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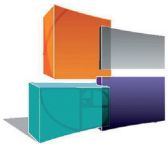

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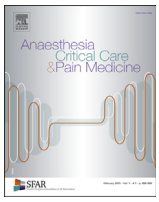

Review

# Adult neurogenesis and brain remodelling after brain injury: From bench to bedside?

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ABSTRACT

*Objective:* Brain trauma and stroke cause important disabilities. The mechanisms involved are now well described, but all therapeutics developed thus far for neuro-protection are currently unsuccessful at improving neurologic prognosis. The recently studied neuro-restorative time following brain injury may point towards a promising therapeutic approach. The purpose of this paper is to explain the mechanisms of this revolutionary concept, give an overview of related knowledge and discuss its transfer into clinical practice.
*Data sources and synthesis:* An overview of the neurogenesis concept using MEDLINE, EMBASE and CENTRAL databases was carried out in May 2014. The clinicaltrials.gov registry was used to search for ongoing clinical trials in this domain.
*Conclusion:* The concept of brain remodelling upset fundamental ideas concerning the neurologic system and opened new fields of research. Therapies currently under evaluation hold promising results and could have a real prognostic impact in future years, but the translation of these therapies from the laboratory to the clinic is still far from completion.


## 1. Introduction

The incidences of stroke and brain trauma have been estimated in the US at 750,000 [1] and 1.5 million per year [2], respectively. Brain damage related to these cerebral pathologies represents a major cause of mortality, morbidity, cognitive impairment and learning disability. The loss of autonomy in public health is dramatic with a median disability-adjusted life year (DALY) of 781 per 100,000 habitants [1]. A better understanding of the mechanisms involved in brain damage is necessary to improve therapy. It is established that excitotoxicity, apoptosis, inflammation and oxidative stress develop after stroke or brain trauma [3]. Unfortunately, neuro-protective therapy focused on these different mechanisms fails to improve functional recovery.

Beyond this neurodegenerative step, a promising neuro-restorative period has recently been discovered based on complex biochemical and micro-cellular mechanisms that develop in viable tissue. This endogenous remodelling of the cerebral nervous system (CNS) is not sufficient to restore neurological function, but stimulation of the pathways involved could be a promising approach. We briefly summarize the endogenous mechanisms involved in this process and review some different potential therapies, which could improve this restorative mechanism.

## 2. The birth of a new concept: adult neurogenesis

Whereas the dogma of a fixed number of neurons in the brain was accepted worldwide over one century ago [4], a revolutionary concept has been developed by Allen et al. [5]. The latter authors first described that some dividing cells persist in the postnatal cerebral nervous system (CNS) in rats. The adult brain continuously supplies new neurons to the olfactory bulb and hippocampus. With the development of new methods for labelling dividing cells, Altman et al. confirmed these data and described different cerebral localizations for these dividing cells [6–8] in animal models. Adult neurogenesis persists in two principal regions: the subventricular zone of the lateral ventricle (SVZ) and the subgranular zone (SGZ) of the hippocampal dentate gyrus (DG) [9] (Fig. 1). Recent data suggest neurogenesis is present also in the

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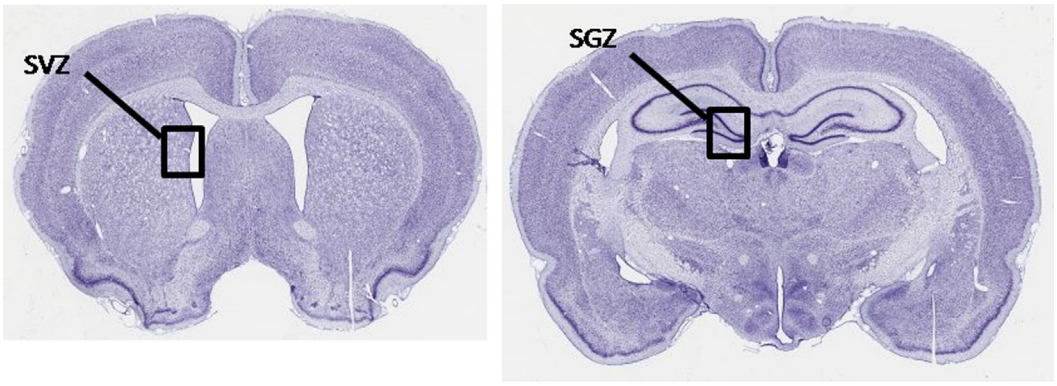


**Fig. 1.** Germinal niches in the adult rat brain.

hypothalamus and the cortex [10–13]. Erikson et al. [14] were the first to describe this cell proliferation in the DG of the human brain.

Cells from the SVZ that are nestin – and glial fibrillary acidic protein (GFAP) – immunoreactive radial glia-like cells, migrate along the rostral migratory stream to the olfactive bulb and differentiate into granule and periglomerular neurons [15]. Adult stem cell-generated progeny is essential for maintaining and reorganizing the olfactory bulb [16]. Dividing cells are also continuously generated from the SGZ and laterally migrate the short distance into the granule cell layer of the dentate gyrus and extend their axonal projection to the target CA3 region [17]. The new synapse connections enhance long-term potentiation and contribute to learning and memory functions [18–21].

## 3. Neurogenesis and vascular remodelling in brain injury

During brain injury, these mechanisms are amplified. Several studies have described that immature cells proliferate significantly in niches after stroke or TBI [22–24]. This occurs within the DG granular layer, where the newly generated cells differentiate into mature DG granule neurons, form synapses and extend axons to the CA3 regions 10 weeks after injury [25]. Depletion of this hippocampal neurogenesis is associated with impaired hippocampal-dependent learning [26,27] after injury. In reality, only a small percentage of cells differentiate into neurons [22]. Neuronal differentiation depends on several proteins (Noggin, neurogenesin-1, Sox, Hes 6) that can modulate the endogenous bone morphogenetic protein (BMP) signalling involved in development [28–30]. Newborn cells are also encountered directly near the lesion where they can persist at least 2 months after injury. This represents only a fraction of precursors because most of them do not survive secondary to the inflammatory response in the microglia encountered during migration [22,31]. The migration from niches to lesions has been described as developing along blood vessels [32,33], which underlines the extreme dependence of these newborn cells on the vasculature system [32].

The vasculature is activated after injury, followed by vascular remodelling [34,35]. The latter includes angiogenesis, development of new capillaries from vessels and vasculogenesis, development of new vessels depending on endothelial progenitor cells moving from bone narrow to the lesions. Angiogenesis is a multistep process involving endothelial cell proliferation, migration, tube formation, branching and anastomosis [36] (Fig. 2). It begins earlier than neurogenesis, probably to provide an appropriate microenvironment for neurogenic progenitors. The increase in endothelial cells begins after 12 h to 21 days, depending on species [37] and is mediated by vascular endothelial growth factor (VEGF), a soluble factor secreted by vascular cells, up-regulated in brain injury. VEGF expression has been described in association with the proliferation of neural progenitor cells (NPC), increased outgrowth from cerebral cortical neurons, the survival of newborn cells [38] and the initiation of angiogenesis. A correlation between this angiogenesis step within the neuro-restorative mechanism framework and survival time has been described in several clinical studies [39,40]. Thus, VEGF, due to its crucial role in activation of angiogenesis, could represent an interesting target for novel therapy strategies.

Besides the vasculature, the vascular environment including the endothelial cells, pericytes, outer vascular adventitial layer, soluble factors and extracellular matrix (ECM) appears to also be intimately linked to the behaviours of NPC and a regulator of neurogenesis. Interestingly, the extracellular matrix acts as an important regulator of proliferation, differentiation, migration and neurite growth. In particular, laminin, metalloproteinases and integrins (β8 integrin, N-Cadherin) may play a role in NPC migration [41], but the ECM can also act as a trap for growth factors to enhance neurogenesis and axonal sprouting [42]. Glial cells, and particularly astrocytes, also create a microenvironment for successful brain remodelling. In brain injury, they down-regulate secretion of proteoglycans, which modulate neuronal plasticity and growth.

After injury, axonal sprouting is enhanced in the ipsi- and contralesional pyramidal tract systems and depends on different mechanisms to regulate its expansion [43,44]. This axonal remodelling depends on neurofilaments (NFs), a neuron-specific intermediate filament abundant in axons and dendrites [45]. In vitro data have demonstrated that the PI3/Akt pathway is involved in this axonal expansion [46]. This mechanism is thought to compensate axon loss in injured zones. Beside these interconnections, transcallosal projections connecting the two motor cortices have also been described [47]. This increased axonal density is maintained for at least 1 year after stroke [48]. Imaging procedures, such as functional MRI, are able to detect this reorganization in the brain [49].

Synaptogenesis is also enhanced after brain injury in a restorative way. Indeed, to restore loss of connections between neurons after brain injury, the surviving neurons can develop new