreover, the loss of synapses and pyramidal neurons has been demonstrated.

In vitro studies indicate that the administration of Aβ reduces the proliferation of NSCs obtained from the SVZ and the

dentate gyrus [40,41]. However, in *post mortem* studies, an increase in the neurogenesis of the hippocampus in the brains of patients with AD has been reported [42]. So far, the molecular factors which regulate the neurogenesis in this disease is unknown. Based on these results, it is suggested that there are other factors besides the Aβ that regulate the neurogenesis in AD [40,42].

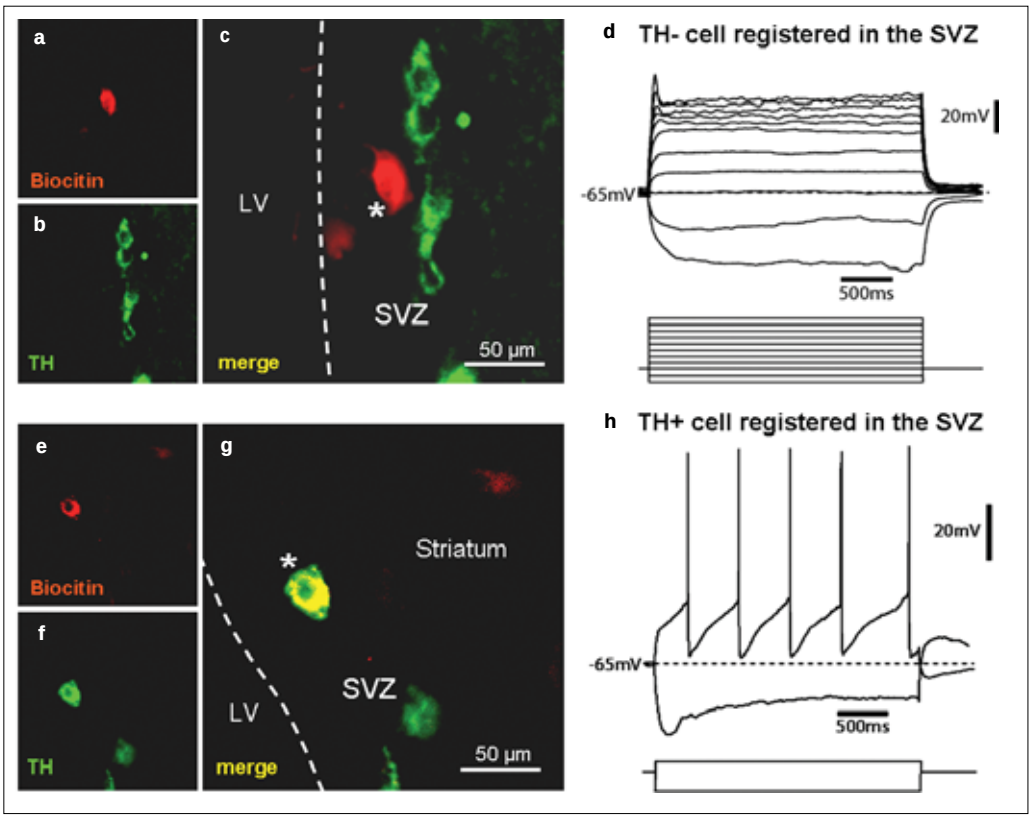

Figure 4. New dopaminergic neurons in the SVZ: a-c) TH– cell registered in the SVZ; d) The majority of SVZ cells recorded were non-excitable. A small, rudimentary spike was recorded occasionally, a characteristic of adult NSCs; e-g) TH+ cell registered in the SVZ; h) A minority of SVZ TH+ cells recorded were excitable and exhibited electrophysiologic responses similar to dopaminergic neurons, such as low frequency tonic firing on membrane depolarization, a sag after hyperpolarizing current injection and a rebound depolarizing hump after the end of the hyperpolarizing current pulse (modified from [8]).

Huntington's disease

Huntington's disease (HD) is a neurodegenerative disorder which affects the striatum, cortex and hippocampus. These alterations are responsible for the movement disorders (chorea and rigidity), cognitive disorders and psychiatric alterations which are manifested by patients with this disease. It is inherited with a dominant autosomic character, due to a mutation in the Huntingtin gene (a protein with an unknown function) [43]. In a *postmortem* study realized on brains of patients which HD, an increase in the cellular proliferation in the SVZ has been reported [44]. So far, it is unknown whether this increase of the neurogenesis rate has functional implications.

Multiple sclerosis

MS is a demyelinating and neurodegenerative disease of the CNS. It is, after epilepsy, the most frequent neurological disease among young adults. Until now, there is no treatment and its ethiopathology is unknown. Because of its effects on the CNS, patients suffer reduced mobility and in the most severe cases, patients become invalids. It has been suggested that autoimmune mechanisms operate in its natural history. In experimental models, it has been observed that by inducing the demyelination, the number of NSCs in the SVZ is increased [45-47]. Recently, a *post mortem* study reports that this process is also observed in brains of patients suffering this disease. In the same study, oligodendrogenesis (generation of new oligodendrocytes) has been reported in response to the degeneration [48].

NEUROGENESIS IN OTHER NEUROLOGICAL DISEASES

Inflammatory processes

It has been demonstrated experimentally that various inflammatory processes in the adult brain, reduce proliferation rate in the hippocampus [49,50]. Studies indicate that this effect is due to the microglial cell activation, which is mediated by cytokines, such as interleukin-6 (IL-6) [49,50]. It has also been shown that when the activation of the microglia is inhibited with minocycline [51] or indomethacin [50], the neurogenesis of the hippocampus is restored during the inflammatory process. The neuroinflammation and the microglial activation have been associated with the pathogenesis of different neurodegenerative diseases, and therefore, the coadjuvant treatment with anti-inflammatories represents a new therapeutic strategy.

Epilepsy

The epileptic seizures, induced by various experimental manipulations (pilocarpine, kainic acid), increase the neurogenesis in the SGZ [49,52-54] and in the RMS of the system SVZ-olfactory bulb [55]. However, the factors inducing neurogenesis in the epileptic brain have not been identified and so far, it is unknown whether it has pathologic or regenerative implications. As a result of epileptic seizures, the new cells participate in the abnormal reorganization of the neuronal networks in the hippocampus [53]. In addition, an ectopic location of newly generated neurons has been observed and located in the *hilus* and the internal molecular layer [56]. These ectopic cells present electrophysiological [56,57] and abnormal morphological properties [58]. These results suggest that neurons which are generated in response to the epileptic status do not contribute to the regeneration of the neuronal network but do possibly generate new seizures. Moreover, the neurological deficit which is observed

after the epileptic status, might be associated which the aberrant circuits that operates it [55,59].

Cerebral ischemia

It has been demonstrated that cerebral ischemia increases neurogenesis both in the SGZ and in the SVZ of the adult brain [60,62]. This increase has been associated with the activation of the NMDA receptor [63]. The neuronal precursors of the SVZ migrate to the ischemic zone of the adjacent striatum [61,62] and through the RMS and the lateral cortical stream to the ischemic zone of the cerebral cortex where the damaged neurons are differentiated and replaced [60].

THERAPEUTIC POTENTIAL OF THE ADULT NSCs

In neurodegenerative diseases, a specific loss of cells is responsible for the psychiatric and neurological symptoms, present in the patients. Therefore, the idea of replacing missing or damaged cells is very attractive [64-67]. However, the adult brain is a major challenge for cell therapy. In this complex organ, implanted cells have to be capable not only to survive, but also to integrate in the pre-existing networks.

The loss of dopaminergic neurons of the SNc is a predominant characteristic of PD. Therefore, embryonic tissue of this region, which is rich in dopaminergic neuroblasts, as well as differentiated chromaffin cells which produce dopamine have been implanted in the striatum of patients with this disease [5,64,67]. These clinical attempts support the strategy of using cell replacement in the human brain. The results, however, though encouraging are fraught with problems of various sorts. Therefore, the development of techniques to expand the adult NSCs is a possible solution. These stem cells can be cultured in laboratories for long periods and can be differentiated in neurons or glia when required [5,6].

The cellular replacement is based on a series of studies on animal models, which have demonstrated that the implant of embryonic neuronal tissue restores the levels of dopamine in the striatum and can lead to a lasting functional recovery [5,64]. Clinical studies have shown that implanted dopaminergic neurons can survive and re-innervate the striatum for at least 10 years, despite the continuous neurodegeneration [5,64]. Functional studies have shown that transplanted cells release dopamine in the striatum, which possibly restores the frontal-cortex activation associated with movements [5,64].

Nevertheless, although some patients show clinical improvement, there is a great variability of results, since many patients have shown only modest improvements or none at all. Involuntary inappropriate movements, also called dyskinesias, have occurred in 7-15% of the patients with grafts [5], though there is no evidence that these dyskinesias are caused by dopaminergic growth or that they are a general characteristics of the replacement of dopaminergic cells *per se.*

In vitro and *in vivo* studies have shown that embryonic stem cells, as well as adult NSCs are able to differentiate into dopaminergic neurons [5-8], However, it is not clear, to what extend these cells are capable of restoring the neuronal circuits that are lost in the PD and will eliminate the symptoms of the disease [7,8].

In the case of MS, a condition in which the oligodendrocytes are degenerated, this translates into sensory and motor impairment as a result of demyelinization of axons. Recently, in an experimental model of genetically induced demyelinization, the capacity of the adult NSCs was determined by differentiating into oligodendrocytes [68]. In this study, neurospheres (adult NSCs from the SVZ) were injected intravenously and intrathecally and resulted in re myelinization both in the brain and in the spinal cord.

Due to its incidence and cost, brain-vascular accidents are one of the most important objects of cell therapy. Recent investigations have suggested some endogenous neuronal replacement in response to ischemia [60-63]. However, its therapeutic implication was not shown, therefore protocols of exogenous transplant continue to be attempted using adult NSCs. These cells should have the capacity to respond to ischemia, in addition to regenerating the microenvironment. The NSCs transplant in animal models has had some positive results, including studies in humans using some tumoral cell lines as a source [5,69,70].

These diseases have not been the only ones in which transplant studies with adult NSCs have been carried out; there are also reports with HD [71,72], epilepsy [5,67,73] as well as in normal brains with kainic acid injury in the cortex, striatum and olfactory bulb [74]. So far, promising results were obtained in different experimental models. Nevertheless, one cannot benefit properly from the cell therapy, if the adult brain does not preserve its regenerative capacity. It does not matter how many cells can be generated in the laboratory, it all would be irrelevant, if the brain does not accept them. The experimental evidences of this revision suggest that the adult NSCs participate in neuronal regeneration in response to different CNS lesions, and thus their therapeutic potential has to be considered.

CONCLUSIONS

To date, experimental evidence has permitted to identify some mechanisms which regulate neurogenesis in the normal adult brain as well as in response to various pathologies. Paradoxically, some signalling mechanisms which are present in the embryo remain in the adult neurogenic niches. However, the cell integration ability, the cell-cell communication and the properties of the extracellular matrix make it difficult for the neurons, which are newly generated by the adult brain, to integrate synaptically into the already existing neuronal networks. Therefore, in order to develop new therapeutic strategies based on the modulation of adult neurogenic niches, it is necessary to understand these microenvironments, as well as its systemic regulation. The overall comprehension could produce new general therapeutic strategies in order to tackle various neurodegenerative diseases and CNS disorders.

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NEUROGÉNESIS COMO ESTRATEGIA TERAPÉUTICA PARA REGENERAR EL SISTEMA NERVIOSO CENTRAL

Resumen. Introducción. *La investigación generada en los últimos años ha demostrado que el cerebro adulto de mamíferos mantiene la capacidad de generar nuevas neuronas a partir de células troncales/progenitoras neuronales. Las nuevas neuronas se integran a las redes preexistentes a través de un proceso denominado 'neurogénesis en el cerebro adulto'.* Desarrollo. *Este descubrimiento ha modificado nuestra comprensión de cómo el sistema nervioso central funciona en la salud y en la enfermedad. Hasta ahora se ha realizado un gran esfuerzo para descifrar los mecanismos que regulan la neurogénesis en el adulto, lo cual puede permitir realizar un reemplazo neuronal endógeno en diversos trastornos neurológicos.* Conclusiones. *Esta revisión se centra en la neurogénesis que se presenta en respuesta a trastornos del sistema nervioso central y aborda su potencial terapéutico en las enfermedades neurodegenerativas. [REV NEUROL 2007; 45: 739-45]*
Palabras clave. *Célula progenitora. Enfermedades neurodegenerativas. Neurogénesis. Regeneración neuronal. Trasplante.*