Review on Adult Neurogenesis in Humans and Other Mammals

Tesfamichael Berhe

Lecturer of Anatomy
Department of Anatomy, BMI, CHS, Mekelle University, Ethiopia
Email- tesfish316@gmail.com

ABSTRACT

Research in the field of adult neurogenesis has recently indicated significant progress.The objective of this paper is to review the basic concepts, new findings and clinical implications of neurogenesis making emphasis on the significance, especially in humans.

Although scientists still debate the extent and purpose of neurogenesis in the adult brain, research has identified certain areas of the brain where it is most evident. These areas include the hippocampus, caudate nucleus, and olfactory bulb. The processes that may promote or inhibit neurogenesis and evidence of specific molecular and cellular regulation of neurogenesis are again discovered. *Adult Neurogenesis* includes discussions on neural stem cell biology; methods and models for studying adult neurogenesis; physiological and molecular processes and their control; related neurological diseases; and comparisons of neurogenesis in humans, birds, fish, and invertebrates. Our understanding of neural stem cells has increased dramatically over the past few years, but there are still many major gaps.

Key words: Adult Neurogenesis, Mammals, Humans, Neural Stem Cells, Clinical significance

INTRODUCTION

It was long thought that loss of neurons to be irreversible in the adult human brain, because dying neurons cannot be replaced. [1] Contrary to the long-held belief that neurogenesis tapers off with the end of early postnatal development; the mammalian brain retains the capacity to generate new neurons throughout life. [2] Over the last 20 years, research has shown that neurogenesis, the process by which neurons are generated, actually occurs in the adult human. What began with the song of a small bird has changed an entire paradigm in neuroscience. It was proposed the ability of adult songbirds to learn new songs showed that their brains created new cells and that these neurons helped them form memories of the new songs. This opened up debate on whether the same process occurred in humans Subsequent research confirmed human neurogenesis and currently, work is shifting to find out where neurogenesis happens, how it happens, why it happens, and, more importantly, how it might help the brain heal itself.[3] Most active during pre-natal development, neurogenesis is responsible for populating the growing brain. It involves active production of new neurons, astrocytes, glia, and other neurallineages from undifferentiated neural progenitor or stem cells. [4] If researchers can harness and enhance neurogenesis, it could lead to improved treatments for many disorders, diseases, or damage -- from Alzheimer's and epilepsy to stroke and traumatic brain injury -- and it can help keep our minds and memories sharp.[5] The discovery that new neurons are born in the adult mammalian brain has also raised hopes that selective stimulation of the formation of new neurons, i.e. neurogenesis, might improve cognitive abilities in disabled or healthy humans.The new neurons confer plasticity to the circuitry and increasing evidence has established a role for adult neurogenesis in specific brain functions.[6]

COMMON NEUROGENIC AREAS AND PATHWAYS

Neurogenesis is considered a rather inactive process in most areas of the adult brain.Research to date suggests that the most active area of neurogenesis is the hippocampus, a region deep within the brain involved in learning and memory. It is believed that thousands of new cells are produced in the hippocampus each day, although many die within weeks of their birth.[7]

New neurons are continually born throughout adulthood in predominantly two regions of the brain: subventricular zone (SVZ) and the subgranular zone (SGZ), part of the dentate gyrus of hippocampus. [8]

More recently, neurogenesis in the cerebellum of adult rabbits has also been characterized. Further, some authors (particularly Elizabeth Gould) have suggested that adult neurogenesis may also occur in regions within the brain not generally associated with neurogenesis including the neocortex. [9]

Subventricular Zone (SVZ)

Subventricular zone (SVZ) is a paired brain structure situated throughout the lateral walls of the lateral ventricles. It harbors the largest population of proliferating cells in the adult brain of rodents, monkeys and humans. In mice, neurons generated in SVZ travel to the olfactory bulb via the rostral migratory stream, which has until recently remained elusive in humans. Four cell types have been described in the SVZ:

- ciliated ependymal cells (type E) facing the lumen of the ventricle, whose function is to circulate the cerebrospinal fluid;
- proliferating type A neuroblasts, expressing PSA-NCAM, Tuj1, and Hu, and migrating in "chains" toward the olfactory bulb (OB);
- slowly proliferating type B cells expressing nestin and GFAP, and unsheathing migrating type A neuroblasts
- actively proliferating type C cells or "transit amplifying progenitors" expressing nestin, and forming clusters interspaced among chains throughout the SVZ

Sub granularZone (SGZ)

SGZ lies deep within the hippocampalparenchyma, at the interface between the granule cell layer and the hilus of the dentate gyrus. It is one of the two major known adult neurogenesis sites of the brain, along with subventricular zone. Two types of neural progenitors can be identified in the SGZ according to their specific morphologies and expression of unique sets of molecular markers

- Type 1 hippocampal progenitors have a radial process spanning the entire granule cell layer and ramify in the inner molecular layer. These cells express nestin, glial fibrillary acidic protein (GFAP), and the Sry-related HMG box transcription factor, Sox2
- Type 2 hippocampal progenitors have only short processes and do not express GFAP. [10]

Rostral Migratory Stream

The rostral migratory stream (RMS) or rostral migratory pathway is a pathway, along which neuronal precursors that originated in the subventricular zone (SVZ) of the brain migrate to reach the main olfactory bulb(OB), where they differentiate into interneurons. [11]

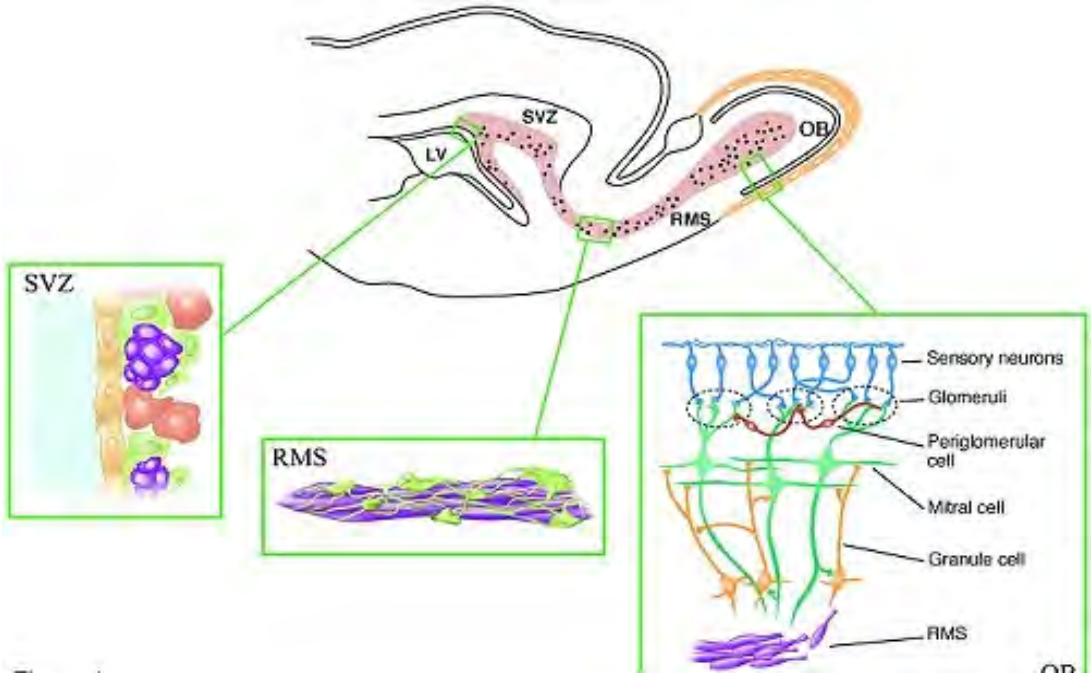

Figure 1: Shows common regions and specific cells of neurogenesis in the brain

Functional role of adultolfactory bulb neurogenesis.

The mammalianolfactory system has a remarkablecapability to rencogniez and discriminante a wide range of odormolecules. This not onlyprovides essential information for animal survival but has alsoprofoundeffects on theirbehaviorInterestingly, adult OB receives about 40,000 neuronal precursorseveryday. This continuos neuronal turnover imposes to the olfactory system an ever-lasting dilemma of preserving normal olfactory information processingdespite persistent changes in the topographic and functionalmaps. [12]

IDENTIFICATION OF NEURAL STEM CELLS

Neural stem cells (NSCs) are the self-renewing, multipotent cells that generate the main phenotypes of the nervous system. Neural stem cells, which exist in various regions of the CNS throughout the mammalian lifespan, can be expanded and induced to differentiate into neurons and glia in vitro and in vivo Stem cells are notoriously difficult to identify, and it has been witnessed a gradual homing in on bona fide stem cells in many tissues. [19]Type 1 hippocampal progenitors have a radial process spanning the entire granule cell layer and

ramify in the inner molecular layer. These cells express nestin, glial fibrillary acidic protein (GFAP), and the Sry-related HMG box transcription factor, Sox2In 1992, Reynolds and Weiss were the first to isolate neural progenitor and stem cells from the striatal tissue, including the subventricular zone — one of the neurogenic areas — of adult mice brain tissue. Since then, neural progenitor and stem cells have been isolated from various areas of the adult brain, including non-neurogenic areas, such as the spinal cord, and from various species including human.Epidermal growth factor (EGF) and fibroblast growth factor (FGF) are mitogens that promote neural progenitor and stem cell growth in vitro, though other factors synthesized by the neural progenitor and stem cell populations are also required for optimal growth. It is hypothesized that neurogenesis in the adult brain originates from NSCs. The origin and identity of NSCs in the adult brain remain to be defined. To determine the cell fate of the BrdU-immunoreactive cells, triple immunofluorescent labeling for BrdU and cell-specific markers, including glial fibrillary acidic protein (GFAP), a marker for astroglia, and one of the neuronal markers, NeuN, calbindin or neuron specific enolase21 (NSE) can be utilized. [1, 13]

While the Neurosphere Assay has been the method of choice for isolation, expansion and even the enumeration of neural stem and progenitor cells, several recent publications have highlighted some of the limitations of the neurosphere culture system as a method for determining neural stem cell frequencies.Direct mitogenic stimulation of progenitor cells in the adult brain appears to be mediated via growth factors and trophicfactors. It is still unclear to what extend endogenous production of several candidate growth factors, such as FGF-2 and BDNF, play a role in the ongoing spontaneous olfactory bulb neurogenesis. In this context it is important to note, that several blood-derived growth factors such as erythropoietin and vascular endothelial growth factor (VEGF) are potent stimulators of neurogenesis, when applied directly into the ventricular system. [14]

MOLECULAR AND CELLULAR MECHANISMS OF ADULT NEUROGENESIS.

During the development of the mammalian central nervous system, neural stem cells and their derivative progenitor cells generate neurons by asymmetric and symmetric divisions. The proliferation versus differentiation of these cells and the type of division are closely linked to their epithelial characteristics, notably, their apical-basal polarity and cell-cycle length. Understanding of how these features change during development from neuroepithelial to radial glial cells, and how this transition affects cell fate and neurogenesis is essential. [15]

Despite recent progress in the field of adult neurogenesis there is still lack of critical information on the molecular and cellular mechanisms orchestrating this process. To fullfil this understanding of how to control stem cells proliferation and differentiation in to specific celltypes, their targeting to particular brainregions and their maturation and integration into neural networks isrequired. To study these mechanisms, use of multidisciplinary approachesis needed. Labeling newly born bulbar interneurons either by intraperitoneal injection of BrdU, a DNA synthesis marker, or by stereotaxic injections of GFP-expressingviruses and celltrackersinto the SVZ and RMS. Then, using a battery of basic molecularbiology, cell culture, in situ hybridization and immunohistochemistry tools combinedwith Ca 2+ -imaging, two-photon and electrophysiologicalrecordings. [16]

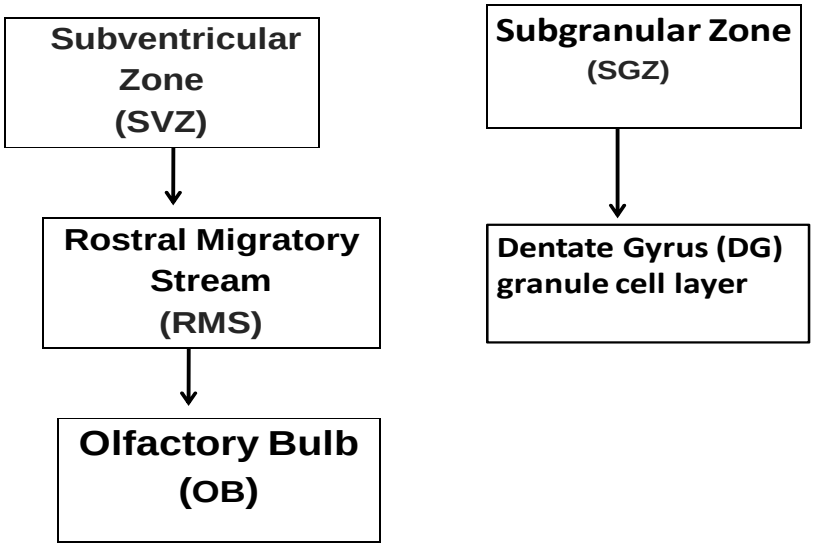

Figure 2: Schematic presentation of migraration and differentiation of neurons originating in the subventricular (SVZ) and subgranular zones (SGZ).

RESEARCHES ON HUMANS

Maurice Curtis and his colleagues examined the brains of deceased cancer patients who had previously been injected with bromo-deoxyuridine (BrdU), a chemical which is incorporated into newly-synthesized DNA, and which is therefore used by oncologists to visualize and monitor the growth of tumoursTo their surprise, they found BrdU-positive cells in the olfactory bulbs of the patients' brains, suggesting that it contained newly-generated neurons. Curtis's team then used antibody staining to show that the neuroblasts begin to differentiate into olfactory neurons while migrating through the rostral migratory stream. Upon arriving at the bulb, the cells continued to differentiate, forming mature olfactory neurons. Because the cancer patients whose brains were examined were aged between 38-70 years of age, the findings suggest that neurogenesis may occur throughout the duration of the human lifespan. The function of these newly-generated cells is unclear, but they may be involved in recognizing and remembering new smells in the later years of life. [19]

It is again indicated that the stem cells not only migrate to the olfactory bulb, but also leave the RMS and migrate into the basal ganglia and cerebral cortex. This is significant, because parts of the basal ganglia degenerate in movement disorders such as Parkinson's disease, and specific regions of the cortex degenerate in Alzheimer's. The possibility that stem cells enter these regions from the RMS could therefore provide a means for developing new treatments for neurodegenerative diseases. [20]

RESEARCHES ON OTHER MAMMALS

In rats and mice, a structure called the rostral extension connects the lateral ventricles and the olfactory bulb. This tube-like structure, which is filled with cerebrospinal fluid, provides a pathway for neurons generated in the subventricular zone to migrate to the olfactory bulb, which contains neurons that bind to odorant receptors and produce nervous impulses related to smell. The rostral migratory stream is the equivalent of the rostral extension in rodents. [21]

Studies show that neurogenesis is induced in the hippocampus and subventricular zone (SVZ) in animal models of ischemia, and the new neurons are generated at the sites of degeneration, where they replace some of the lost nerve cells. The enhanced neurogenesis suggests the involvement of the hippocampus and SVZ in the physiopathology of cerebral strokes, and the generation of new neuronal cells at the sites of degeneration suggests that the central nervous system (CNS) may attempt to repair itself. [22]

CLINICAL IMPLICATIONS OF NEUROGENESIS

The pathogenesis of neurological diseases and disorders remains mostly unknown. The confirmation that neurogenesis occurs in the adult brain and neural stem cells (NSCs) reside in the adult central nervous system (CNS) of mammals has tremendous implications for our understanding of the physiopathology of the nervous system. The generation of newborn neuronal cells in the adult brain is modulated in neurological diseases and during inflammation. This suggests that adult neurogenesis is involved in the pathogenesis of neurological diseases and disorders, particularly during neuroinflammation.[8]Different studies have indicated neurogenesis can have effect in hypothyroid animals, analyzing stress and depression ,treatment of Spinal Cord injury, memory and learning, effect of exercise in neurogenesis and its promise in treating other neurodegenerative disorders such as Parkinson's disease,Huntington's Disease and Alzheimer's Disease. [23]

Growing knowledge about the role of neural progenitor cells supports the hope that stem cell-based therapeutic approachesaimed at restoring function in the lesioned central nervoussystem can be established. The presence of progenitor cells in the spinalcord displaying self-renewal and multipotent features was demonstratedin vitro more than a decade ago. However, very little about the in situ location, activity, regulation, and function of adult spinal cord SPCs is known. Possible therapies for promotingrecovery after spinal cord injury include stimulating the formationof neurons and glial cells by endogenous progenitor cells. [24]

REGULATION OF NEUROGENESIS

Many factors may affect the rate of hippocampal neurogenesis. Exercise and an enriched environment have been shown to promote the survival of neurons and successful integration of newborn cells into the existing hippocampus. Another factor is central nervous system injury since neurogenesis occurs after cerebral ischemia, epileptic seizures, and bacterial meningitis. On the other hand, conditions such as chronic stress and aging can result in a decreased neuronal proliferation. [25]

CONCLUSION

The discovery of life-long neurogenesis in humans has redefined our understanding of the brain and spinal cord. Although still in its infancy, the study of neurogenesis already has provided insights into the mechanisms of learning and memory, depression, and other disorders and diseases of the nervous system. It also has inspired hope that new strategies will be developed to treat injuries and diseases of the brain and spinal cord. While much progress was made over the past decade, many questions remain unanswered, ensuring that the investigation of neurogenesis in the adult mammalian brain will remain an exciting and intense area of research well into the future.

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