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Neurogenesis and Ischemic Brain Injury

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ABSTRACT

Neuronal self-renewal following injuries to the adult brain has been clarified by many recent studies. Ischemic brain injuries have now been demonstrated as a trigger for neurogenesis via endogenous neural stem cells or progenitor cells located in the dentate subgranular zone, the subventricular lining of the lateral ventricle, and the posterior periventricle adjacent to the hippocampus. New neurons migrate to the granule cell layer or to the damaged CA1 region and striatum, where they express morphological markers characteristic of the local neurons. If the new neurons are fully integrated and become functional, a novel therapeutic strategy might be developed for stroke in humans.

Key words：stem cell, neurogenesis, stroke

INTRODUCTION

Ischemic brain injury remains as one of the most common causes for death and disability throughout the world. Unlike many other tissues, the mature brain has limited regenerative capacity, due to its unusual degree of cellular specialization which restrains the residural healthy tissue from assuming its function. However, recent studies have demonstrated that new neurons are derived from neural stem cells or progenitor cells which persist in the adult mammalian brains including those of rodents and primates[1)-7)]. Thus, stimulation of endogenous neural stem cells and progenitor cells in the adult brain might lead to a novel therapeutic strategy for stroke[8)].

Neurogenesis in the adult brain

The adult brain possesses persistent neural stem cells with self-renewal capacity and

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multiple potentiality. Isolated cells from the adult mammalian brain form colonies of undifferentiated cells in vitro that can be dissociated to form many more secondary colonies, demonstrating renewal. These cells are also multipotent since they can be induced to differentiate into neuron, astrocytes, and oligodendrocytes[7),9)-11)]. Stem cells can give rise to other stem cells as well as progenitor cells. Progenitor cells give rise to neurons, astrocytes, and oligodendrocytes. Both stem cells and progenitor cells occurs in discrete regions, including the rostral subventricular zone (SVZ) of the lateral ventricles[12)] and the subgranular zone (SGZ) of the dentate gyrus (DG)[13)]. Neurons that arise in the SVZ travel via the rostral migratory stream to the olfactory bulb[14)] and also enter association neocortex[4)], while new neurons leaving the SGZ migrate into the adjacent DG granule cell layer. Neurogenesis in these regions increases in conditions such as exogenous neurotrophic factor supplement[15),16),] enriched environment[17)], anti-depressant treatment[18)], seizure[19)], and ischemia[20),21)]. It decreases under stress[3)] and supplementation of excitatory amino acids[22)] or adrenal steroids[23)].

Ischemia induces neurogenesis

Ischemic brain injuries trigger molecular and cellular repair mechanisms including neurogenesis that might contribute to recovery in the adult brain. Liu, et al. showed that neurogenesis increased in SGZ of gerbils after transient global ischemia induced by bilateral common carotid artery occlusion[20)]. Immunohistochemistry was performed to detect the incorporation of the thymidine analog 5-bromo-2'-deoxyuridine-5'-monophosphate (BrdU) into newly synthesized DNA, and that 60% of newborn cells expressed neuronal markers neuronal nuclear antigen (NeuN), calbindin-D28K, and micro tuble-associated protein 2 (MAP-2). The newborn cells migrate into the granule cell layer (GCL) and become mature neurons. Neurogenesis is also increased by focal ischemia (Fig.1). Arvidsson, et al. showed middle cerebral artery occlusion (MCAO) leads to a marked increase of neurogenesis in the ipsilateral SGZ[24)]. These effects in the SGZ are not dependent on ischemic hippocampal damage since it rarely occurs after focal ischemia. The stroke-induced neurogenesis is most likely mediated through glutamatergic mechanisms acting on N-methyl-D-aspartate (NMDA) receptors.

Clinicaly, the striatum and cerebral cortex are main sites injured by stroke. Recent studies also show neurogenesis in the SVZ. Parent JM, et al. showed that striatal neurogenesis occurs following MCAO in adult rats[25)]. Cell proliferation is increased in the SVZ, and newly generated neuroblasts migrate into the periinfarct striatum. The new neurons express morphological markers of striatal mediumsized spiny neurons. Thus, stroke induces new neurons to differentiate into the phenotype of the majority of the neurons lost to ischemia. Gu, et al. used photothrombotic lesion to identify a small proportion of proliferated, BrdU-positive cells co-labeled with NeuN in the cortical penumbral zone[26)]. The same group subsequently reported the presence of double labeled cells in the cerebral cortex, particularly in the periinfarct area after MCAO[28)]. However, other studies did not detect any BrdU-positive cells co-labeled with neuronal marker in the injured cortex following MCAO[29)]. Thus, the cortical neurogenesis is still controversial.

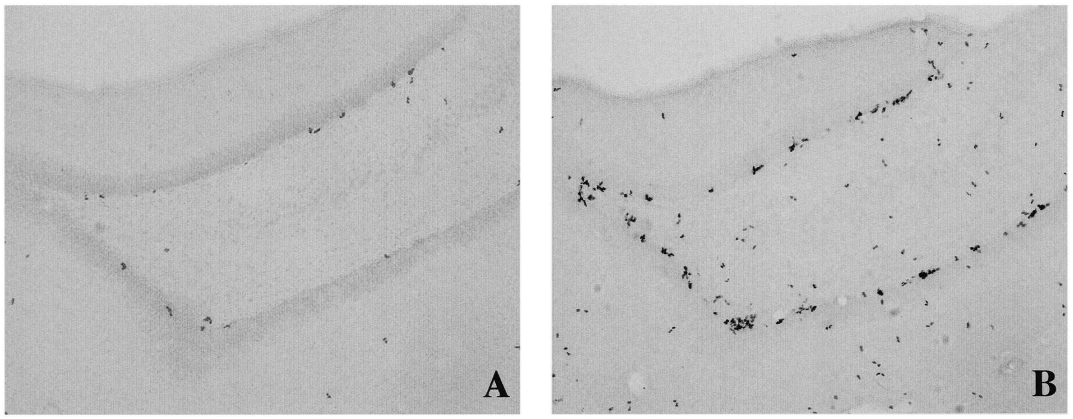

Fig.1. Ischemia increases cell proliferation in the dentate gyrus of adult rats. Animals were subjected to 90 min, of right distal middle cerebral artery occlusion. BrdU was administered 1 day before the animal was killed, and brains were processed BrdU immunohistochemistry. A, Control: sham surgery. B, 90 min, ischemia.

Neural transplantation for stroke

Transplantation of human neural cells is a new approach for improving functional deficits caused by brain injury or disease. Several investigators have evaluated the effects of transplanted fetal neural tissue, immortalized cell lines, or embryonic stem cells into rodent stroke models[30]. The standardization of these models is invaluable to the reliable testing of various experimental protective and regenerative therapies. Among them, cell transplantation of fetal hippocampal neurons has shown that they can survive and integrate in the ischemic brain[31]. A number of different mechanisms relate with cell survival and integration. These include provision of neurotrophic support, provision of neurotransmitters, reestablishment of local interneuronal connections, cell differentiation and integration, and improvement of regional oxygen tension. Methodological issues are still to be resolved since subsequent studies questioned the capacity of rat fetal neocortical tissues, implanted in an infarcted area, in integrating to the surrounding host tissue[32]. However, it has been shown that the chronic ischemia region can support graft tissue.

CONCLUSION

Recovery from stroke is thought to involve reactivation of molecular and cellular processes quiescent since development. These processes may include not only mechanisms in promoting cell survival or function but also the regeneration of lethally injured cell population.

Ischemic brain injuries still rank high among the common causes of death and disability in humans. The treatments to restore brain function after stroke are largely confined to rehabilitation therapies. Obviously, the self-renewal mechanisms are currently insufficient and functional recovery is incomplete. However, the recent findings that neuron can arise in adult mammalian brain from resident, or even circulating precursors

raise the possibility that amplification of self-renewal mechanisms might in the future come to be of thrapeutic value for patients affected by ischemic brain injuries.

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