REVIEW ARTICLE

Effectiveness of Neurogenesis in treating Children with Cerebral Palsy

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Objective
Tissue-specific stem cells divide to generate different cell types for the purpose of tissue repair in the adult. The aim of this study was to detect the significance of neurogenesis in the central nervous system in patients with cerebral palsy (CP).

Materials & Methods
A search was made in Medline, CINAHL, PubMed, ISI Web of Science and Google Scholar from 1995 to February 2011. The outcomes measured in the review were classified to origins, proliferation, and migration of new neurons, and neurogenesis in CP.

Results
According to the review of articles, neurogenesis persists in specific brain regions throughout lifetime and can be enhanced from endogenous progenitor cells residing in the subventricular zone by growth factors or neurotrophic factors and rehabilitation program.

Conclusion
Most of the studies have been conducted in the laboratory and on animals, more work is required at the basic level of stem cell biology, in the development of human models, and finally in well-conceived clinical trials.

Keywords: Stem cells; Neurogenesis; Cerebral palsy

Introduction

Plasticity is derived from the Greek word plaistikos meaning to form. This word mentions the brain's proficiency in learning, remembering and forgetting, together with its replanning and injury recovery potential (1). Plasticity involves the change of excitation and inhibition stability; a long-term potentiation (LTP) or long term depression (LTD); alteration of the neuronal membrane excitability; and finally anatomical changes, mainly construction of new axon terminals and new synapses (2).

Plasticity is a characteristic of the young human brain. Disorders and brain lesions such as cerebral palsy (CP) that occur during the developmental process involve the natural course of the brain evolution (3). CP is a disorder that influences movement and posture development; subsequently leading to restriction of activity (4). CP has been reported in 2 to 2.6 of 1000 live births in Iran (5), which is reasonably similar to other countries (6,7). As a result of better neonatal care, the survival of premature infants is increasing; therefore, CP is seen more often (8). Periventricular leukomalacia (PVL) injury is the cause of spastic diplegia, which is the most common form of CP. This defect occurs before 30-32

weeks (9). An increasing regional gray matter volume due to axonal sprouting, neuronal hypertrophy and neurogenesis is reported in preterm children affected by PVL, which may show brain plasticity (10). Therefore, neurogenesis is one of the neuroplasticity mechanisms in preterm children with PVL. Furthermore, review articles showed that mechanisms of neuroplasticity after stroke and CP consist of axonal and dendrite sprouting, cortical reorganization and neurogenesis (11).

Nowadays, it is widely accepted that new neurons are formed and recruited into specific brain circuits probably in all adult vertebrate species, including humans (12). Distinct areas of the central nervous system (CNS) are responsible for neurogenesis in the adult brain; the subventricular zone (SVZ) Fig (1), the lining of the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus within the hippocampus. Neural stem cells (NSCs) are the source of new neurons in the adult brain. The NSCs, which are multi potent and self renewing, are regulated by a number of molecules and signaling pathways.

Certain areas in the brain show that adult neurogenesis continues throughout lifetime. Endogenous progenitor cells located in the subventricular zone enhance this neurogenesis by growth factors or neurotrophic factors, putting forward for consideration that this strategy has the potential to treat the damaged brain. Neural stem cells, neurogenesis, young neuron migration, their differentiation and death have been studied in the subventricular zone-olfactory bulb (SVZ–OB) system which has turned into an appealing experimental model. Furthermore, basic questions are mentioned regarding proliferation and migration of the nerve cells.

Materials & Methods

We searched Medline, CINAHL, Pub Med, ISI Web of Science and Google Scholar from 1995 to February 2011 using a combination of terms such as "Neurogenesis"[Mesh], Stem cell therapy, origin, proliferation dynamics, and migration, brain damage, "Cerebral Palsy"[Mesh], children. The database search identified 51 articles which were retrieved for evaluation. Finally, the results of 48 investigations, including original and review articles were categorized based on origins, proliferation, and migration of new neurons, and neurogenesis in CP.

Literature Review

There are epidemiological, clinical and review studies about the origins, proliferation, and migration of new neurons, and neurogenesis in children with CP.

Origins

The ceaseless process of producing new neurons in the adult SVZ mentions the possibility of neural stem cell existence within the germinal layer. There are a minimum of four types of cells in the SVZ-ependymal region. These cells have different morphologies, ultrastructures and molecular markers (13) (Fig. 1). Young migratory neurons (type A cells) make up chains which are enclosed in a sheath by astrocytes (type B cells). Type C cells which are more spherical and highly proliferative precursors are gathered together to create migrating A cell chains. Type E cells are ependymal cells that remarkably separate the SVZ from the ventricle cavity. B cells join with E cells intimately leading to occasional contact with the ventricle lumen.

Subventricular zone- astrocytes from the cortex, cerebellum, and spinal cord can also act as stem cells (14) and the primary precursors for new granule neurons (15).

Radial astrocytes (type-B cells) are the primary progenitors in SGZ. They asymmetrically divide in order to produce type-D cells (15). After four stages of maturation, these intermediate progenitors (D1, D2, D2h and D3) finally differentiate into granular neurons (15, 16). Some authors called these SGZ precursors as neuronal progenitors instead of NSCs. The function of these newly generated neurons appears to play a fundamental role in the memory process, learning and depression.

Proliferation

These cells can be proliferated by the administration of growth factors such as epidermal growth factor (EGF) (17), fibroblast growth factor (FGF) (18,19) or their combination (20) into the ventricle after focal

cerebral ischemia. Additionally, newborn neurons are mobilized to migrate not only toward the olfactory bulb (OB) along the rostral migratory stream, but the subependymal overexpression of brain-derived neurotrophic factor (BDNF) also causes neuronal progenitor cells to recruit into a non-neurogenic neostriatum (21,22). The immune system targets neurogenic niches and exerts a considerable effect on proliferation, survival, differentiation and migration of NSCs (23).

Migration

In adult mice, there are millimeters of distance between SVZ and the BO. Doetsch and Alvarez-Buylla reported that "A cells, the SVZ neuroblasts, originate throughout most of the lateral wall of the lateral ventricle and traverse a complex network of interconnected paths before joining the rostral migratory stream (RMS)" (24). It has also been suggested that similar migrations such as migration of SVZ derived cells which is remarkably long may happen in the infant human brain which is large in contrast to mice brain. A study also suggested a migration from the SVZ to neocortex (25, 26), but this migration has not been demonstrated.

A cells in adult rodent SVZ and RMS form chains by moving along each other (Fig. 2) (27). A cells with a long structure and a noticeable leading process are covered at the end by a growth cone (28,29). Neuroblasts move incrementally in chains reconstituted in vitro at mean speeds of 120 m/hr (28). The cellular construction that causes these young neurons to move at such high speeds is not known. Microtubule polymerization and depolymerization may probably have a significant function in both the exploratory behavior and net translocation happening during a step. Doublecortin, a protein related to microtubule has an important role in neuronal migration.

A cells have an outstanding growth cone and a principal mechanism (28) mentioning that these cells may use motion processes also used by growing axons. A process emerges from the neuron cell body. The forward end of the process expands to form a growth cone that samples the environment, contacting other cells and chemical cues. When the growth cone contacts its target cell, synaptic vesicles soon form and microtubules that formerly ended at the apex of the growth cone project to the presynaptic membrane.

Besides, during migration and types of signal trigger, factors secreted by astrocytes appear to enhance the migration of SVZ neuroblasts (30). These astrocytes probably play important roles such as enhancement of migration. The glial cells surrounding the chains may also help A cells to survive and/or may provide directional information.

Neurogenesis in CP

Migration of thousands of young neurons (A cells) into the OB happens daily, but only some of them accomplish completely. The characteristics of neural stem cells include the ability to self-renew, differentiate into most types of neurons and glial calls and populate developing and degenerating regions of CNS (31).

Lesions occurring in the perinatal period cause severe impairment of skilled movement learning and also secondary disruption in the development of alpha motor neurons and their afferent segmental reflex control. Because no explicit treatment has been mentioned for CP due to neonatal hypoxic-ischemia (HI), recent research shows that using growth factors can have beneficial effects on ischemic brain injury (32-34).

Neural stem cells and progenitors of the subventricular zone (SVZ) of the adult mammalian brain (35) can be proliferated by the administration of growth factors such as epidermal growth factor (EGF) (17), fibroblast growth factor (FGF) (18,19) or their combination (20,36) into the ventricle after focal cerebral ischemia. Likewise, adult neurogenesis persists in specific brain regions throughout lifetime and can be enhanced from endogenous progenitor cells residing in the SVZ by growth factors or neurotrophic factors, suggesting that this strategy will be able to treat the damaged brain. In other words, if the proliferation and differentiation of newly generated neurons can be directed toward specific functional brain regions, it may be possible to use the recovery of specific functions in the treatment of incurable neurological diseases.

Therefore, induction of striatal neurogenesis by the intraventricular administration of brain derived neurotrophic factor (BDNF) and EGF promoted

functional recovery in an adult animal model of neonatal HI brain injury and this treatment may offer a promising strategy for the restoration of motor function for adults with CP (37).

Besides, stimulation from the external environment could affect the plasticity process. The neural basis of experience-dependent processes appeared to involve active formation of new synaptic connections in response to the events providing the information to be stored (38). Many experiences indicated that nervous system optimizes neural connection during critical periods and lack of necessary experience during critical periods in human development of gross motor and cognition provides retardation in these areas (31). Perhaps using growth factors accompanied with rehabilitation therapy such as neurodevelopmental therapy (NDT) is a good option in the process of neurogenesis.

In this regard, transplantation of several types of stem cells including neural stem cells (39), multipotent adult progenitor cells (40,41) and mesenchymal stem cells (MSCs) may be beneficial in acute injuries of the CNS (42). Daadi et al. (2010) reported that human neural stem cells (hNSCs) engrafted into the ischemic brain enhanced axonal sprouting and the expression of genes involved in neurogenesis, gliogenesis and neurotrophic support modulated microglial response and improved motor function of the animals. It is generally believed that transplanted non-neural cells such as those derived from bone marrow or cord blood exert neurotrophic effects on ischemia-injured tissue and may not survive long term; (43) whereas, neural stem cells are thought to provide cell replacement and neurotrophic support (44,45).

In the injured brain, growth and differentiation factors released from transplanted MSCs enhance the local trophic milieu; subsequently, improving endogenous repair processes (46,47, 48). It has also been suggested that MSCs can differentiate into neurons and oligodendrocytes and thereby contribute to repair the injured brain (42).

Van Velthoven et al. (2010) suggested that two MSC

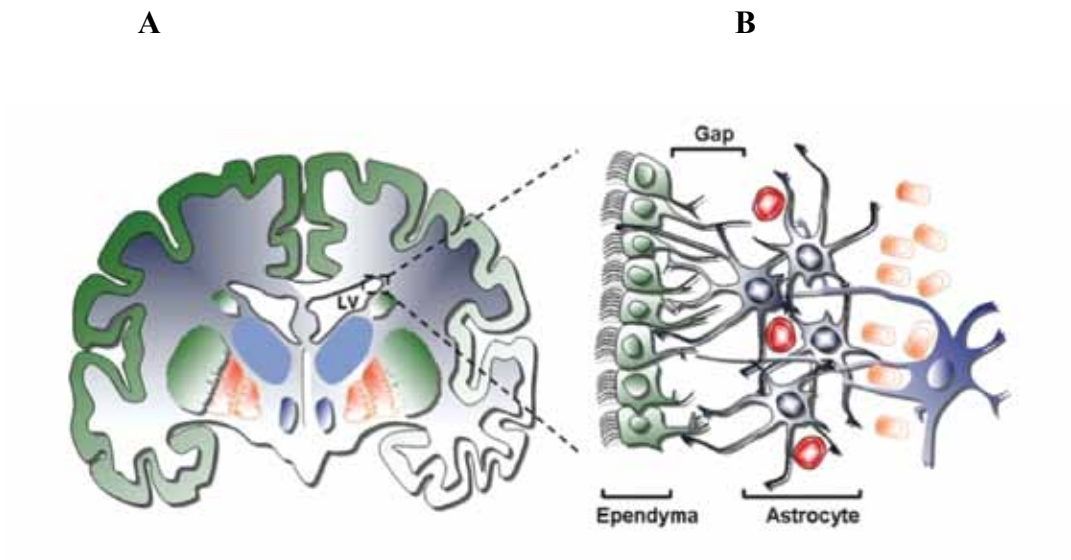

Fig 1. The anatomy of the neurogenic subventricular zone in the human brain. (A) Coronal view of the adult human brain showing the basal ganglia and lateral ventricles. (B) Schematic drawing depicting the cellular composition and cytoarchitecture of the adult human SVZ, consisting of four layers: Layer I – ependymal cell layer (green), Layer II – hypocellular gap, Layer III – astrocytic ribbon, containing astrocytes and migrating neuroblasts, Layer IV – transitional zone (From Wikipedia, the free encyclopedia)

injections at 3 and 10 days after neonatal HI markedly improved sensorimotor function 4 weeks after the insult and MSC transplantation after neonatal HI decreased gray and white matter loss and enhanced neurogenesis and oligodendrogenesis. In this study, bone marrow from the femur and tibia of mice was cultured in DMEM/15% fetal bovine serum and was infused into the ipsilateral hemisphere (42). In another study on rats with left carotid artery ligation and hypoxic exposure, it was reported that MSC may be a treatment for neonatal HIE (40).

Obviously, today it is confirmed that using erythropoietin (EPO) with granulocyte colony-stimulating factor (G-CSF) promoted cell migration in MSCs.

In conclusion, after ischemic brain injury various cell types including neurons, glial and endothelial cells are damaged and lose their function. Effective regeneration of brain tissue requires all these cell types to be replenished and combined to form a new functional network. This review showed that most studies have been conducted in the laboratory and on animals, more work is required at the basic level of stem cell biology, in the development of human models, and finally in well-conceived clinical trials.

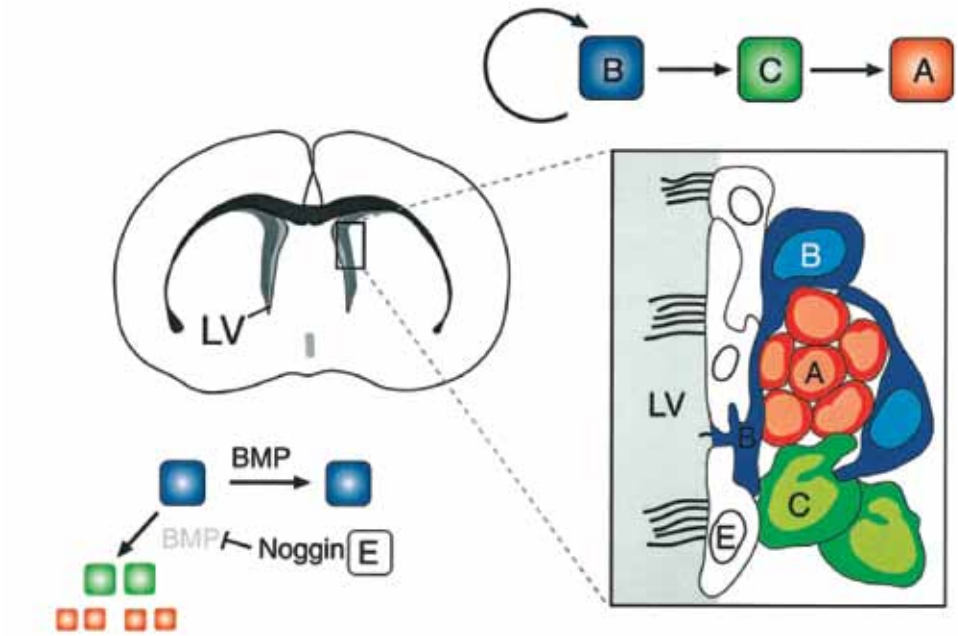

Fig 2. Organization and lineage in the SVZ. Left, Cross section of the anterior rodent brain indicating the location of the SVZ on the lateral wall of the LV. On the right is the cellular composition and organization of the SVZ. Chains of young neurons (A cells, red) are surrounded by B cells (blue) that have astrocytic characteristics and form tube-like structures. Ependymal (E), Lateral Ventricle (LV)

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