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NEUROGENESIS: CLINICAL AND NEUROPATHOLOGICAL CORRELATES

Neelam U Kanade*, Rachana Sarawade, Nasreen Chaudhary and Pranali Paradkar

HSNCB's Dr. L. H. Hiranandani College of Pharmacy, Ulhasnagar, Maharashtra, India.

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***Correspondence for Author**
Neelam U Kanade
HSNCB's Dr. L. H. Hiranandani College of Pharmacy, Ulhasnagar, Maharashtra, India.

ABSTRACT

Neurogenesis occurs in the adult brain in a constitutive manner under physiological circumstances within two regions: the dentate gyrus of the hippocampus and the subventricular zone of the lateral ventricles. Accumulating evidence has indicated the molecular mechanisms commonly underlying embryonic and adult neurogenesis. In the hippocampus, physical exercise and cognitive stimuli robustly increase the proliferation of precursor cells, whereas physical/psychosocial stress decreases the proliferation of newborn neurons. Thus, adult neurogenesis is intriguingly regulated by several genetic and environmental factors. In this review we first present a comprehensive view on Signaling pathways and transcription factor that are involved in mechanism of neurogenesis. And then we focus on regulation of neurogenesis and we consider the evidence that a regulation in neurogenesis underlies cognitive deficits and neurodegenerative disorders such as AD, Parkinson disease, Huntington's disease, Depression, Epilepsy, etc.

KEYWORDS: Neurogenesis, Regions of Neurogenesis, Cellular mechanism, clinical correlations.

INTRODUCTION

Formerly, majority of neuro-scientist believed the nervous system was a fixed system that was not capable of regeneration. It was commonly stated that in higher vertebrates neurogenesis of nerve cells is restricted to the early stages of embryonic development. This belief is based on the observation that neurons with mitotic figures are absent in the central nervous system of most higher vertebrates but in 1962, the first evidence of adult neurogenesis was demonstrated by Joseph Altman who furthermore identified rostral

migratory stream in 1969. Joseph Altman first reported that some dividing cells in brain survived and differentiated into cells with morphology similar to neurons using tritiated thymidine autoradiography.[1] In the early 70's, two more researchers challenged this dogma: Fernando Nottebohmand and Michael Kaplan. Dr. Nottebohm's work showed adult neurogenesis in birds, while Michael Kaplan worked on rodents. In the early 1990s, a series of papers initiated an explosion of research on existence and implication of neurogenesis. Several researches also discovered that cells with stem cell properties could be isolated and expanded in culture. Under a variety of culture conditions with different factors, these isolated cells can be induced to differentiate into glia and neurons.[2] Neurogenesis in the adults mammalian brain is now a widely accepted neuroplastic event that enables the brain to adapt to intrinsic and extrinsic stimuli. as In fact, during the past few years, a large amount of data has provided evidence that the production, differentiation and survival of neurons in the adult brain have significant implications for several physiological processes. Such as Memory and learning..[3] Moreover, many studies have linked neurogenesis with several neuropsychological disorders. However, the role of neurogenesis in these disorders is yet to be entirely established. In many cases, neurogenesis is seemed to be regulated due to various factors. Therefore, understanding the regulation of neurogenesis is of considerable relevance to understanding the pathology of neurodegenerative disorders. Basically, Neurogenesis (Birth of neurons) reflects the process by which new neurons are created from the brain's own neuronal stem and progenitor cells. This process is most active during pre-natal development. Neurogenesis is responsible for populating the growing brain with neurons.[4] Neural stem cells (NSCs) are self-renewing, multipotent cells that generate the main phenotypes of the nervous system. Stem cells are characterized by their capability to differentiate into multiple cell types via exogenous stimuli from their environment. They undergo asymmetric cell division into two daughter cells, one non-specialized and one specialized. NSCs primarily differentiate into all type of neural cells including neurons, astrocytes, and oligodendrocytes.[5,6] Shortly, this capability of the NSCs to replace lost or damaged neural cells is called neurogenesis. The term ''neural progenitor'' has been used to loosely describe all dividing cells with some capacity for differentiation.[7] The most important difference between stem cells and progenitor cells is that stem cells can replicate indefinitely, whereas progenitor cells can divide only a limited number of times.[8] 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).

Type 2: hippocampal progenitors have only short processes and do not express GFAP.[9] Neurogenesis is one of the components of brain plasticity, which plays a role in the learning process as well as in the recovery after brain injury or stroke.

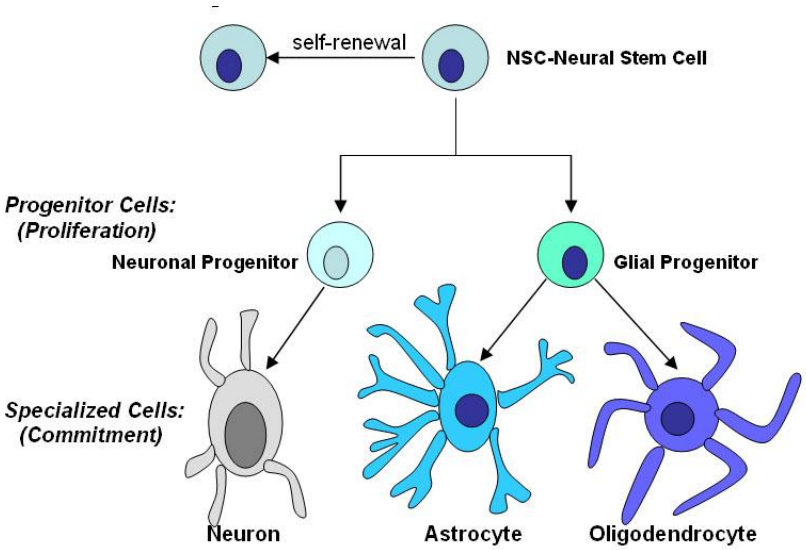

Figure No.1: Differentiation of stem cells

AREAS OF NEUROGENESIS

Neurogenesis prominently occurs in only two areas of the brain where stems cells initially reside and proliferate prior to migration and differentiation.

1.Subventricular Zone

2.Subgranular Zone.

Subventricular zone: It is a largest neurogenic region in brain wherein, neural stem cells continuously generate new neurons via transit-amplifying neural progenitors.[10]

In the adult rodent SVZ, there are four distinct types of cells: ependymal cells (type E cells), astrocytes (type B), transit-amplifying cells (type C), and migrating neuroblasts (type A) (Fig. 2) (4)(5). Astrocytes act as a neural stem cells and genetare transit amplifying cells which further proliferate and generate neuroblasts. These new neurons form chain-like cell aggregates and migrate toward the olfactory bulb (OB) through the rostral migratory stream (RMS), after arriving at the OB, the new neurons (neuroblasts) dissociate into individual cells

and migrate radially inside the OB and differentiate into olfactoryinter-neurons. Most of the neuroblasts differentiate further into granule cells and form a synapse with mitral/tufted cells. A small fraction of neuroblasts continue their migration and differentiate into periglomerular cells. Interestingly, SVZ neurogenesis can be activated by various injuries and neurological diseases, suggesting that endogenous neural stem cells in the SVZ may be used for brain repair in lower animals and might be exploited for therapeutic strategies in humans.[11,12]

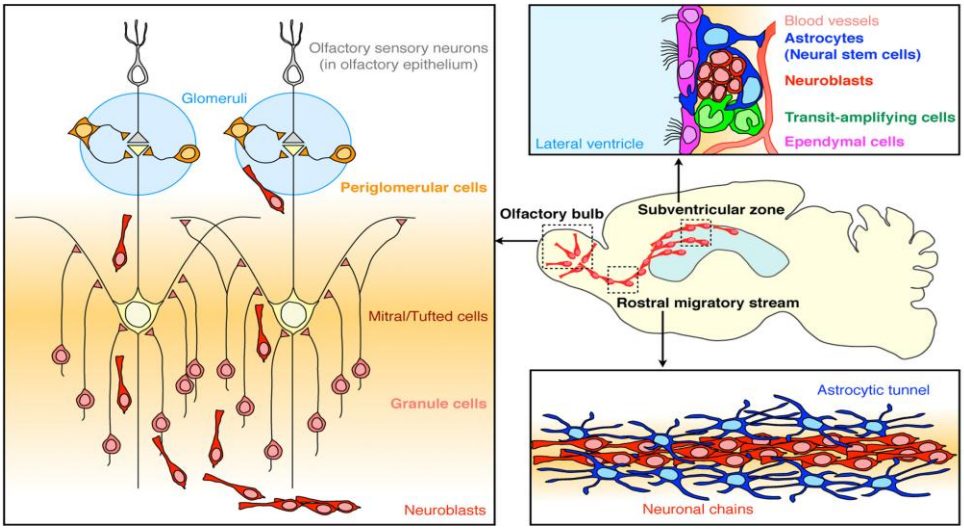

Figure no. 2 Neurogenesis in subventricular Zone.

Subgranular zone: It is a brain region in hippocampus where neurogenesis occurs. Subgranular zone is a narrow layer of cells located between granular cell layer and hilus of dentate gyrus. This layer is characterized by several types of cells, the most prominently neural stem cells (NSCs) in various stages of development. However, in addition to NSCs, there are also astrocytes, endothelial cells, blood vessels, and other components, which form a microenvironment that supports the NSCs and regulates their proliferation, migration, and differentiation.[14]

In SGZ, glial fibrillary acidic protein (GFAP) & Nestin positive radial glia-like type 1 progenitor slowly divides to give rise to proliferative stem cells (Type 2 intermediate progenitor cells (IPC)). Type 2 IPC form cluster around the processes of Type 1 cells,Where they rapidly divide to produce neuronal progenitor (Type3 IPC). Under neurogenic stimuli, Type3 IPC generates immature neurons, which develop predominantly into mature granule cells. The SGZ generates only one type of neurons i.e granule cells, which are thought to contribute to cognitive functions such as memory, learning, etc. Neurogenesis in the hippocampus has been extensively studied due to desirable connection between hippocampus

and formation of memory.[15,16] Therefore, it is of great interest to identify the approaches, both physiological (e,g running) and pharmaceautical (antialzeihmers, antidepressants) that preserves or enhance neurogenesis and hippocampal function.

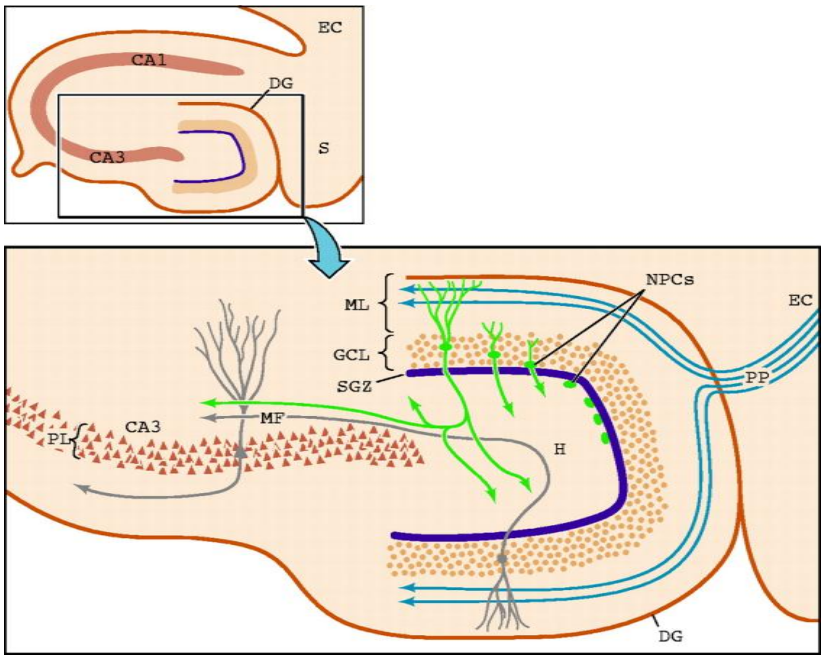

Figure no.3 Neurogenesis in Subgranular Zone

Top: a transverse section of the rodent hippocampal formation illustrating the major cytoarchitectonic divisions. DG, dentate gyrus; EC, entorhinal cortex; S, subiculum. *Bottom*: Neural progenitor cells (NPCs) are distributed along the subgranular zone (SGZ), the boundary between the granule cell layer (GCL) and the hilus (H). The SGZ is the neurogenic region where NPCs proliferate, differentiate into neurons (mainly granule cells), and migrate superficially through the GCL toward the molecular layer (ML). Cell bodies stay at the GCL, dendrites project through the ML, and axons project toward the hilus and CA3. New neurons (green) receive glutamatergic afferents from the perforant path (PP). Mature neurons born during development are shown in gray. Interneurons have been omitted only for simplicity, but they are equally relevant to hippocampal function. MF,mossy fibers; PL, pyramidal layer.

MECHANISM INVOLVED IN NEUROGENESIS

Adult neurogenesis occurs throughout life in discrete regions of the mammalian brain and is tightly regulated via both extrinsic environmental influences and intrinsic genetic factors. In recent years, several crucial signaling pathways such as Wnt, notch, growth and neurotropic factors, bone morphogenetic proteins, neurotransmitters, transcription factors have been

identified in regulating self-renewal, proliferation, and differentiation of neural stem cells, as well as migration and functional integration of developing neurons in the adult brain.

1.Notch Pathway

The Notch pathway, an important signaling pathway controls various cell differentiations and mediates neurogenesis in pathophysiological studies. Recent studies have led to recognition of the role of Notch pathway in neurogenesis in Ischemia damage and in myelination and axonal damage of neurodegenerative disease.[17] Notch receptors are single-pass transmembrane heterodimers that are activated upon forming a binding complex with their membrane-bound ligands on the neighboring cell, Ligand binding results in gamma-secretase mediated cleavage of the transmembrane domain, and subsequent release of the notch intracellular domain (NICD) into the cytosol. NICD then translocates to the nucleus where it forms a complex with the DNA-binding protein RBPj. Inactivation of RBPj resulted in an initial increase in hippocampal neurogenesis by inducing premature neuronal differentiation of Sox2-positive progenitors. This in turn resulted in subsequent depletion of the Sox2-positive neural stem cell pool and eventual suppression of adult hippocampal neurogenesis, indicating an important role for Notch signaling in the maintenance of adultneural stem cells.[18,19]

2.Wnt/β signaling pathway

The Wnt signaling pathway is a highly conserved signaling pathway that has been implicated in nervous system development.[20] Disruption of the physiological Wnt–signaling pathway has been associated with several CNS pathologies, including schizophrenia, mood disorders, autism, and Alzheimer's disease.[21] Wnt proteins have two distinct downstream signaling pathways. The canonical Wnt pathway is mediated by β-catenin. In the absence of Wnt stimulation, β-catenin is constantly phosphorylated by casein kinase I/GSK3β complex and degraded by the ubiquitin-proteasome system. This process is inhibited by Wnt-mediated inhibition of GSK3β; the unphosphorylated β-catenin then accumulates in the cytosol and translocates into the nucleus. In the adult SVZ, Wnt/β-catenin signaling is activated in the astrocytes and transit-amplifying cells and regulates their proliferation. The non-canonical Wnt pathway is mediated by Wnt/planar cell polarity (PCP) signaling, which regulates cytoskeletal dynamics and cellular polarity through JNK and Rho family small GTPases. Diversin is a component of both the canonical and non-canonical Wnt signaling pathways. The Diversin-mediated Wnt/PCP pathway regulates the proliferation of neuroblasts in the

adult SVZ. Wnt3 is strongly expressed in dentate gyrushilar cells and in cultured hippocampal astrocytes, and that GSK3beta/beta-catenin-signaling is active in the adult SGZ and dentate granule cell layer. Astrocyte-derived Wnt-signaling mediates neuroblast proliferation and neuronal differentiation in adult-derived hippocampal progenitor cells via the beta-catenin pathway.[22,23]

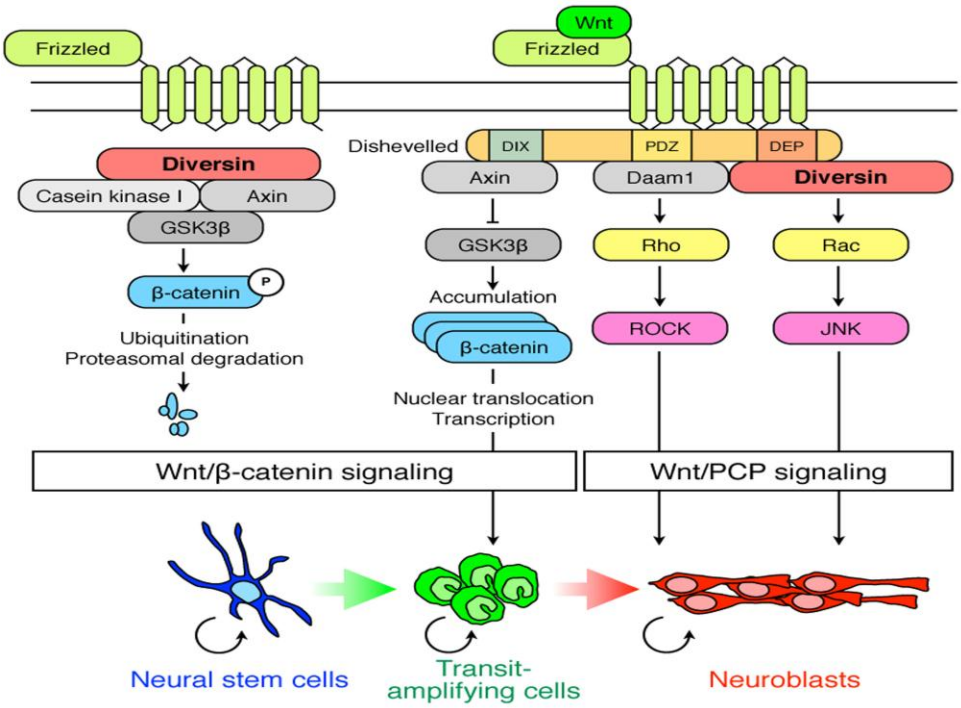

Figure no. 4 Regulation of SVZ neurogenesis by Wnt signaling.

3. Transcription Factor

Recent data suggests that transcription factor sequences expressed during the embryonic generation of neocortical glutamatergic neurons are part of a conserved program of neurogenesis responsible for the generation of glutamatergic neurons in the adult dentate gyrus.[29]

1. Paired box (Pax) genes

During embryonic generation of cortical glutamatergic neurons, Pax6, a paired domain and homeodomain-containing transcription factor, is expressed in radial glia.[26] Radial glia act as the primary progenitor cells of the cerebral cortex, and divide to give rise to IPs that, in turn, are responsible for generating most cortical glutamatergic neurons.[27]

2.cAMP response-element binding protein (CREB)

The transcription factor cAMP response-element binding protein (*Creb1*, CREB) is a member of the CREB transcription factor family that acts in conjunction with its transcriptional coactivators p300/CBP/*Crebbp* as an intracellular effector that has been implicated in regulating neuronal survival and plasticity.[28] CREB is activated via phosphorylation (pCREB) and this activated form is expressed predominantly in immature neurons in the adult dentate gyrus, where it co-localizes with DCX and calcitenin. Pharmacological activation of the CREB signaling cascade has been shown to increase proliferation in adult hippocampal progenitor cells.[29] Increased CREB activity has been shown to enhance dendrite length and increase dendritic branching, whereas cell autonomous loss of CREB function has been shown to decrease dendritic branching and expression of DCX and NeuroD1.[30]

REGULATION OF NEUROGENESIS

Several endogenous and exogenous factors have been shown to affect neurogenesis, each playing an important role at one or more of its specific stages. Approximately 50% of the new neurons in adult hippocampus survive while the remaining cells degenerate within four weeks after birth.

1. Up regulation of Neurogenesis

Physical activity such as exercise leads to increase in level of growth factors. Amongst the classes of growth factors, mainly BDNF, IGF, FGF, and EGF are responsible for regulation of neurogenesis.[31] In addition to protecting neurons, these factors have been shown to stimulate proliferation of adult-derived neural stem cells and their differentiation during development, growth factors provide important extracellular signals for regulating the proliferation and fate determination of stem and progenitor cells in the CNS in dentate gyrus, hilus and CA3 region of hippocampus. BDNF is a member of the "neurotrophin" family of growth factors, support the survival of existing neurons, and encourage the growth and differentiation of new neurons and synapses. In the developing mammal, growth hormone increases IGF binding proteins & thereby promotes proliferation of neurogenesis.[32, 33]

The neurotransmitter serotonin (5-HT) is well established modulator of neurogenesis. 5-HT enhances the production of new neurons in prominent neurogenic niches in the brain, including dentate gyrus (DG) hippocampus. Out of the numerous serotonergic receptors, the 5-HT 1A receptor is the one most likely involved in regulation of neurogenesis in the DG.

Other types of serotoninergic receptors which may be involved in mediating the effects of serotonin on proliferation in the DG are the 5-HT4, 5-HT 6 and 5-HT 7 receptors.[34] All of them, when activated, trigger the cAMP cascade. One of the results of increased signaling in that pathway is triggering expression of the cAMP response element binding protein (CREB). The cAMP-CREB cascade may then increase expression of BDNF. BDNF does not directly change the rate of neurogenesis in the DG, but it may increase the release of serotonin and that in turn may stimulate neurogenesis through increased activation of the 5-HT 1A receptors. , the role of the NMDA receptor (one of the receptors for the excitatory neurotransmitter glutamate) in adult neurogenesis has been extensively studied. Although cell genesis in the dentate gyrus does not require a functional NMDA receptor, global NMDA receptor-dependent activity is inversely correlated with the level of hippocampal proliferation. Glutamate increases neuronal differentiation in hippocampus. In contrast to the elusive mechanism of glutamate, the neurotransmitter GABA directly depolarizes type 2 progenitors in the adult hippocampus, which results in calcium ion influx and increased expression of the neuronal differentiation factor, suggesting that direct GABAergic input promotes the differentiation of type 2 hippocampal progenitors. Some pathological conditions such as seizures, excitotoxic or physical lesion of hippocampal granule cell layer induce neurogenesis.[35]

2.Downregulation of neurogenesis

In contrast to the positive effects of exercise and enriched environment, stress significantly down-regulates neurogenesis in adult hippocampus. Exposure of marmoset monkeys or tree shrews to intruder stress for only a short period of time (1 h) down-regulates the rate of neurogenesis in adult hippocampus.[36] Administration of adrenal-glucocorticoids also decreases neurogenesis in adult hippocampus, indicating that activation of the HPA axis and release of glucocorticoids underlies the downregulation of neurogenesis in response to stress.[37] Stress increases the circulating levels of endogenous glucocorticoids, which in turn decreases adult hippocampal neurogenesis. The molecular mechanisms by which glucocorticoid hormones regulate hippocampal neurogenesis are poorly understood. Various types of stress such as ‘social stress’ or ‘physical stress’ and their effects on the HPA axis in many different circumstances. Stress activates HPA axis and thus elevates cortisol (endogenous glucocorticoids) levels. Glucocorticoid receptor (GR) has low affinity for cortisol and is thus predominantly activated by high cortisol concentrations. GR activation decreases the proliferation and neuronal differentiation whereas, MR activation increases

hippocampal progenitors cell proliferation while concomitantly shifting cell fate from neuronal toward astrocyte differentiation.[38] Also, physiologically produced NO reduces the number of cells undergoing proliferation in the adult mouse SVZ and OB, with a selective action on a specific cell subpopulation that expresses nestin but not neuronal- or glial-marker antigens.[39] Thus far, an age-dependent decline of adult hippocampal neurogenesis is the only common finding in all species investigated. Hippocampal neurogenesis occurs throughout adulthood, but declines with age. This age-related decline could be due to a depletion of multipotent precursors with time, a change in precursor cell properties, or a change in the levels of molecular factors that influence neurogenesis. Adrenal steroids production is lowest in early prenatal period hence rate of neurogenesis is more while in older animals steroids production is comparatively higher hence rate of neurogenesis low.[40] Specific substance such as Methylaoxymethanol acetate (MAM) is a neurotoxin which reduces DNA synthesis. It is used in animal models of neurological disease including Schizophrenia and epilepsy. Methylaoxymethanol selectively targets neurblast in CNS and causes newly proliferated neurons to die & decreases the number of newly generated cells in dentate gyrus.[41]

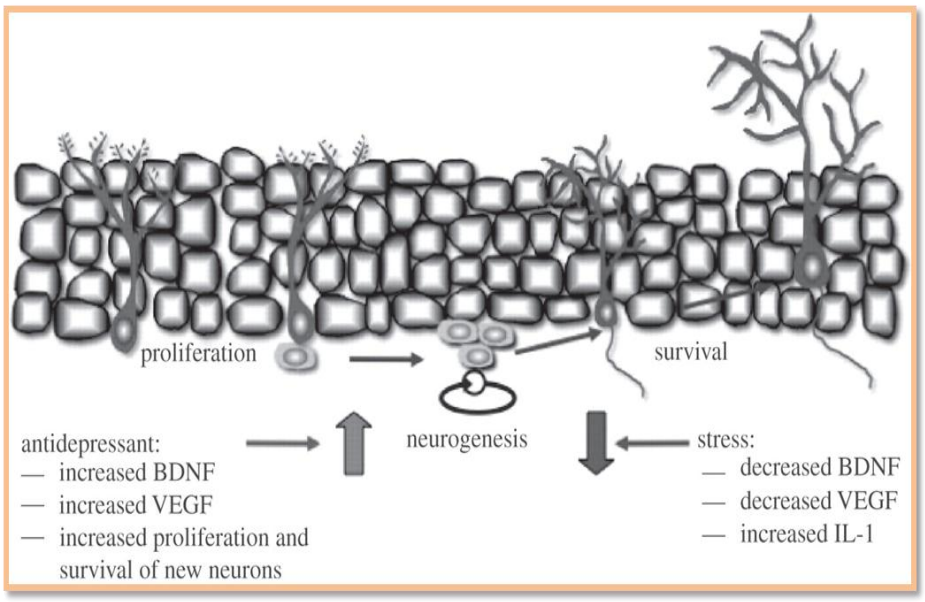

Figure no. 5 Factors influencing Neurogenesis

CLINICAL CORRELATIONS OF NEUROGENESIS IN PATHO-PHYSIOLOGICAL CONDITIONS

Regulation of neurogenesis by environment and behavior has been extensively reviewed. One of the first studies that hinted about a role for adult neurogenesis in hippocampal physiology and function showed that mice housed with a running wheel, a treatment that increases

neurogenesis in the DG, displayed improved learning in the Morris water maze and enhanced LTP at perforant path DGC synapses. This strong correlation between neurogenesis, learning, and LTP suggested that improved learning might be a consequence of increased plasticity which in turn suggest that neurogenesis increases synaptic plasticity.[42,43]

The neurodegenerative disorders like Parkinson's disease (PD), Huntington's disease (HD), Alzheimer's disease, Depression, all present with a gradual loss of relatively well-defined neuronal populations. Under all of these conditions, progression is slow.[44] Neurodegenerative diseases comprise a wide range of diseases that share the common characteristic of progressive loss of structure or function of neurons and glial cells in the brain and spinal cord.[45] Many neurodegenerative diseases are a result of neuronal loss, although glial cells are also involved.[46] In some cases, the neuropathology is relatively restricted, leaving significant parts of the nervous system unaffected. Thus, it might be possible to direct newborn cells in the adult brain to migrate to the regions affected by the disease and there differentiate into the specific types of neurons that succumb due to the disease.[47] This concept has based on the realization that the adult mammalian brain has a capacity to generate new neurons.

Depression

It is well known that chronic stress can provoke a depression.[48] Through various studies with rats and humans, researchers have now discovered a possible explanation for the phenomenon. Stress reduces the brain's innate ability to keep itself healthy. As a result, the hippocampus – a vital part of the brain – shrinks, impacting negatively on both our short-term memory function and our learning abilities.[49] Down-regulation of neurogenesis by exposure to stress, including learned helplessness, raises the possibility that decreased granule cell number could contribute to the reduction in hippocampal volume observed in depressed patients. Decreased neurogenesis could also contribute to selected symptoms of mood disorders, including cognitive abnormalities and loss of inhibitory control of the HPA axis. This gives us good idea that neurogenesis is correlated to pathophysiology of depression.

A major finding in the field of depression is that treatment with antidepressant drugs increases hippocampal neurogenesis.[50] It has been demonstrated that multiple classes of antidepressant drugs increase hippocampal cell proliferation and neurogenesis in a chronic and not acute time course, which corresponds to the therapeutic time course necessary for

effects.[51] This data indicates that reduced hippocampal cell number may be involved in the pathophysiology of depression and reversal of this may be one way the antidepressant drugs exert their effects. Antidepressant drugs increase the number of new neurons born in the hippocampus. Multiple classes of antidepressant drugs (Fluoxetin, specific serotonin reuptake inhibitor,etc) as well as electroconvulsive shock (ECS) produced an increase in cell proliferation and neurogenesis in the adult rat hippocampus.[52] Antidepressants increase neurogenesis particularly in the SGZ of the hippocampus, with no effect on subventricular zone neurogenesis. This data indicates that stimulating sub granular neurogenesis offers better therapy for treatment of depression. However, the mechanism of neurogenesis is poorly understood.[53]

Parkinson Disease

The most common movement disorder in the world is PD. Similar to the amyloid β (Aβ) and huntingtin proteins, abnormal oligomerization and accumulation of α-synuclein in synapses and neuritis are proposed as central mechanisms leading to neurodegeneration of dopaminergic and nondopaminergic neurons in PD and related disorders. Therefore, strategies aimed at reducing α-synuclein, oligomerization and aggregation is suggested as potential therapies.[54] Current treatment strategies are mainly limited to symptomatic approaches aimed at increasing dopamine levels in the degenerating nigrostriatal system. Considerable attention has been placed on developing therapies based on cell replacement. Cell therapies such as transplantation of dopamine-producing fetal cells provided the proof of principle that transplanted neurons can survive, innervate the patient's brain, and elicit beneficial effects. However, limited access to suitable donor tissue, variability in the outcome, and adverse side effects (graft-related dyskinesias) in some patients discourage this therapeutic option. The pool of endogenous neuronal stem cells of the adult brain provides an alternative and attractive cell source for cell-based therapies.[55] New developments encourage research to determine the possible impact of changes in neuronal stem and progenitor cells on the symptoms of PD. Therefore, several animal models of PD have been examined in detail concerning the potential and modulation of endogenous neurogenesis.

The primary symptoms of Parkinson's disease result from greatly reduced activity of dopamine-secreting cells caused by cell death in the region of the substantianigra. Multiple signaling factors are investigated for the induction of dopamine neurons from several sources of stem cells, such as early developing human embryo that provides the human embryonic

stem cells, and adult brain that provides adult neural stem cells. Reprogrammed somatic cells also used to provide induced pluripotent stem cells and mesenchymal stem cells that differentiate into neural stem cells.[56]

Epilepsy

Epilepsy is common & diverse set of chronic neurological disorder characterized by recurring seizures (also known as "seizure disorder").[57] Neurogenesis in the dentate gyrus is particularly interesting in the context of epilepsy, for several reasons. First, the hippocampus is an area that is particularly susceptible to seizures, and thought to be involved in the etiology of some forms of epilepsy (e.g., temporal lobe epilepsy). Second, the dentate gyrus is thought to play a major role in preventing seizures from invading the hippocampus by acting as a type of gate or barrier.[58] Third, the major cell type of the dentate gyrus, the granule cell, is the primary cell type that is born during neurogenesis in the adult dentate gyrus. Finally, the granule cell and its neighbors express many types of growth factors and growth factor receptors, and these changes dramatically with seizures.[59] Neurogenesis depolarizes the membrane by increase in calcium release, increases excitatory neurotransmitters which leads to CNS excitability. Excess increase in number of neurons prolongs depolarization which leads to abnormality in sodium, potassium and calcium channels. A seizure occurs when too many nerve cells in the brain "fire" too quickly causing an "electrical storm". The majority of adult neurogenesis in the hippocampus is thought to occur as a result of division of cells that lie within the SGZ.(Aberrant seizures neurogenesis).[60] As mentioned above, seizures greatly increase neurogenesis in the dentate gyrus. This is an extremely robust phenomenon, because many different ways to induce seizures exist, and thus far all appear to increase dentate neurogenesis. Thus kindling, electroconvulsive shock, and status epileptics all increase neurogenesis in the dentate gyrus.[61]

CONCLUSION

Accumulating evidence demonstrates that neurogenesis in the adult brain consists of complex biological events including the genesis, migration, differentiation, and maintenance of new neurons. Several principles have emerged from these studies. (1) Neurogenesis appears to be conserved across all mammalian species. (2) The process of neurogenesis from cell birth to functional integration is readily influenced by external factors. (3) Distinct developmental origins lead to the production of different types of adult-born neurons through SVZ and SGZ

neurogenesis. (4) Despite the differences between SVZ and SGZ neurogenesis, the activities of immature newborn neurons from both origins are critical for their survival, maturation, and subsequent integration into the existing neural circuits. (5) Although the exact nature of their contribution to adult brain function remains unknown, these newborn neurons are certainly playing some role in behavior or any other pathological conditions.

FUTURE PROSPECTIVES

In particular, new knowledge regarding the downstream signaling pathways is warranted, which is important both for understanding the mechanisms of neurotransmitter signaling in the context of cell fate decisions and for pinpointing possible drug targets There will be a pressing need for new therapies to address the age-related increase in neurological disease as we approach the estimated threshold in the year 2050 when 20% of the population will be older than 65 years of age. As the brain continues to generate new neurons throughout the life, Neurogenesis is now being translated through to new drugs for treating depression and neurodegenerative disease. But the ability to stimulate neurogenesis offers the prospect of revitalizing pharma's interest in psychiatric disorders and of providing effective treatments in an area of huge unmet medical need. It appears unlikely that drugs being developed to treat neurodegenerative diseases will be beneficial if they impair neurogenesis. And, most tantalizing, therapeutic approaches that stimulate neurogenesis might stimulate repair and even recovery from these devastating diseases.

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