J Rehabil Med 2003; Suppl. 41: 17–19

NEUROGENESIS AND ITS IMPLICATIONS FOR REGENERATION IN THE ADULT BRAIN

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Recent findings concerning the regenerative potential of the adult brain suggest a more pronounced plasticity than previously thought. One such finding is the generation of new neurons in the adult brain (neurogenesis). Loss of neurons has long been considered to be irreversible in the adult human brain, i.e., dead neurons are not replaced. The inability to generate replacement cells is thought to be an important cause of neurological disease and impairment. In most brain regions, the generation of neurons is generally confined to a discrete developmental period. Exceptions have recently been described in several regions of the brain that have been shown to generate new neurons well into the postnatal and adult period. One of the best characterized regions is the subgranular zone of the dentate gyrus in the brain, where granule neurons are generated throughout life from a population of progenitor/stem cells. Furthermore, recent findings suggest that neurogenesis may be of importance for memory function as well as mood disorders. Several very important questions can be formulated on the basis of these discoveries, for instance, what factors influence the generation of new neurons and whether it is possible for enhanced neurogenesis to contribute to functional recovery.

Key words: stem cells, neurogenesis, plasticity, enriched environment

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INTRODUCTION

The plasticity in fetal and young nervous system is pronounced and thus differs from the mature nervous system, which shows an age-dependent decrease in plasticity, adaptive ability, and neurogenesis (1, 2). The adult brain is vulnerable because of its decreased adaptive capacity; therefore, new methods of enhancing plasticity in the mature nervous system might be of relevance in both pathology and physiology. Several studies have shown that environmental stimuli, including environmental enrichment, induce neuroanatomical changes in the rodent brain (3–6). Changes in the hippocampus include increased dendritic arborization (7), increased hippocampal thickness (8, 9), and an increased number of glial cells (10).

In general, replacement of neurons following degeneration or damage is not a characteristic of the mammalian brain. Neuronal loss is thus considered permanent. Prolonged postnatal neurogenesis has been described in the granule cell layer of the hippocampal formation (1, 11–14). Neurogenesis has been shown to persist well into adulthood in the rodent (15–17). Recently, neurogenesis was shown in the adult human dentate gyrus (18). Neuronal progenitor cells reside in the subgranular zone (SGZ) of the dentate gyrus, where they continuously proliferate, migrate into the granule cell layer, and differentiate into granule cells (19, 20). These newborn granule cells express markers of differentiated neurons and have morphological characteristics corresponding to differentiated granule cells (16, 19, 21). Furthermore, they establish axonal processes into the mossy fiber pathway and form synaptic connections with their targets in hippocampus CA3 (22, 20). The neurogenesis in the dentate gyrus is very interesting, since the hippocampal region with the dentate gyrus is intimately associated with spatial learning and memory (23).

The proliferation of progenitor cells in the SGZ can be influenced by the administration of N-methyl-D-aspartate (NMDA) receptor antagonists or by the removal of the adrenal glands (24, 25). Furthermore, neurogenesis in the dentate gyrus in young mice has been shown to be facilitated by enriched environments. It was shown that exposure to enriched environments leads to an increased number of surviving newly formed granulae cells and an increased total number of neurons in the dentate gyrus (26–28). Plasticity is reduced with increasing age, and recent studies have demonstrated that proliferation of progenitor cells also decreases with age (2). Therefore, we have initiated studies to determine whether the proliferation of progenitor cells and the subsequent generation of new neurons within the dentate gyrus in adult rats is induced by environmental stimuli.

Rats housed in an enriched environment show an increase in the rate of neurogenesis (the number of newborn neurons). This effect is mediated via an increased survival of stem cell-derived neurons as opposed to an increased proliferative rate. In addition, these animals perform better spatial learning paradigms (26, 29).

In the adult mammalian brain, there is at least one other site of active cell proliferation and neurogenesis throughout life: the subventricular zone, from which newly generated neurons migrate via the rostral migratory stream to the olfactory bulb (30, 31). Active cell proliferation also takes place in the cortex. However, the progeny of the proliferating cells remain undifferentiated and only rarely become mature glia in vivo. Mitotically ac-

DOI 10.1080/16501960310010098

tive cells isolated from cortex have in vitro been shown to be heterogeneous and to commit mainly to the glial lineage or remain undifferentiated. However, cortical precursors can be induced to become multipotent neural progenitors and generate neurons after exposure to basic fibroblast growth factor (FGF-2) in vitro (32). Progenitor cells from the adult rat spinal cord, another non-neurogenic region, also constitute a population of cycling glial precursors which, similarly to cortical progenitors, become multipotent upon in vitro stimulation with FGF-2. Furthermore, upon transplantation to the hippocampus the multipotent neural progenitors differentiated into neurons in the dentate granule cell layer, while when transplanted back into the spinal cord they only generated glial cells (33). Thus, microenvironmental cues are pivotal for fate determination of neural progenitor cells, and the neocortex seems to normally lack the necessary instrumental cues to generate neurons. This perception has been challenged, since it has been suggested that cortical neurogenesis persists in rat and primate cortex (34–36). Another study, however, reports that physiological cortical neurogenesis could not be detected in adult primates (37). Several in vivo studies have proposed the occurrence of lesion-induced cortical neurogenesis. Magavi et al. (38, 39) demonstrated induction of neurogenesis in adult mouse cortex by selective apoptotic degeneration of corticothalamic neurons in lamina VI. Gu et al. (40) and Jiang et al. (41) reported induction of cortical neurogenesis in a photothrombotic stroke model and after transient middle cerebral artery (MCA) occlusion, respectively.

Postischemic environmental enrichment is well known to improve functional recovery in experimental models of stroke (42, 43) and also after traumatic brain injury (44). Since environmental enrichment has been shown to increase neurogenesis in the hippocampus and increase hippocampus-dependent learning and memory (26–29, 45), and since effects of environmental enrichment on hippocampal cell genesis were demonstrated in the postischemic phase (46), we aimed to also examine whether postischemic housing in enriched environment might influence cortical cell genesis and how such an influence could be related to functional recovery. We hypothesize that postischemic environmental enrichment increased cell genesis and even a putative neurogenic response in the cortex in parallel with sensorimotor improvement. Ongoing studies in our laboratories and others will show to what extent gliogenesis and/or neurogenesis contribute to the functional improvement after experimental stroke consistently observed in association with enriched environment. Further studies along these lines may in the future lead to more refined and efficient programs for neurorehabilitation.

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